Indian Journal of Pharmac Practice ijopp

The Official Publication of APTI

EDITORIAL OFFICE

INDIAN JOURNAL OF PHARMACY PRACTICE
An Official Publication of Association of Pharmaceutical Teachers of India
H.Q.: Al-Ameen College of Pharmacy,
Opp. Lalbagh Main Gate, Hosur Road, Bangalore 560 027, INDIA
Mobile: +91 9845399431 | +91 9845659585 | +91 9900434646
+91 9916069842 | Ph: +91 80 22234619; Fax: +91 80 22225834
Printed and Published b : Prof. B.G. Shivananda, Secretary, on behalf of Association of Pharmaceutical Teachers of India
Printed at : Graphic Point, #55/44, 4th 'B Cross, K.S. Garden, lalbagh Road, Bangalore - 560 027. Ph: 080-2227310

www.ijopp.org | ijopp@rediffmail.com

Indian Journal of Pharmac Practice ijopp

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Editorial

Dear Readers,

Thank you for all your contributions to ijopp. I am happy to inform you all that ijopp is now indexed in Copernicus and we are trying to get it indexed in other bibliographical databases also

During our routine discussion with the clinicians, we invariably come across a few drug molecules which follow dose dependent kinetics what we call as "Non-Linear Pharmacokinetics."

Unlike linear pharmacokinetic models, which use simple first order kinetics to describe ADME, non-linear pharmacokinetic models require the application of more complicated saturation [Michaelis-Menten] kinetics. Although linear pharmacokinetics describes a large majority of drugs used in the hospital, few drugs follow saturation kinetics. Such drugs cause a disproportionate increase in serum levels when dosage is increased.

Drugs following non-linear kinetics also known as dose dependent kinetics, cause saturation of the metabolic carrier mediated system. This can occur in the glycine conjugation of salicylates, glucuronate conjugation of phenytoin and hydroxylation and subsequent glucuronate conjugation of theophylline to name a few. Another example is saturation of renal process with penicillin. As dosage increases renal clearance decreases.

For those drugs exhibiting non-linear kinetics, a small change in daily dose could result in a large change in plasma concentration. For instance, a 10% change in dose could yield a100% (or greater) change in concentration. This could lead to toxicity.

Understanding of drugs following non-linear pharmacokinetics is much more challenging and needs thorough understanding of Michaelis-Menten Kinetics.

This will help the clinicians to prevent the adverse reactions of many important drugs such as phenytoin by dose adjustment to achieve a target steady state concentration. Knowledge of V_M[Maximum elimination rate of a drug] and K_M[Michaelis-Menten constant] is required for the determination of new dose.

This area can be explored by pharmacy practice researchers to contribute to better patient care. Do share your views, expertise and work in this area through letter to editor, review and research articles respectively.

Dr. Shobha Rani R Hiremath
Editor-in-Chief
ijopp

India's Progress towards the health related Millennium Development Goals –HIV/AIDS

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ABSTRACT

Submitted: 18/10/2011 *Accepted: 25/11/2011*

Controlling and reversing the spread of AIDS/HIV is the key focus of the 6th Millennium Development Goal (MDG) proposed by United Nations. One of the critical links for attaining MDG 6 targets is India. India has one of the largest populations of HIV infected individuals in the world and addressing this issue requires multidimensional, complex solutions. This paper looks at various social and economic factors contributing to the prevalence of HIV/AIDS in India. An overview of steps being taken by government and various other organizations to address the threat of HIV/AIDS is presented with particular emphasis on vulnerable populations like commercial sex workers (CSWs), injecting drug users (IDUs), men having sex with me (MSMs) and HIV positive children due to mother to child transmission (MTCT). The paper presents a brief overview of the challenges faced by the Indian government and the NGOs to combat HIV/AIDS and provides recommendations discussing issues and interventions based on economic efficiency perspective.

Keywords: HIV/AIDS, commercial sex workers, injecting drug users, MSMs, MTCT, NACO

INTRODUCTION

MDG 6 aims to halt and reverse the spread of HIV/AIDS by 2015. The indicators selected to measure this target were measuring HIV prevalence among pregnant women aged 15-24 years, use of condom during last high risk sex, percentage of women aged 15-24 years who are knowledgeable about HIV/AIDS, number of orphans attending school compared to non orphans aged 10-14 years, condom use rate and contraceptive prevalence rate other than condoms (MDG Report 2005). In 2007, in the age group 15-49 years, about 2.5 million people were living with HIV/AIDS and the prevalence of HIV in adults was 0.3%. Prevalence of HIV/AIDS was 6-15% in people receiving anti retroviral therapy, 7.2% in vulnerable and high risk populations like Injecting Drug Users (IUDs), 7.4% in men having sex with men (MSMs), and 5.1% in commercial sex workers.[1,2,3]

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A majority of IV drug users reside in the metropolitan cities of India, mainly Chennai, Delhi, Mumbai and Chandigarh contributing to almost 3.8% of all the HIV/AIDS infections. Among pregnant women aged 15-24 years, the prevalence decreased to 0.49% (0.95 million) in 2007 from 0.86% (1.67 million) in 2002. According to the District Level Household & Facility Survey conducted in 2007-08, only 79.9% urban women and 48.8% rural women had HIV/AIDS awareness.[4,5,6] HIV/AIDS exerts a considerable burden on India's economy comprising about 1 percent of its annual GDP.[7]

Past measures:

In 1987, the Indian government established National Aids Control Organization (NACO) to monitor spread of HIV/AIDS in India on a nationwide basis. From 1992-1997, NACO launched Phase I, consisting of State Aids Control Sites (SACS) to collect data, perform behavioral sentinel surveillance surveys for risk assessment, perform screening of blood and blood products, and conduct public education campaigns.[8] Phase II (1999-2006) launched by NACO aimed to reduce the spread of HIV/AIDS by providing interventions

and cheap treatment to high risk populations, strengthening institutions and facilitating inter-sectoral collaboration. Currently, Phase III launched by NACO (2007-2012) aims at reversing the spread of HIV/AIDS, prioritizing prevention efforts, integrating care, support and treatment.[8,9,10]

Present measures:

Until 2004, NACO had been promoting voluntary testing centers (VTC), voluntary counseling, support networks for HIV/AIDS patients, development of clinical trials for testing HIV vaccines and partnering with media agencies like BBC and Doordarshan (government supported broadcaster) for HIV/AIDS related programming. In recent years, several community care centers run by NGOs have been established, generic anti retroviral drugs are available and free ART (anti-retroviral therapy) is provided to about 5% HIV/AIDS patients residing in the six high HIV prevalent states of India.[10] To control the transmission of HIV, several collaborative public education initiatives like the Heroes Project in partnership with Kaiser Family Foundation, the Avahan initiative by the Gates Foundation and the Population Services International (PSI) in about 22 states in India were undertaken.[11] In 2005 and 2006, the Indian government encouraged global business corporations to outsource their work to India in order to strengthen Indian pharmaceutical industry's response to HIV/AIDS,.[9]

Outreach programs for vulnerable populations with HIV/AIDS in India- a few examples:

A: Sex workers:

The Sonagachi project was started in 1992 by Dr. Jana. The term "Sonagachi", translates to "golden tree" in local language, is the oldest red light areas in Calcutta, a metropolitan city in state of West Bengal. This project is being recognized as one of the finest projects that helped in controlling HIV/AIDS among sex workers in Calcutta. The seroprevalence reduced among prostitutes by 11 percent as opposed to 50 percent in the other metropolitan cities of Bombay, Delhi and Madras.[12]

Fig. 2: A summary of the Sonagachi model comprising of interventions at the community, group and individual level:

Community based interventions	Individual based intervention	Sustainability
Considering HIV/AIDS reduction a community priority	***Skills and Competencies***	Intervention programs should be:
- Through involvement of economic stakeholders comprising of sex worker industry, landowners renting rooms, madams arranging clients, babus (clients), police getting pay offs for keeping sex workers out of the jail, political parties whose future could be jeopardized if HIV infection increases in their constituency.	- At individual level, the peer outreach workers serve as role models for other sex workers as gainers of literacy, employment, self confidence and respect.	Cost effective.
Political Advocacy for rights of equality	***Social Cognitive Perceptions***	Useful to the target population and the society.
- Advocacy for right to equal opportunity to work, free expression, and education for sex workers	- The program progressed on the mere perception of hope that changes could be brought about as opposed to the US belief of achieving outcomes.	Sustainable over time to achieve long term results.
Group based interventions	Environmental Barriers and Resources	Realistic and must abide with the skills of the people involved.
Social relationships	***Literacy***	Evolving over time.
- Creation of an environment of trust through interaction between sex workers, change agents, and power brokers to encourage voluntary participation in interventions,	- Addressed through literacy programs initiated by Professional staff followed by the outreach peer workers upon acquiring education.	
Peer outreach workers	***Economic Programs***	
- Training sex workers to help educate peers about HIV/AIDS and STDs	- Creation of sources of economic assistance through collaboration with financial institutions to mitigate the economic pressure that may contribute to risk prone practices by them.	
Sex Workers and Professional Advocates	***Condom sales***	
- Professional advocates transfer ownership of initiatives to sex workers in order to facilitate ownership of the initiative by them and thus make the initiative more sustainable and organic.	- Initially condoms were sold free followed by a subsidized rate for condoms when the program gained impetus.	
	Trade Unionization	
	- Upon achieving success in Sonagachi, the peer outreach workers formed committees which now help other red light areas in the state.	

Reference: S Jana, I Basu, MJ Rotheram-Borus, PA Newman. The Sonagachi Project: A Sustainable Community Intervention Program. pp: 405–414

Sonagachi project has been replicated in many parts of India including many areas in northeast India. Studies using the Sonagachi model have achieved positive outcomes with sex workers in terms of lower number of STDs, increase in the preventive and treatment seeking behavior accompanied by emergence of optimistic attitude towards coping with the disease.[13,14] The tenets of the Sonagachi model have been successfully implemented in the cities of Mysore, Delhi, Madras, Bombay and Pune for carrying out interventions among CSWs.

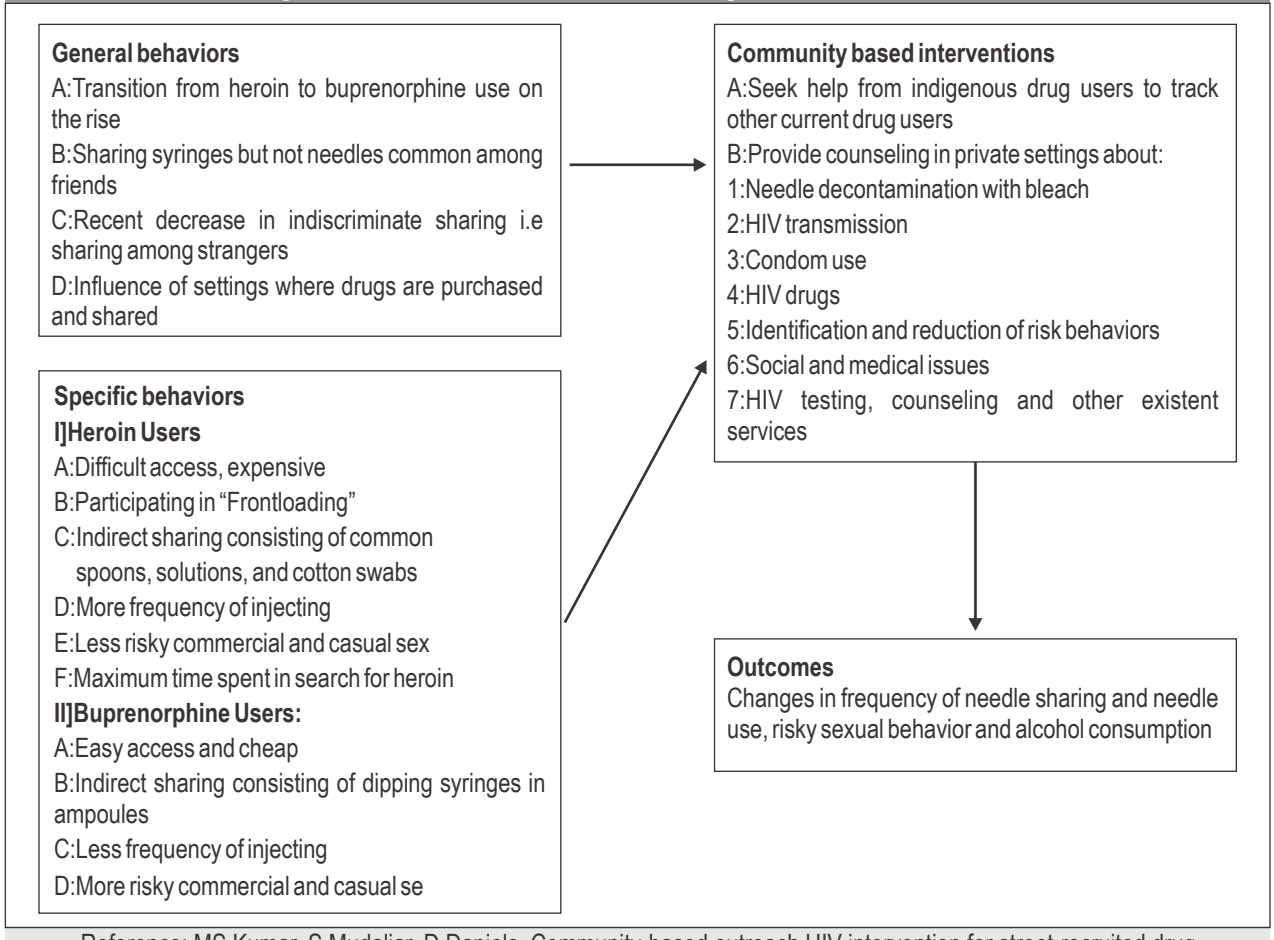
B: Male sex workers and Men having sex with men (MSM):

Since the last decade, the prevalence of HIV/AIDS has been on a rise among the male sex workers and MSM. Agencies like 'NAZ' (translates to "pride" in local language) foundation and 'Humsafar' (translates to "companion" in local language) thrust focus on the sexual health needs of the MSM and the gay men. In the last few years, these agencies have sponsored several consultation meetings, have worked with local male sexual networks to address the concerns of emerging sexual identities, and have helped develop community service projects in Calcutta and Delhi. The members of the agencies work with the objective of helping lesbians and gay men establish a public arena to articulate identity issues and speak out against homophobic traditions and cultural values, thereby willing to challenge the system. However, representation in these kinds of organizations is an issue since the members mostly represent the upper class societies who have access to more life style choices compared to individuals from middle or lower middle class, irrespective of the disease condition.[15,16]

C: Injecting drug users (IDUs):

Northeast India and some cities in the Southern part of India have a high prevalence of IDUs. Outreach programs include interventions geared towards sub cultural changes, and influencing individual behavior with support from family members and peers.

Fig. 3: Interventions to reduce HIV risk among IDUs are described below:



Reference: MS Kumar, S Mudaliar, D Daniels. Community-based outreach HIV intervention for street-recruited drug users in Madras, India. Pp: 59-63

Outreach programs provide a chance to work with hard to reach IDU populations. Locating IDUs is a concern for most of the organizations working with IDUs. Society for Prevention, Research and Education on Alcohol and Drugs (SPREAD) is an umbrella organization that has brought all drug agencies under one roof by making them realize the importance of risk reduction associated with HIV/AIDS transmission in IDUs. SPREAD continuously strives to reduce needle sharing among IDUs, augmented by police harassment of IDUs in possession of needles. [17]

D: Blood transfusion:

Nearly 5 million liters of blood worth 29 million pounds is purchased every year in India. Bombay has many professional HIV blood donors who sell their blood to blood banks who in turn accept it without any tests or inquiries. In wake of this situation, the Indian government increased import of most blood products. The government has also established blood screening centers in eight cities to minimize blood contamination. Members of the Indian Health Organisation (IHO) have been carrying out community interventions to minimize the infected blood transfusion by educating blood donors.[13] Intervention studies comparing and screening various commercially available blood products for the presence of HIV-1 antibodies have been conducted in specific cities in the country. These studies have shown more contamination in blood products manufactured in cities like Bombay and Pune compared to Delhi. [18]

E: Couples transmission: HIV positive males visiting brothels and having multiple sexual partners and HIV positive IDUs generally transmit the disease to their monogamous wives or partners. Studies involving interventions carried out in males going to STD clinics aim at impacting their sexual behavior by convincing them to uptake monogamy and frequently use condoms. One such intervention study conducted in collaboration with the John Hopkins University and the National AIDS Research Institute enrolled HIV negative males with STDs and called them at regular three month intervals for follow up for the period of four years. During each follow up session, males were tested for STDs by performing their detailed physical examination. They were provided with counseling about monogamy, HIV prevention, abstinence or condom uses with all sexual partners or extra marital sexual partners till their STD was cured and were also offered free lubricated condoms. Such intervention studies provide insight about the factors leading to risky sexual behavior among males. Factors like lack of information about HIV/AIDS, presence of STDs, type of sexual partners (extra marital, CSWs), marital status (single, married), lack of concern about family planning and beliefs about reduction in pleasure contributed lower rates of condom use. [19]

F: Mother to child transmission (MTCT): A study conducted in Bombay to reduce MTCT administered zidovudine to mothers in the last 6 weeks of pregnancy, administered oral zidovudine to infants and also requested the mothers to avoid breast feeding[20]. A number of multi site studies implemented by NACO in high HIV prevalence Indian states have studied the uptake of zidovudine in pregnant females and nevirapine to prevent parent to child transmission (PTCT). Use of breast milk alternatives and attending antenatal clinics is also encouraged at certain sites.[21]

Donor role:

The World Bank, the major donor to NACO, provided up to $84 million and $191 million for phases I and II respectively. India is one of the 15 focus countries of President's Emergency Plan for AIDS Relief (PEPFAR), receiving aid of almost $36 million in 2004. The Global Fund has provided 8 grants of approximately $26 million each at regular intervals to India for combating HIV/AIDS, TB and malaria. Also, bilateral assistance provided by the US government through its contribution to the Global Fund, help from USAID since 1995, and help from CDC since 2001 have helped support HIV prevention and intervention activities in India. UNAIDS, WHO, UNICEF, UNDP, other UNAIDS co-sponsors, and countries like U.K, Australia and Canada have provided donor aid to help improve technical efficiency in in-country offices and NGOs. The Gates Foundation has also contributed more than $200 million towards the Avahan initiative which is involved in community based interventions and HIV/AIDS research.[11,22]

Major challenges:

A) Diversity among the vulnerable population: Acute conditions like poverty, illiteracy and unemployment drive vulnerable populations to resort to sex work. This in turn not only increases their risk of exposure to HIV/AIDS, but also increases the risk of HIV/AIDS among the variety of clients who come in contact with them. The diverse vulnerable population requires targeted interventions characteristic of the specific high risk population.

(B) Hidden and mobile populations: Vulnerable populations have to be on a constant move due to high economic instability. Furthermore, they remain hidden due to disempowerment, abandonment, and ostracism by society. These factors facilitate the spread of the disease and present hurdles in obtaining preventive services. As a result, it is difficult to target focused interventions consistently towards these populations.

C) Stigma and discrimination: Stigma, fear, apathy, absence of treatment-seeking behavior, low SES, gender based

inequity in access and use of services, and prejudiced provider behaviors create social hurdles for health. These factors affect medication adherence and drug supplies, quality of care, supervision, referrals and communication, leading to drug resistance and adverse drug reactions (ADRs).[23,24]

D) Health service delivery and policy: Inadequate monitoring systems and infrastructure, improper human resources allocation management, lack of coordination between donors, NGOs, and government agencies, and absence of regulations to affect the private and public sectors alike pose challenges to achieving MDG 7. [24]

E) HIV positive children: Children orphaned by HIV/AIDS are more likely to have poor health, education and protection, are more prone to child labor, abuse, neglect, sexual exploitation and may be denied education, shelter and opportunities to play. Most of the newborns (i.e. about 90%) suffering from HIV/AIDS have acquired it in their mother's womb or during breast feeding and this can decreased by treating the mothers with ART during pregnancy.

F) ART: There are certain challenges with ART therapy like discontinuation of ART treatment, denial and under reporting of the need for second line ART (i.e. more expensive drugs), and difficulty in enrolling in government funded ART programs due to tough exclusion criteria. The 3 by 5 initiative was a global effort launched in 2005 to provide 3 million people in developing countries with ART. However, with every 2 patients starting ART, about 5 people are newly acquiring HIV, making the fulfillment of the initiative challenging. [25,26,27]

G) Other factors: Other factors that increase the risk of HIV/AIDS among girls and young women are lack of knowledge about HIV, sexual debut before age 15, forceful sexual intercourse and tacit social acceptance of violence. Besides these risk factors, the use of unsafe injections , mostly in the rural areas and the urban slums, poses a major threat for the spread of HIV/AIDS. [4,5,6]

Anti retroviral treatment:

A proper transmission minimizing ART consists of structured ART, provision of incentives to NGOs at state and local levels for prevention and program evaluation inititatives. Preventive therapy helps control the disease in high risk populations with higher tendency to indulge in risky sexual behaviors (disinhibition). In India, prevention programs are mostly run by the NGOs and sometimes might lack the desired level of physician participation. Better response to prevention programs could be achieved if physicians could team with social workers to generate an emotional and fear based approach, visit the homes of HIV/AIDS CSWs, hand out free condoms, educate CSWs about ART medication adherence and motivate them to regularly visit clinics. Interventions targeting illiterate sex workers should emphasize the incurable nature of HIV/AIDS, involve screening of educational films or displaying slides.[28,29] Private health insurance plans are slowly gaining popularity among the educated population in India and the prospects of universal health insurance seem promising in the near future. However, the current absence of universal healthcare insurance poses several access issues among the ART users resulting in medication non compliance, increased risk of development of ART resistant HIV strains, increased difficulty in controlling opportunistic illnesses, more uptake of monotherapy and shortened life span of the HIV/AIDS patients. [28,29]

Structured antiretroviral therapy consists of counseling, testing the disease stages, taking triple drug antiretroviral medications and regular physician visits. Information about structured ART should be made available to the people when they visit physicians or through public initiatives organized by the government and NGOs, both at the local and state level.[30,31] A structured ART can minimize disease transmission by modeling the therapy on the basis of existent performance based fiscal mechanisms in India.[28] Even though generic versions of antiretroviral medications are manufactured by some big Indian pharmaceutical companies, like Cipla and Ranbaxy, these medications are unaffordable to the poor people.[32] Introduction of universal health insurance in India could potentially aid the poor people in procuring not only the anti retroviral medications at a subsidized rate but also medications for opportunistic illnesses like TB that commonly affects HIV/AIDS patients[30]. The patient specific toxicity associated with ART can be alleviated by maintaining a healthy diet and life style and use of cheaper alternative forms of medications like Ayurveda and Homeopathy which aim at strengthening the immune system with minimum side effects.[28, 29] As the availability of ART increases, more people will be motivated to undergo testing and start ART, thereby making it possible to monitor more people. Clinical data has to be combined with authentic laboratory data containing information about various tests indicating, a) diagnosis in order to start ART, b) viral load to determine disease progression, c) CD4 count to assess the state of the immune system, and d) blood biochemistry to start second line ART upon resistance development. The data from all the above tests should be obtained by proper management procedures conducted by physicians and well informed staff.[28,33] In India, due to unequal access to services, cost savings obtained from subsidized treatment of opportunistic diseases are consumed up by HIV/AIDS patients who do not have access to

HIV/AIDS care. However, treating opportunistic illnesses is a small aspect of ART. Even though structured ART is expensive, it increases the number of saved life years. [28] The expenses associated with structured ART can be offset by cost savings achieved by postponing the treatment of opportunistic illnesses if structured ART is used.[28] Like pharmaceutical companies located in the Western world, big pharmaceutical companies in India should be encouraged by the government to donate money for philanthropic causes like HIV/AIDS awareness campaigns whereby the companies could disclose their sponsorship to generate consumer goodwill. Currently, the Indian government is partnering with several international donors like WHO and Avahan to implement interventions and ensure access to structured ART and HIV/AIDS care at an affordable price. In order to extend this affordable care to each and every HIV/AIDS patient in India, it is important that monetary resources are allocated towards long term sustainability of both the treatment and prevention of HIV/AIDS.

Recommendations:

There is an indisputable association between poverty and communicable diseases. HIV/AIDS is a resurgent infectious disease which is a developmental issue, a public health crisis and a human rights issue facing the nation in the era of globalization and liberalization. The policies pertaining to neo liberal globalization in India have constrained health care services to cost effective interventions, increased cost of services, led to privatization of health services and imposition of user fees in government health facilities, ignored shortage of healthcare personnel in rural areas, promoted medical tourism leading to brain drain and affected agriculture which has reduced job opportunities and increased social insecurity. Vertically designed programs focus on interventions targeting limited risk factors identified through reductionist theories and cost effectiveness criteria. Horizontal programs which focus on the broader issues related to the spread of HIV/AIDS, involve community and consider socio economic factors like poverty, lack of education, unemployment, marginalization of women, development concentrated in urban areas and migration patterns should be designed (MDG India report 2009, Wada Na Todo Abhiyan 2010, MDG report 2010). With highly diverse individuals in vulnerable populations, it is necessary to use population specific interventions. For this purpose, it is necessary that centers be established centrally in NACO corresponding to specific vulnerable populations. Most of the states in India are dominated by specific vulnerable populations. NGOs work at the grassroots level and are involved with community based participatory research and interventions. In light of the work done so far by NGOs, the government must collaborate with NGOs in discovering and prioritizing the vulnerable population specific needs for optimum dissemination of funding and resources. A hierarchical structure in NACO comprising of national, state and local level centers will be effective in dealing with the disparate individual state specific problems. It is essential to adopt a disease specific approach when dealing with micro issues and a health system specific approach when dealing with macro issues (Travis 2004).

Table 1: A summary of the sentinel surveillance data collected by NACO classifying the Indian states based on the prevalence of HIV/AIDS:

Groups	States	High risk population (people attending IDUs and STI clinics)	Low risk population (women attending antenatal clinics)
Group I	Maharashtra, Tamil Nadu, Karnataka, Andhra Pradesh, Manipur, Nagaland	> 5%	> 1%
Group II	Gujarat, Goa, Pondicherry	> 5%	<1%
Group III	Remaining states	< 5%	< 1%

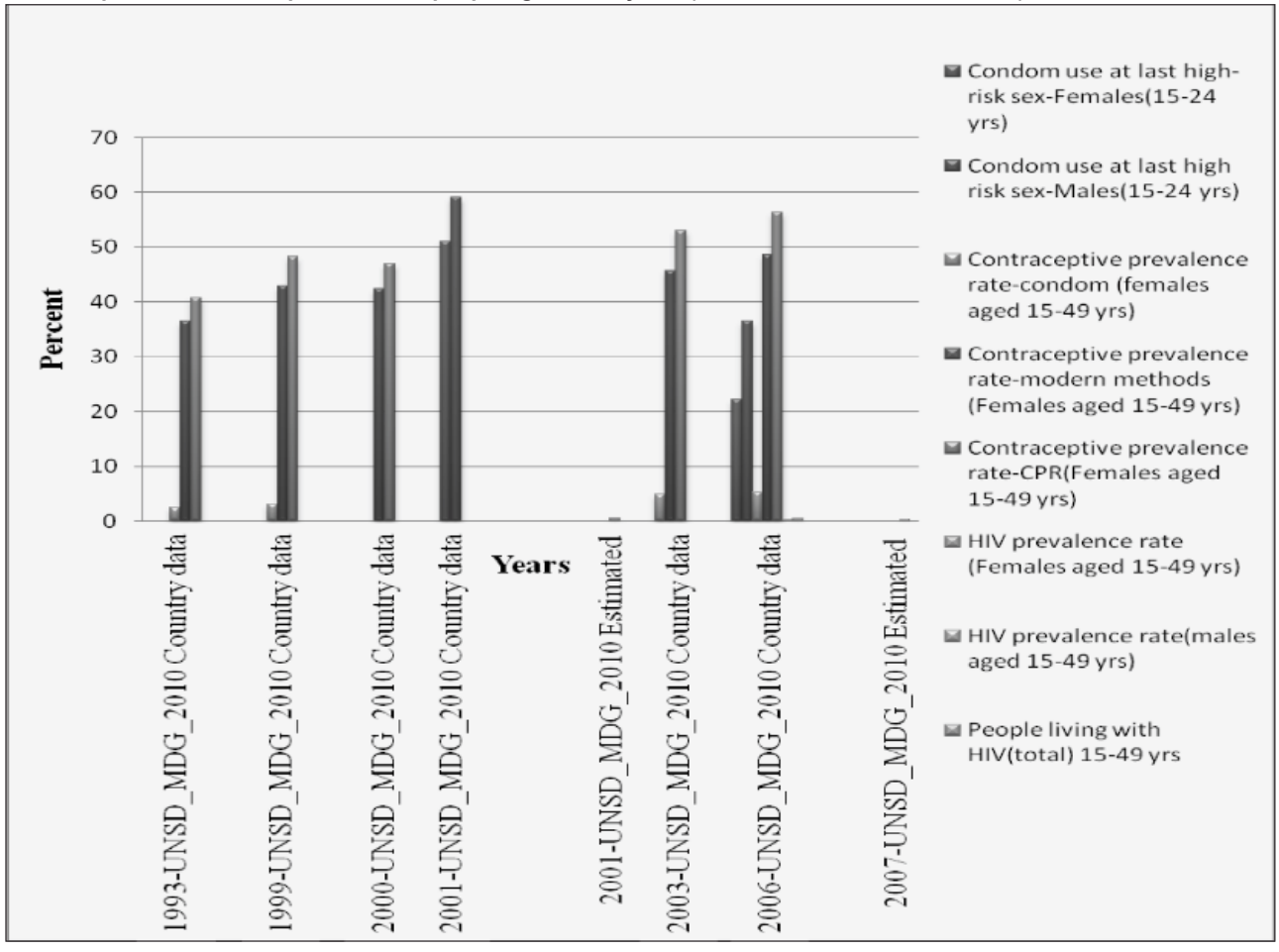
Reference: S Mohammed, S Panakadan. HIV/AIDS in India: Problem and Response. pp: 192

Table 2: A brief summary of the short term and long term goals to combat the challenges faced by the centers in NACO while working with both the private and public sectors:

Challenges	Short term goals to combat micro issues	Long term goals to combat macro issues
Financial problems, user fees	Provision of HIV/AIDS drugs and services at a subsidized rate	Development of generic HIV drugs
Transportation problems	Provision of outreach facilities (mostly done by NGOs)	Construction of facilities with respect to concentration of the population
Lack of technical skills and knowledge in the staff	Provision of updated continuous education about newer available techniques when renewing their medical licenses (like in US).	Incorporate AIDS related information, technical skills in the training curriculum of doctors, nurses and other staff
Lack of motivation	Provision of rewards with respect to services rendered	Promotions, empowering people, involve them in decision making
Deficits in planning and management	Up taking and incorporating managerial models, skills which have been successful in other situations, countries	Assigning experienced managers in the health ministry capable of bringing about a change
Compromised care by private practitioners	Proper education to combat stigma	Establishing regulatory system, penalty on service refusal

Reference: Travis 2004.

Contraceptive use and HIV prevalence in people aged 15-49 years (1993,1999-2001,2003,2006-2007)



Time period	Condom use at last high risk sex- Females (15-24 years)	Condom use at last high risk sex males (15-24 years)	Contra-ceptive preval ence rate- condom (females aged 15-49 years)	Contraceptiv e prevalence rate modern methods (females aged 15-49 years	Contra-ceptive prevalence rate CPR (females aged 15-49 years)	HIV preval-ence rate (Females aged 15-49 years)	HIV Preval - ence rate (males aged 15-49 years)	People living with HIV (total) 15-49 years
1993 *	Na	Na	2.4	36.5	40.7	Na	Na	Na
1999 *	Na	Na	3.1	42.8	48.2	Na	Na	Na
2000 *	Na	Na	Na	42.3	46.9	Na	Na	Na
2001 *	51.0	59.0	Na	Na	Na	Na	Na	Na
2001 †	Na	Na	Na	Na	Na	Na	Na	0.5
2003 *	Na	Na	4.8	45.7	53.0	Na	Na	Na
2006 *	22.2	36.5	5.2	48.5	56.3	0.3	0.4	Na
2007 †	Na	Na	Na	Na	Na	Na	Na	0.3

Footnotes: * UNSD_MDG_2010 country data, † UNSD_MDG_2010 estimated data,
Reference: UNSD_MDG Report_2010

CONCLUSION

HIV/AIDS in India presents an extremely complex task for policy makers and other organizations working towards addressing this issue. On one hand, issues like stigma associated with HIV/AIDS, lack of trust towards government and interventions, lack of awareness and underdeveloped medical infrastructure create a complex set of social and medical constraints, on the other hand, limited availability of funds makes it essential to evaluate the efforts and intervention from a return on investment perspective. The only way to attain sustainable and long lasting solution may be to conceptualize the issue as a multidimensional problem and attempt to address it through policy making and initiatives at various levels. From this perspective, Behavioral and psychosocial support systems, economic incentives, sustainable partnerships, strengthening intervention programs and effective public health policies can together make a huge difference in achieving the greater good of the AIDS patients in the Indian communities.

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Indian Journal of Pharmacy Practice | Association of Pharmaceutical Teachers of India

Evidence Based Medicine: Use of Probiotics in Pediatric Population for Diarrhoea.

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ABSTRACT

Submitted: 18/1/2012 *Accepted: 12/2/2012*

Diarrhoea is the most common problem in pediatric population. Different causes and types of diarrhoea has been identified, i.e., diarrhoea during antibiotic treatment, non rota virus diarrhoea, or based on severity of diarrhoea like mild, moderate and severe form of diarrhoea. Several drugs like loperamide can be used but due to its side effects like stomach ache and bloating, drowsiness, constipation, etc use of these drugs has been limited. Probiotics- live microorganisms has also shown effective results in treatment of diarrhoea in pediatric population. Several types of probiotics are available that showed effective results. Evidence Based Medicine is the proof for drugs that can be used safely and for it several research works have been performed. Probiotics, in the same way, has been tested in different forms (Eg: *Lactobacillus rhamnosus, Saccharomyces boulardii*; *Bacillus clausii*, etc.) and has shown evidently that they can be safely administered at several doses for the treatment of different types or forms of diarrhoea in pediatrics.

Keywords: EBM, Diarrhoea, Pediatric, Probiotics.

INTRODUCTION

The World Health Organization defines **Probiotics** as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[1]

The "live microorganisms" that the WHO refers to are the good bacteria in your yogurt or the Brand X supplement you bought, and "the host" is you. And the two of you are going to get along just fine because the human body is not only designed to perform whilst carrying a cargo of these little critters, but Probiotics are essential for your good health.

When scientists deliberate the definition of Probiotics they like to add a few more riders for a bacteria to qualify.

- Probiotics must be identified at the genus, species and strain level, using appropriate molecular and physiological techniques.
- The strain should be deposited in an internationally recognized culture collection so that scientists are able to replicate published research on the strain.
- Appropriate in vitro and animal assessments must be conducted to better understand the physiological attributes of the strain. However, the choice of what assessments are used should be based on assessments that are relevant to the probiotic function in the target host. Care must be taken to not overextend conclusions from in vitro and animal tests that have not been validated and shown to have relevance in the target host.
- Before use, the safety of the microbe must be fully considered.
- Properly controlled studies must be conducted which document a health benefit in the target host.
- Ability to keep the Probiotics alive at required levels in the final product through to the end of shelf life.

There are other requirements that could be asked of our Probiotics - things like its ability to adhere to intestinal cells and resistance to bile and gastric juices - but these other requirements need only be met by *some* Probiotics. If your task is to confer a health benefit in the mouth or throat, it really doesn't matter whether you enjoy the hurricane winds that might whistle through the bowel!.

Probiotics [2,3]

Probiotics are live, nonpathogenic microbial preparations that colonize the intestine and have a beneficial effect on the health of the host. Probiotic micro-organisms commonly used are strains of lactobacillus and bifido-bacterium. Enteral administration of probiotics has been shown to significantly decrease the risk of NEC (Necrotizing Enterocolitis) and death and shorten the time to full feedings in VLBW (very low birth weight) infants. One major concern is that exposing immunologically immature VLBW infants to probiotics may potentially increase the risk for infections. However, in a recent meta-analysis, no significant risk of sepsis was noted in infants treated with probiotics. Currently, there is no strong evidence to recommend a specific type of probiotics (species, strains, single or combined, live or killed), the timing, dosage,

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or duration of therapy. In addition, the long-term effects of probiotics for the prevention of NEC in VLBW infants are unknown.

Pathogenesis and Presentation of Diarrhoea [4]

Diarrhoea refers to an increase in frequency, volume, or liquidity of stool when compared with normal bowel movements. In developing countries, diarrhoea is a common cause of death. In the United States, approximately 38 million cases of diarrhoea will occur annually, resulting in approximately 2 to 4 million physician visits, 220,000 hospitalizations, and about 400 deaths.

Acute diarrhoea in infants and children generally is abrupt in onset, lasts a few days, and usually is caused by viruses. Diarrhea is considered chronic if it is longer than 2 weeks in duration and can be caused by malabsorption, inflammatory disease, alteration of intestinal flora, milk or protein intolerance, and drugs. Infants and children are at high risk for morbidity and mortality secondary to diarrhea for several reasons. Dehydration can occur easily as acute net intestinal fluid losses are relatively much greater in young children than in adults. This may result from inefficient transport systems in the developing intestine. In addition, the percent of total body water in children is higher than in adults; thus, they are more susceptible to body fluid shifts. Total body water changes from 80% of total body weight in premature infants to 70% in term infants and 60% in adults. Finally, the renal capacity to compensate for fluid and electrolyte imbalances in the infant is limited compared with an adult's.

Probiotics, live microbial foods containing species of lactobacillus, bifido-bacterium, saccharomyces, and streptococcus, can improve the balance of intestinal flora and diminish the effect of enteric pathogens. These microbes are thought to exert their beneficial effects through various mechanisms (e.g., producing antibacterial chemicals, competing with enteric pathogens, inhibiting the adhesive capabilities of pathogens, altering toxins or toxin receptors). Probiotics are most useful in infectious viral gastroenteritis (but not in bacterial infections) when used early in the course of disease. Lactobacillus GG (GG-Named after discovery by scientists, Sherwood Gorbach and Barry Goldin), in doses of at least 10^6 to 10^9 colony-forming units per day, has been the most consistently beneficial in clinical trials. The manufacture of Probiotics is not regulated; therefore, the organism count per dose might be based on the number present at the time of production and not at time of expiration, and the labeling might incorrectly identify the species of organism. As a result, the efficacy of Probiotics is difficult to ascertain reliably. Probiotics are not recommended for use in immuno-compromised individuals because systemic infections after use have been reported. Zinc supplementation holds promise for the treatment and prevention of diarrheal disease; however, its mechanism of action, best method of administration, and its efficacy in different populations are unclear.[5]

Evidence Based Medicine: [6]

It requires the integration of best research evidence with our clinical expertise and our patient's unique value and circumstances.

- By *best research evidence*-Means valid and clinically relevant research.
- By *clinical expertise*-Means the ability to use our clinical skills and past experience to rapidly identify each patient's unique health state and diagnosis.
- By *Patient value*-Means the unique preference, concerns and expectations each patient brings to clinical encounter and which must be integrated into clinical decision if they are to serve the patient.
- By *Patient circumstances*-Means their individual clinical state and clinical setting.

How do we Practice EBM? [6]

The full blown practice of EBM comprises five steps:

Step 1) Converting the need for information (about prevention, diagnosis, prognosis, therapy, causation, etc.) into answerable question

Step 2) Tracking down the best evidence with which to answer that question.

Step 3) Critically appraising the evidence for its validity, impact and applicability.

Step 4) Integrating the critical appraisal with our clinical expertise and with our patient's unique biology, values, and circumstances.

Step 5) Evaluating our effectiveness and efficiency in executing steps 1-4 and seeking ways to improve them

Limitations of EBM: [6]

Discussion about the practice of EBM naturally endangers negative and positive reactions from clinicians. Some of the criticisms focus on misunderstanding and misinterpretations of EBM, such as EBM will be hijacked by managers to promote cost-cutting tool, since providing evidence-based care directed towards maximizing patients' quality of life often increases the cost of their care and raises the ire of health economist. In addition, the self –reported employment of the

"searching" mode by a great majority of front line GPs dispel that the contention that EBM is an ivory tower concept (another common criticism). EBM actually leads to therapeutic nihilism in the absence of randomized trial evidence.

Use of Probiotic in Pediatric Population for Diarrhoea: [7, 8, 9]

Aims and basic rules:

1) Make a diagnosis

- Find the type of diarrhea (Viral Gastroenteritis, Infantile, etc.)
- Find out the cause of diarrhea (Antibiotics induced, bacterial infection, etc.)

2) Assess the degree of dehydration in percent and grams

- Mild 4%, Moderate 8%, Severe 12%
- In children below 1 year 5%, 10%, 15%, in adults 3%, 6%, 9% respectively.
- Dry mucus membrane, decrease in tears and oliguria suggests mild dehydration.
- Above-listed signs combined with cool periphery, loss of skin elasticity and prolonged (>2 sec) capillary refill time on the palmar surface of the distal fingertip suggests moderate dehydration.
- Above listed signs and deep, gasping breathing, ice cold periphery and poor general condition suggests severe dehydration.
- Observed or estimated pace loss should also be used to estimate dehydration in grams (in acute disease dehydration almost equals weight loss).

3) Choose the place of care

- Usually the child's home.

4) Plan and instruct how to give treatment

5) Give a prognosis

- Viral gastroenteritis usually continues for 4-7 days, rotavirus disease sometimes even longer.

TREATMENT:

Use of Probiotics:

- Oral rehydration solution (control group); *Lactobacillus rhamnosus* strain GG; *Saccharomyces boulardii*; *Bacillus clausii*; mix of *L delbrueckii* var *bulgaricus*, *Streptococcus thermophilus*, *L acidophilus*, and *Bifidobacterium bifidum*; or *Enterococcus faecium* SF68; Not all commercially available probiotic preparations are effective in children with acute diarrhoea. [10, 11, 12]
- Nonrotavirus diarrhea can be cured using *Lactobacillus*. [13,14]
- Diarrhoea during antibiotic treatment can be cured using Probiotics (10^9 *Lactobacillus GG, L. sporogens* or *Saccharomyces boulardii* at 5–40 x 10^9 CFUs daily). [15] But does not show effective outcome. [16]
- Administration of L. rhamnosus(573L/1; 573L/2; 573L/3) strains shortens the duration of Rota viral diarrhoea in children but not of diarrhoea of any aetiology. [17, 18]
- S. boulardii therapy in otherwise healthy infants and children with acute gastroenteritis, mainly a shorter duration of diarrhoea. [19]
- Drug: Lacidophil can be given in emergency treatment of diarrhea in pediatric population but should be administered with caution. [20]
- Probiotic agent (Lacidophil) is effective in reducing the severity of cute infectious gastroenteritis among children. [21]
- Dietary Supplement: probiotics (antibiophilus, bio-three) probiotics (antibiophilus, bio-three) 10^9 cfu/40kg/day can be given in diarrhea for the age group of 3 months to 12 years. [22]

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Gastroprotective agents use with Nonsteroidal Antiinflammatory Drugs: an Overview

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ABSTRACT

Submitted: 8/1/2012 *Accepted: 17/2/2012*

Non-steroidal Anti-inflammatory Drugs (NSAIDs) are widely used in clinical set up for patient care because of their analgesic, anti-inflammatory and antipyretic properties. Most of the NSAIDs can cause gastrointestinal damage by inhibiting cyclooxygenase-1 (COX-1) enzyme. Strategies are recommended to reduce the risk of NSAIDs associated gastrointestinal (GI) adverse events. Prevention of GI morbidity induced by NSAIDs with co-prescription of Gastro protective agents (GPA) has been clinically approved. Administration of GPA in all NSAIDs users is unnecessary. Selection of GPA mainly depends upon the NSAID related GI risk and also the patient risk factor for GI complication as well as efficacy and tolerability of both NSAID and GPA.

Keywords: Non-steroidal Anti-inflammatory Drugs, Gastrointestinal, Gastro protective agents.

INTRODUCTION

Non-steroidal anti-inflammatory drugs are among the most widely used drugs of all and are used to relive pain for a brief period. They are also often prescribed to the chronic disease patients for long term therapy. It is estimated that 1 to 2% of the world population take at least one Aspirin tablet daily.[1, 2] Non steroidal anti-inflammatory drugs are popular by virtue of their analgesic, anti-inflammatory and antipyretic actions and also valuable agents in the treatment of arthritis and musculoskeletal disorders. These drugs block both the intracellular cyclooxygenase and lipoxygenase enzyme systems, which interferes with the normal inflammatory response and decreases the production of various prostaglandin compounds. Each NSAID has its own pharmacodynamic characteristics and patient response to each drug may vary greatly.[3,4]

Non selective NSAIDs inhibit both COX-1 and COX-2 isoforms of the COX enzyme. Cyclooxygenase-1 is a constitutive enzyme expressed in most tissues including blood platelets and is involved in cell-cell signaling and in tissue homeostasis. Cyclooxygenase-2 is induced in inflammatory cell when they are activated and the primary inflammatory cytokines-interleukin-1 and tumor necrosis factor α are important in this regard. Thus COX-2 is responsible for the production of the prostanoid mediators of inflammation.[5] Anti-Inflammatory action of the NSAIDs is mainly related to their inhibition of COX-2 and their unwanted effect is due to their inhibition of COX-1. The clinical importance of COX-2 selectivity has been investigated. Efficacy is likely to be unaffected but gastrointestinal safety may be improved.[6]

The factors associated with increased risk of NSAID-associated serious complications are mainly history of ulcer, concomitant anticoagulant therapy, advanced age (>65 years), concomitant corticosteroid use, chronic major organ impairment, use of high dose or multiple NSAIDs and severe rheumatoid arthritis.[7,8,9]

Strategies in prevention of NSAID-induced gastrointestinal events are: (1) acetaminophen as the first-line therapy in musculoskeletal disorders (2) use of less gastrointestinal toxic NSAIDs such has selective COX-2 inhibitors (3) use of the lowest effective dose of NSAID (4) concomitant use of gastro protective agents in patients with increased risk.[10] Prevention of NSAID-induced GI morbidity by co-prescription of GPAs has been validated in many clinical studies.[11,12] The use of GPAs has focused on two approaches: prostaglandin replacement (misoprostol) and inhibition of acid secretion (proton pump inhibitors and histamine2-receptor antagonists). Histamine2-receptor antagonists (H2RA) heal almost all NSAID ulcers when the patient discontinues NSAID use. However, in patients who continue NSAID use, H2RA in traditional doses are more effective in healing duodenal ulcers than gastric ulcers.[13,14] Several studies have confirmed the superior efficacy of proton pump inhibitors (PPIs) in the short and longer-term prevention of NSAID-induced ulcers as compared to H2RA.[15] However, prophylactic use of PPIs in all patients is cost-prohibitive even though it is unnecessary.[16]

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Rational and evidence based drug prescribing is one of the main goal in pharmaceutical care so underutilization, as well as inappropriate use of GPAs, can contribute to increased health care costs.[17,18]

NSAIDs INDUCED GASTROINTESTINAL RISKS

The NSAIDs are mainly COX-2 inhibitors and their unwanted effects are due to the inhibition of COX-1. It is believed that the role of COX-1 in gastric protection accounts for the common side effect of upper gastrointestinal symptoms among chronic NSAID users. The risk for serious upper GI events (Perforations, Ulcers and Bleeds) is four times higher in chronic users of NSAIDs than non-users.[19]

Mucosal injury caused by NSAIDs likely occurs by several different mechanisms and it can be divided into topical and systemic effects. Most NSAIDs, including aspirin are carboxylic acid derivatives and consequently not ionized in the acidic pH found in the stomach. The nonionized drug is readily absorbed across the gastric mucosa into the pH-neutral mucosa where it is ionized and temporarily trapped within the epithelial cells. The high intracellular concentration of drug induces cellular injury and ultimately causes damage to the gastrointestinal mucosa. The main cause for pathogenesis of NSAIDs induced ulcer is by the systemic effects exhibited by the post-absorptive inhibition of gastrointestinal cyclooxygenase activity. Indeed, peptic ulcer disease has been demonstrated in humans following the intravenous and intramuscular administration of NSAIDs, which suggests a systemic mechanism of action. Cyclooxygenase, which is present in at least two isoforms in humans, is the principal enzyme involved in the biochemical conversion of membrane phospholipids and arachidonic acid into prostaglandins. Various prostaglandins may either prevent or potentiate the inflammatory response. Like most tissues, healthy gastric and duodenal mucosa constitutively expresses COX-1, which produces prostaglandins that act locally in the stomach and duodenum to help protect against mucosal injury. In contrast, the expression of COX-2 occurs largely in response to inflammatory mediators and generates various prostaglandin effectors that are responsible for attenuating the inflammatory response.

From a gastrointestinal standpoint, the ideal NSAIDs would inhibit the inducible COX-2 isoform, thereby reducing inflammation, without acting on COX-1 and its constitutively expressed cytoprotective effectors. Most NSAIDs, including aspirin and ibuprofen inhibit COX-1 and COX-2 equally. However, some NSAIDs, such as celecoxib, selectively inhibit COX-2 and exhibit less suppression on the locally protective gastric prostaglandins. The inhibition of COX-1 and the loss of the protective gastrointestinal prostaglandins may cause a local ischemic injury by reduction in mucosal blood flow at the sub mucosal and mesenteric levels. While associated with less gastrointestinal toxicity, selective COX-2 inhibitors are still associated with some risk for gastrointestinal toxicity particularly at higher doses and in high risk patients.[19]

Oesophagus:

The effect of NSAIDs on the esophagus reported less in number. Some studies had shown a higher incidence of esophageal strictures in patients taking NSAIDs.[20, 21] An endoscopy performed on 50 patients who had taken Indomethacin for at least a year showed, 10 (20%) had erythema, erosions, or ulcers in the esophageal mucosa.[22]

Stomach and Duodenum:

Many patients taking NSAIDs complain of symptoms related to dyspepsia, abdominal pain, ulcers, hemorrhage, and acute perforation. Now it is clear that NSAIDs can damage the gastro duodenal mucosa. Evidence of mucosal injury may occur within weeks to a few months of starting NSAID therapy. The mucosa of the stomach is protected from noxious agents (cytoprotection) by numerous defensive mechanisms including the secretion of mucus and bicarbonate, mucosal blood flow, local production of prostaglandins and rapid cellular repair. By decreasing the local cellular production of prostaglandins, NSAIDs cause a disruption of these protective measures. There is subsequent increased permeability to acid and pepsin within the damaged mucosal cell, and erosions and ulcers may result.[23,24]

McCarthy DM reviewed eight articles surveying patients on long-term NSAID therapy, one study noted a 46-fold greater chance of gastric ulcer and 8-fold increase for duodenal ulcer when compared with the normal population.[25]

Small Intestine:

One study had shown the evidence of increased small intestine permeability, ileal inflammation, blood loss, protein-losing enteropathy and bile salt malabsorption due to NSAID ingestion. Similar study have showed no signs of distal small bowel inflammation in arthritis patients not taking NSAIDs. .[26]

Non-steroidal anti inflammatory drugs reduce the local cellular production of prostaglandin leading to increased mucosal permeability allows the luminal substances and bacteria to damage the mucosa; finally it results in secondary adverse effects. Occasional clinical reports have linked NSAIDs to small bowel disease.[27]

Colon:

A case report showed NSAIDs damage colonic mucosa, wherein ulcerative colitis developed in patients taking NSAIDs, after the drug stopped, the patients improved, and then they relapsed on resuming NSAID therapy.[28]

A case study report shown that patient developed thin colonic strictures after several years of NSAID (diclofenac) therapy. The patient also had a history of anemia and ulcers in the ascending colon. The other case study report described two patients developed colonic bleeding due to ulcers in the right side of the colon, with diclofenac treatment.[29,30]

PHARMACOTHERAPEUTIC STRATEGIES FOR PREVENTION AND TREATMENT OF NSAID RELATED ULCERS:

Several strategies are recommended to reduce the risk for NSAID associated gastrointestinal adverse events. First, risk may be reduced by use of non-NSAID analgesics such as acetaminophen, but this strategy is unlikely to be sufficient in all patients or in those with more severe disease. Second, the use of the minimum effective dose of NSAID may reduce the risk for complications. Third, co-therapy with gastro protective agents may be necessary in patients at high risk for complications. Although these agents reduce the risk for gastrointestinal events, each is associated with its own spectrum of side effects. In addition, increased medication burden (cost and compliance issues) must be considered, particularly in elderly patients who are likely to be receiving multiple medications for concomitant conditions. Recommendations for the treatment of NSAID related dyspepsia and mucosal injury are summarized in Table 1.[31]

Table 1: COX, cyclo-oxygenase; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor

Recommendations for the treatment of NSAIDs related d yspepsia and mucosal injury	
Clinical situation	**Recommendation**
Dyspepsia	Empirical treatment with H2 receptor antagonist or PPI; individualize therapy
Helicobacter pylori infection	Treatment to eradicate infection in patients with a history of peptic ulcer; PPI therapy
Active gastro duodenal ulcer: NSAID discontinued NSAID continued	 Treatment with H2 receptor antagonist or a PPI Treatment with a PPI
Prophylactic therapy	Treatment with a PPI or misoprostol or a COX-2 (preferential) or selective NSAID

Misoprostol:

Many data indicates that misoprostol is effective in the prevention of ulcers. But poor compliance in proper dosing frequency and relatively high rate of adverse events has led to improper usage and it is the important concern in usage of misoprostol. . One study found that lower doses of misoprostol are better tolerated. However, the drug has to be taken at least twice daily to provide effective prophylaxis against NSAID related ulcers.[32] Misoprostol may also be effective in the treatment of patients with established NSAID associated ulcers, but comparative studies suggested that the proton pump inhibitors (PPIs) are substantially more effective in NSAID associated ulcer patients.[33]

Sucralfate:

Sucralfate, a basic aluminum salt of sucrose octasulfate, forms an ulcer adherent complex at duodenal ulcer sites, protecting the ulcer and promoting healing. It may also inhibit pepsin activity in gastric fluid. Sucralfate has been shown to be effective in the treatment of NSAID associated duodenal ulcers, particularly when the NSAID administration is stopped. But it is not effective in the treatment or prevention of NSAID related gastric ulcers.[34]

H2 receptor antagonists:

H2 receptor antagonists modulate gastric pH through the competitive inhibition of the action of histamine at H2 receptor sites on the gastric parietal cell. The efficacy of the H2 antagonist famotidine at high dose (double the usual dose) for preventing ulcers in patients receiving long-term therapy with NSAIDs was examined in a double blind, parallel group, randomized study, the percentage of patients with gastro duodenal ulcers were significantly lower in the famotidine 20 mg group (4%) and the 40 mg group (2%) compared with the placebo group (13%). Although this agent has been shown to be effective in preventing ulcers in patients taking NSAIDs, H2 receptor antagonists are not recommended for routine treatment of asymptomatic patients for a variety of reasons, including their potential to mask dyspeptic symptoms associated with mucosal injury.[34,35]

Furthermore, data suggested that the H2 receptor antagonists are less effective in healing gastro duodenal ulcers than PPIs, whether or not NSAIDs are continued, and are inferior in preventing ulcer recurrence.[36]

Proton pump inhibitors:

Proton pump inhibitors (PPIs) act by binding irreversibly to resident proton pumps (H^+/K^+ATPase), thus inhibiting the final common pathway for acid secretion. Proton pump inhibitors are administered as prodrugs that are activated in

the acidic environment of the parietal cell secretary canaliculus, once converted to their active form; PPIs bind to cysteine residues in the proton pump and inhibit acid secretion into the canalicular lumen.[37]

Omeprazole, the most extensively studied PPI, has a protective effect against NSAID-related mucosal injury. Because of its potent acid-inhibiting property, it prevents duodenal ulcer (DU) in patients taking NSAIDs. There is evidence that omeprazole also protects against gastric ulcer (GU). Three large Randomized Controlled Trials have been carried out by comparing omeprazole with placebo, misoprostol, and ranitidine for the prevention of GU and DU. Overall, omeprazole significantly reduced the total number of NSAID-related ulcers when compared with placebo and ranitidine. It was more effective than misoprostol in preventing DU, and equally so in reducing GU.[37, 38]

CONCLUSION

The most common side effect of NSAIDs therapy relates to gastrointestinal damage. A wide variety of disorders may develop in patients taking NSAIDs, ranging from minor dyspepsia to life-threatening ulcer bleeding or perforation. Although NSAIDs induced gastropathy has been the complication most evaluated, other parts of the gastrointestinal tract including the esophagus, small bowel and colon may be seriously injured, leading to mucosal inflammation, hemorrhage, and obstruction due to strictures. The treatment of NSAID gastropathy depends on the clinical situation and anatomic area involved of the patient.

Gastro protective agents in all NSAID user patients are unnecessary. Gastro protective agents selection in NSAID user mainly depends upon the NSAID related gastrointestinal risk, the selection must be individualized according to the patient's risk factors for gastrointestinal complications, as well as the efficacy and tolerability of both the NSAID and gastro protective co-therapy.

Rational drug use and evidence based medicine practice required among hospital physicians about possible NSAID-induced gastrointestinal complications, as well as sufficient knowledge about recommended drug of gastroprotectives in NSAID-induced ulcer prophylaxis and gastrointestinal toxicity of different types of NSAIDs.

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Efficacy and Tolerability of Different Antihypertensive Drugs in Diabetic Patients with Mild to Moderate Hypertension in a Multi Speciality Hospital - A Prospective Comparative Study

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ABSTRACT

Submitted: 28/10/2011 *Accepted: 25/11/2011*

Aim: To compare the efficacy and tolerability of different antihypertensive drugs in diabetic patients with hypertension. Materials and methods: A prospective, comparative study was conducted in 370 diabetes patients suffering from mild to moderate hypertension of either sex aged between 30-80 years. Patients with systolic blood pressure (SBP) above 130 mm Hg and patients with diastolic blood pressure (DBP) above 80 mm Hg were included in the study. Drugs used were ACE Inhibitor (ACE I), Beta blocker (BB), Calcium channel blocker (CCB) and Diuretic in monotherapy (n=134) and in 2 and 3 drugs combination (n=236). After 8 weeks of therapy patients were assessed for efficacy and tolerability. Results: Males were 51.3% and females 48.6%. There was a significant control (P<0.01) in mean blood pressure in 90% of patients. Highest decrease in SBP was seen with ACE I+BB+Diuretic combination (39%) and in DBP with CCB+Diuretic combination (18.8%). A total of 74.5% of patients were prescribed ACE I in monotherapy and combination therapy groups. Adverse drug reactions (ADRs) reported were pedal edema, dry cough, headache, dizziness and muscle cramps. Discussion and conclusion: All the drug groups from monotherapy and combination therapy reduced BP effectively. Most effective groups were ACE I+BB+Diuretic and CCB+Diuretic combination. ACE I was effective and most frequently used drug. Two drug combination therapies were commonly prescribed – 50.2%.

Keywords: Hypertension, blood pressure, diabetes, monotherapy, combination therapy.

INTRODUCTION

Hypertension in diabetes is one of the most widespread, substantial and treatable cardivascular risk factors of importance in clinical practice. As the number of diabetes patients increases on a global scale, so too does the number of patients with concomitant hypertension. Data from randomised trials have increasingly shown the benefits of tight blood pressure control in patients with type 2 diabetes. [1]

Management of hypertension in diabetics demands special attention, more so in Indian scenario. Higher prevalence of hypertension amongst diabetics in India has been reported since 1985.[2] The presence of hypertension in diabetic patients substantially increases the risks of coronary heart disease, stroke, nephropathy and retinopathy. Indeed, when hypertension coexists with diabetes, the risk of cardiovascular disease is increased by 75%, which further contributes to the overall morbidity and mortality of an already high-risk population.[3]

In general, only 25 percent of patients with hypertension have adequate control of their blood pressure.[4] Blood pressure goals are lower, and thus more difficult to achieve, in patients who also have diabetes. Elevated blood pressure is known to contribute to diabetic microvascular and macrovascular complications. Fortunately, reductions in blood pressure can decrease the risk of these complications.[5]

Numerous national and international guidelines exist for the management of hypertension. Currently, the most influential guidelines in the United States addressing the appropriate treatment of hypertension in patients with diabetes are the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (JNC-7),[6] National Kidney Foundation (NFK) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines,[7] and American Diabetes Association (ADA) guidelines.[8]

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Rigorous blood pressure control to the targets recommended in treatment guidelines is paramount for reducing the progression of diabetic nephropathy to End Stage Renal Disease (ESRD). The JNC-7[6] NKF KDOQI, [7] and ADA[8] guidelines all recommend a blood pressure goal of <130/80 mm Hg in patients with diabetes (versus <140/90 mm Hg for patients without diabetes) to optimally preserve renal function and reduce cardiovascular events.

Although a number of monotherapies and multidrug therapies are available for the treatment of hypertension, current guidelines provide evidence-based recommendations for the use of specific antihypertensive agents in patients with diabetes. The JNC-7,[6] KDOQI,[7] and ADA[8] guidelines recommend the use of either ACE Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) as initial therapy to achieve the blood pressure target in patients with type 2 diabetes mellitus. If one class is not tolerated, the other should be substituted if it is not contraindicated. Neither ACE inhibitors nor ARBs appear to produce any clinically significant changes in metabolic measurements, such as blood glucose and the lipid profile, which is an important consideration in the presence of diabetes.

Most patients with diabetes will require two or more antihypertensive therapies from different classes with complementary mechanisms of action to control their blood pressure.[9] Thiazide diuretics, ß-blockers, or calcium channel blockers (CCBs) can be added to ACE inhibitor or ARB treatment to achieve target blood pressure, either as an individual drug component or as part of a fixed-dose combination product.[6, 7, 8]

The choice and doses of drugs used in combination therapy should be such that their synergistic effect on blood pressure is maximised, the tolerability of the drugs is maintained and side effects are minimized. The present study was designed to assess the drug use pattern of antihypertensive agents in diabetic patients with hypertension, to evaluate the tolerability and cost effectiveness related to hypertension and their effect on therapy.

MATERIALS AND METHODS

It was a prospective and comparative study carried out at Apollo K.H Hospital, Melvisharam, Tamilnadu, India. Diabetic patients of either sex aged between 30-80 years suffering from mild to moderate hypertension were selected from General Medicine and Pharmacy outpatients units. Patients with systolic blood pressure above 130 mmHg and diastolic blood pressure above 80 mmHg were included in the study. Pregnant and lactating women were excluded from the study. Patients declared their willingness to participate in the study and written informed consent was obtained from them. Patients who fulfilled inclusion and exclusion criteria were enrolled in the study. Complete medical history, physical examination, concomitant diseases and medication taken, ECG (electrocardiogram) and baseline blood pressure, were recorded in the case record form. The following baseline investigations were done such as random blood sugar, blood urea, serum creatinine, serum electrolytes, serum cholesterol, serum bilirubin, serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT).

Depending on the severity of hypertension, patients were prescribed antihypertensive drugs either as monotherapy or combination therapy in (2 and 3 drug combination). Drugs included in the treatment were ACE Inhibitor 5mg once daily orally, Beta blocker 50mg once daily orally, Calcium channel blocker 10mg thrice daily orally and Diuretic 40mg twice daily orally. Drugs used in monotherapy included ACE Inhibitor and Beta blocker, while in combination therapy included ACE Inhibitor, Beta blocker, Calcium channel blocker and Diuretic. A+B, A+D, B+D, A+C, B+C, C+D, A+B+D, A+B+C and A+C+D combination were prescribed. After two months of therapy, patient's response to the ongoing antihypertensive treatment was checked by obtaining BP (though BP was checked every two weeks for the duration of the study), their baseline ECG and biochemical parameters were repeated. Patient's compliance to medication was recorded. They were interrogated for any adverse effects. A decrease in blood pressure (SBP <130 mmHg and DBP <80 mmHg) was the primary outcome measure. Secondary outcome measures were a) Safety variables including incidence, nature and intensity of adverse drug reactions (ADRs)-dry cough, pedal edema, dizziness, rash, flushing and diarrhoea. b) Changes in ECG and biochemical parameters.

Statisitcal Analysis: All the values were expressed as Mean ± SD. Parametric test was done using Student's Paired't' test. P value <0.05 was considered as significant with 95% Confidence Interval.

RESULTS

A total of 370 patients participated in the present study. Out of which 190 (51.3%) were males and 180 (48.6%) were females. The demographic data of all the patients is shown in Table-1.

Table 1 Demographic data (n=370)				
S. No	Age in years	No. of patients	Male	Female
1	30 - 40 1	0	06	04
2	41 - 50	38	24	14
3	51 - 60	96	38	58
4	61 - 70	148	78	70
5	71 - 80	78	44	34

Patients were divided in different groups on the basis of monotherapy and combination therapy. 36.21% patients belonged to monotherapy group and 63.78% patients belonged to combination therapy group.

Monotherapy group: n = 134 (36.21%)

ACE inhibitor – n = 76

Beta blocker – n = 58

Combination therapy group: n = 236 (63.78%)

1. Two drug combination therapy, n = 186 (50.27%)

ACE inhibitor + Beta blocker – n = 88

ACE inhibitor + Diuretic – n = 34

Beta blocker + Diuretic – n = 14

ACE inhibitor + Calcium channel blocker – n = 28

Beta blocker + Calcium channel blocker – n = 14

Calcium channel blocker + Diuretic – n = 08

2. Three drug combination therapy, n = 50 (13.51%)

ACE inhibitor + Beta blocker + Diuretic – n =34

ACE inhibitor + Beta blocker + Calcium channel blocker – n = 10

ACE inhibitor + Calcium channel blocker + Diuretic – n = 06

Effect on systolic blood pressure: A highly significant decrease in mean SBP was observed with ACE I and BB monotherapy groups (P<0.001). Similarly there was highly significant decrease (P<0.001) observed with A+B, A+D, A+C, A+B+D, A+B+C and A+C+D combination therapy whereas there was significant reduction with B+D, B+C and C+D groups. (Table - 2)

Effect on diastolic blood pressure: A highly significant decrease in mean DBP was seen in monotherapy groups (P<0.001). There was also highly significant reduction (P<0.001) in A+B, A+D, B+C, C+D, A+B+D and A+B+C combination groups. Other combination groups showed a significant reduction with B+D, A+C and A+C+D combination groups. (Table - 3)

Table 2: Effect of drugs on systolic blood pressure (n=370)							
Drugs	Systolic BP		Decrease in SBP	% decrease in SBP	95% CI		p value
	Baseline	After treatment			Baseline	After treatment	
Monotherapy							
A (n=76)	158.6 ± 30.86	129.7 ± 9.41	28.94 ± 4.03	28.5	150.9 ± 166.3	127.3 ± 132.0	<0.001
B (n=58)	162.3 ± 23.55	131.1 ± 9.00	31.17 ± 3.63	31.1	155.4 ± 169.1	128.5 ± 133.7	<0.001 2
Combination therapy							
A+B (n=88)	158.9 ± 26.32	131.1 ± 12.88	27.78 ± 6.90	27.7	145.8 ± 172.0	124.7 ± 137.5	<0.001
A+D (n=34)	146.6 ± 12.02	123.7 ± 5.53	22.92 ± 2.70	22.9	141.5 ± 151.7	121.3 ± 126.0	<0.001
B+D (n=14)	168.5 ± 30.55	132.0 ± 11.14	36.50 ± 11.50	36.5	143.0 ± 194.0	122.7 ± 141.3	0.006
A+C (n=28)	160.3 ± 27.59	131.1 ± 12.38	29.21 ± 3.42	29.2	154.0 ± 166.5	128.3 ± 133.8	<0.001
B+C (n=14)	158.6 ± 28.52	131.7 ± 10.27	26.86 ± 8.10	26.8	142.1 ± 175.0	125.8 ± 137.6	0.002
C+D (n=08)	155.0 ± 17.73	128.0 ± 9.04	27.00 ± 7.03	27.0	140.2 ± 169.8	120.4 ± 135.6	0.001
3 Combination therapy							
A+B+D (n=34)	175.0 ± 17.32	136.0 ± 4.61	39.00 ± 8.96	39.0	147.4 ± 202.6	128.7 ± 143.3	<0.001
A+B+C (n=10)	151.2 ± 17.78	127.0 ± 8.35	24.19 ± 3.47	24.1	144.8 ± 157.6	124.0 ± 130.0	<0.001
A+C+D (n=06)	140.8 ± 0.95	121.5 ± 0.57	19.25 ± 0.55	18.5	139.2 ± 142.3	120.6 ± 122.4	<0.001

A –ACE inhibitor, B – Beta blocker, C – Calcium channel blocker, D – Diuretic;
CI – confidence interval (lower & upper limits), SBP – systolic blood pressure; Values are expressed as mean ± SD

Table 3: Effect of drugs on diastolic blood pressure (n=370)

Drugs	Diastolic BP		Decrease in DBP	% decrease in DBP	95% CI		p value
	Baseline	After treatment			Baseline	After treatment	
1. Monotherapy							
A (n=76)	96.88 ± 16.22	80.94 ± 7.70	15.94 ± 2.24	15.9	92.82 ± 100.9	79.01 ± 82.86	<0.001
B (n=58)	97.92 ± 15.15	79.58 ± 8.98	18.33 ± 2.54	18.3	93.52 ± 102.3	76.98 ± 82.19	<0.001
2. Combination therapy							
A+B (n=88)	92.50 ± 6.07	77.50 ± 6.42	15.00 ± 1.80	15.0	89.93 ± 95.07	74.79 ± 80.21	<0.001
A+D (n=34)	99.90 ± 14.28	81.60 ± 8.43	18.29 ± 1.87	18.3	96.68 ± 103.1	79.70 ± 83.50	<0.001
B+D (n=14)	100.0 ± 13.09	83.75 ± 11.57	16.25 ± 6.17	16.2	89.05 ± 110.9	74.07 ± 93.43	0.019
A+C (n=28)	97.14 ± 14.37	80.00 ± 10.00	17.14 ± 4.68	17.1	88.84 ± 105.4	74.23 ± 85.77	0.001
B+C (n=14)	92.22 ± 2.55	75.00 ± 4.20	17.22 ± 1.15	15.5	90.95 ± 93.49	72.91 ± 77.09	<0.001
C+D (n=08)	96.00 ± 8.15	77.14 ± 7.26	18.86 ± 2.91	18.8	91.29 ± 100.7	72.95 ± 81.34	<0.001
3. Combination therapy							
A+B+D (n=34)	96.67 ± 5.16	78.33 ± 6.83	18.33 ± 3.49	18.3	91.25 ± 102.1	71.16 ± 85.50	<0.001
A+B+C (n=10)	95.00 ± 5.34	77.50 ± 5.97	17.50 ± 2.83	17.5	90.53 ± 99.47	72.50 ± 82.50	<0.001
A+C+D (n=06)	92.50 ± 2.88	77.50 ± 2.88	15.00 ± 2.04	15.0	87.91 ± 97.09	72.91 ± 82.09	0.003

A –ACE inhibitor, B – Beta blocker, C – Calcium channel blocker, D – Diuretic;
CI – confidence interval (lower & upper limit), DBP – diastolic blood pressure; Values are expressed as mean ± SD

A total of 90% of patients showed significant control in BP after 8 weeks of therapy. In both monotherapy and combination therapy ACEI was used most frequently in 74.5% followed by Beta blocker 58.9%, Diuretic 25.9% and Calcium channel blocker 17.8%. Few patients were on concomitant medication. Aspirin was prescribed to 60 patients, statins to 68 patients and aspirin + statin to 242 patients. As many as 110 (29.7%) of patients were without any co-existing diseases. 208 patients (56.2%) had Coronary artery disease (CAD), 52 patients (14.0%) were suffering from cerebrovascular accident (CVA).

No serious adverse drug reactions were reported. Some of the common ADRs reported were pedal edema, headache, dry cough, dizziness and muscle cramps/myalgia. However percentage of ADRs increased when given in combination therapy. Biochemical parameters were within normal limits. Patients' compliance was good.

DISCUSSION

In the present study most common classes of antihypertensive drugs such as Angiotensin Converting Enzyme Inhibitors (ACEIs), Calcium Channel Blockers (CCBs), Beta-blockers (BBs), and Diuretics were used to treat mild to moderate hypertension in diabetes patients. Differences between antihypertensive drugs were assessed principally by comparing their antihypertensive efficacy and tolerability. All the drug groups were shown to be effective in controlling BP.

We used the same classes of drugs in our study, which were given in JNC 7 classification of antihypertensive drugs. Our results were consistent with the previous studies where they used the same classes of drugs.[10,11]

ACE inhibitors are considered preferred therapy in patients with hypertension and diabetes, according to guidelines from the ADA, the NKF, the World Health Organization, and the JNC VI.[12,13,14,4] Findings from the Heart Outcomes Prevention Evaluation (HOPE) study also support the above recommendations.[15] This trial showed a reduction in cardiovascular events in patients taking a maximum dosage of ACE inhibitors. Our study also shows that ACE inhibitors were the most frequently used drug in both monotherapy and combination therapy.

There have been several studies using combination therapy compared to monotherapy to assess cardiovascular outcomes in hypertensive patients, which have demonstrated a greater reduction of cardiovascular events with a combination of two agents than with each of the components. Recently, a meta-analysis of trials evaluating the use of antihypertensives in high-risk patients, including those with diabetes, showed that ACE inhibitor therapy resulted in a 20 to 30 percent decrease in the risk of stroke, coronary heart disease, and major cardiovascular events.[16] A second meta-analysis compared ACE inhibitors with other antihypertensive agents in patients with diabetes.[17] Three of the four studies evaluated showed ACE inhibitors to be of significantly greater benefit when

compared with other antihypertensives in the reduction of acute myocardial infarction, cardiovascular events, and all-cause mortality. In our study we noted that majority of patients were on 2 drug combination therapy, mostly with ACE inhibitor, Beta blocker or diuretic combination, hence supporting the above studies.

Studies conducted previously showed that BB reduced mean SBP by 18.2 ± 11.3 mmHg[18] and ACE I by 10.0 ± 2.0 mmHg,[19] whereas in our study BB and ACE I monotherapy reduced mean SBP by 31.1 ± 3.6 mmHg and 28.9 ± 4.0 mmHg respectively, which showed more effective reduction than previous studies. Edward et al found reduction in mean SBP by 18.0 mmHg with BB+CCB combination[20]. Our study showed 26.8 mmHg reductions, which was more effective reduction than the above study. There was significant reduction of 22.9 ± 2.7 mmHg in mean SBP with ACE I and Diuretic combinations in diabetic patients with moderate hypertension. Similarly in one study there was effective reduction of mean SBP in moderate HTN with ACE I and a diuretic combination.[20]

In our study, combination of ACE I+BB reduced mean SBP by 27.7 ± 6.9 mmHg whereas ACE I alone in monotherapy showed 28.9 ± 4.0 mmHg reduction. We found that monotherapy with ACE inhibitor was more effective than combination of ACE inhibitor with BB. Wing et al found that the combination of ACE I+BB to be largely ineffective when compared to ACE I alone[21] hence supporting our study. Several studies reported that the combination of ACE I with dihydropyridine CCB was especially effective.[22, 23] Our study also showed effective reduction in mean SBP by 29.2 ± 3.4 mmHg with ACEI+CCB combination. Reduction in mean SBP with ACE I+BB+CCB was 24.1 ± 3.4 mmHg, while ACEI+BB+Diuretic combination showed 39.0 ± 8.9 mmHg reduction. Previous studies were also reported that the combination of an ACE I plus BB plus Diuretic was more effective than an ACE I plus BB plus CCB[24,25] hence supporting our study.

In the present study we found significant reduction in mean DBP with both monotherapy as well as combination therapy. Previous studies reported 11.5 ± 8.3 mmHg and 8.0 ± 1.0 mmHg reduction of mean DBP with BB and ACEI monotherapy respectively,[18, 19] whereas our study showed 18.3 ± 2.5 mmHg and 15.9 ± 2.5 mmHg reduction in mean DBP with BB and ACEI monotherapy, which showed more effective reduction than previous studies. In a previous study there was 13.0 mmHg fall in mean DBP with BB+CCB combination, [20] we observed more effective reduction of 17.2 ± 1.1 mmHg with the same combination therapy. Effective reduction in mean DBP was seen with ACEI+CCB, ACEI+Diuretic and BB+Diuretic combination therapy which were 17.1 ± 4.6 mmHg, 18.2 ± 1.8 mmHg and 16.2 ± 6.1 mmHg respectively. Previous studies also proved effective reduction with the above combination therapy.[19,21] Combination of ACE I+BB+Diuretic showed 18.3 ± 3.4 mmHg reduction in means DBP whereas ACE I+BB+ CCB showed reduction of 17.5 ± 2.8 mmHg. Our results support the previous studies[24,25] which reported that ACE I+BB+Diuretic is more effective than ACE I+BB+CCB combination and we also found the same results with mean SBP with the above combination therapy.

We observed that combination therapy was used for both mild and moderate HTN. Among all the groups ACE I+BB+Diuretic combination was highly effective in reducing SBP and CCB+Diuretic was highly effective in reducing mean DBP.

It was noted that diabetic patients with HTN were mostly given ACE I. Patients with CAD and CVA were on ACE I+BB. We had observed that there was frequent use of ACE I in various comorbid conditions associated with HTN. According to JNC 7 classification, compelling indication for use of ACEIs are CVA, CAD, DM, heart failure and chronic kidney disease. Hence ACEIs are a valuable addition to the pharmacotherapy of HTN.[6] These studies recommended better adherence to JNC 7 guidelines.

In addition to antihypertensive drugs, patients were advised to take adjuvant therapy like aspirin and statins. Several studies demonstrated that use of aspirin leads to 16% reduction in all cardiovascular events and 20% reduction in myocardial infarction in hypertensive patients.[26, 27] HTN and hypercholesterolemia often co-exist as risk factor and one study (ASCOTLLA) observed the benefits of lipid lowering therapy in hypertensive patients. [28]

Patients on ACE I monotherapy (20%) complained of dizziness and this was increased with combination ACE I+CCB+Diuretic. Pedal oedema was reported by 22% of patients, who were on CCB treatment. No serious ADRs were observed in our study. Most frequently encountered side effect with ACE was dry cough (10%). Constipation, pedal edema and headache were reported in patients who were on CCB. Patients with BB, CCB and Diuretic combination therapy complained of myalgia and dizziness, which are all predictable ADRs.

Life style modifications also termed as non-pharmacological therapy can decrease and help in controlling BP. These changes are useful when implemented in conjunction with drug therapy. They can enhance the efficacy of

antihypertensive agents and decrease cardiovascular risks and may even reduce the number of required drugs and their dosage. Major life style modifications include weight reduction in those individuals who are overweight or obese[29] and adoption of Dietary approaches to Stop Hypertension (DASH) eating plan which is rich in potassium, calcium and dietary sodium reduction and physical activity[30, 31, 32] which have shown to achieve better results in lowering BP.

CONCLUSION

There is a strong epidemiological connection between hypertension in diabetes and adverse outcomes of diabetes. Clinical trials demonstrate the efficacy of drug therapy in reducing these outcomes and in setting an aggressive blood pressure–lowering target of <130/80 mmHg. It is very clear that many people will require three or more drugs to achieve the recommended target. Achievement of the target blood pressure goal with a regimen that does not produce burdensome side effects and is at reasonable cost to the patient is probably more important than the specific drug strategy.

Because many studies demonstrate the benefits of ACE inhibitors on multiple adverse outcomes in patients with diabetes, including both macrovascular and microvascular complications, in patients with either mild or more severe hypertension and in both type 1 and type 2 diabetes, the established practice of choosing an ACE inhibitor as the first-line agent in most patients with diabetes is reasonable.

We could conclude from our study that all groups in monotherapy and combination therapy were equally effective in reducing BP. Combination therapy was used in large proportion of patients to treat hypertension in diabetes, in which two drug combinations were used more. Monotherapy with ACE I was more effective than ACE I+ BB combination.

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Drug Prescribing and Economic Analysis for Skin Diseases in Dermatology OPD of an Indian Tertiary Care Teaching Hospital: A Periodic Audit

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ABSTRACT

Submitted: 10/2/2012 *Accepted: 17/2/2012*

Dermatological problem in India manifests as primary and secondary cutaneous complaints. Among them allergy and itches are widely observed in most of the patients. Periodic auditing of prescriptions is essential to increase the therapeutic efficacy, decrease adverse effects, provide feedback to prescribers and analyze the observance of standards of medical treatment. Study objectives were to assess drug prescribing pattern and cost analysis in dermatology out patient department (OPD) in a tertiary care teaching hospital. The prescriptions from dermatology OPD were collected randomly by twice weekly survey for the duration of 6 months which were analyzed in consultation with clinical collaborators and evaluated using WHO drug use indicators. A total of 260 prescriptions were analyzed from 226 patients. Average drugs prescribed were 2.39/ prescription. Topical drugs (62.7%) were most commonly prescribed than systemic drugs (37.3%). Topical drugs were mostly in combination (26.66%) followed by antifungals (20.51%) and steroids (17.44%) alone. Antihistaminics (33.62%) commonly prescribed systemically followed by antifungals (22.41%) and antibiotics (20.69%). In 43.47% instances high potency steroids were prescribed while mild potency (15.22%) were least prescribed. Frequency of administration was specified in majority of prescriptions (99%) for topical administered drugs but dose/strength was specified in 54 (13.85%) prescriptions only. Average cost of drugs per prescription was found to be 196.74 INR. A great majority of drugs were prescribed in brand names. Though, dose/strength for topical drugs was inadequately mentioned but chances of error were negligible as the brand had availability in single dose/strength in pharmacy. Clinical Pharmacist can conduct such periodic audit to rationalize the prescription, reduce errors and suggest a cost effective management of skin diseases.

Keywords: Dermatology, Prescribing pattern, Outpatient, WHO indicators.

INTRODUCTION

Dermatological problem in India manifests as primary and secondary cutaneous complaints. Among them, allergy and itches are widely observed in most of the patients. Yellowish coloration or dryness of skin in normal old age, pruritus, hypersensitivity reactions, eczemas, pellagra etc were the type of skin problems that are quite observed as well. Usually for peak level skin disorder, the therapy of skin problems is longer for complete removal of problems. Use of drug like benzoyl peroxides, proactive antibiotics, retin-A, oral retinoid, salicylic acid, anti-histaminics, vitamins and minerals, steroids and analgesics are of more interest for skin specialist for the treatment.[1,2]

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Principles of good prescribing are based on sound knowledge, understanding of the pathophysiology of disease to be treated and the knowledge of risks and benefits of the medicine.[3, 4] Appropriate drug use by patients and adherence to instructions given by the prescriber is an integral part of successful rational drug use programme. Patient's non-adherence to the prescribed treatment is a global problem. The reasons for poor compliance could be lack of instructions provided with the prescription, low literacy and poor dispensing practice. Rational prescribing can be achieved by practicing evidence-based medicine. Better interaction between pharmacists and the patient can lead to better patient knowledge about drug use and compliance to therapy as pharmacist is a vital link between prescribed medication and the patient.[5]

The pattern of drug use in a hospital setting need to be monitored intermittently in order to analyze their rationality.[6] Periodic auditing of prescriptions is essential to increase the

therapeutic efficacy, decrease adverse effects and provide feedback to prescribers[7] therefore used to oversee, monitor and analyze the observance of standards of medical treatment at all levels of the health care delivery system.[8]

Collection of data on the utilization of drugs at the hospital out-patient level has been shown to be an effective tool to constitute guidelines for improving drug utilization patterns. This has resulted in more effective and rational therapy as well as economic benefits in the use of drugs.[9]

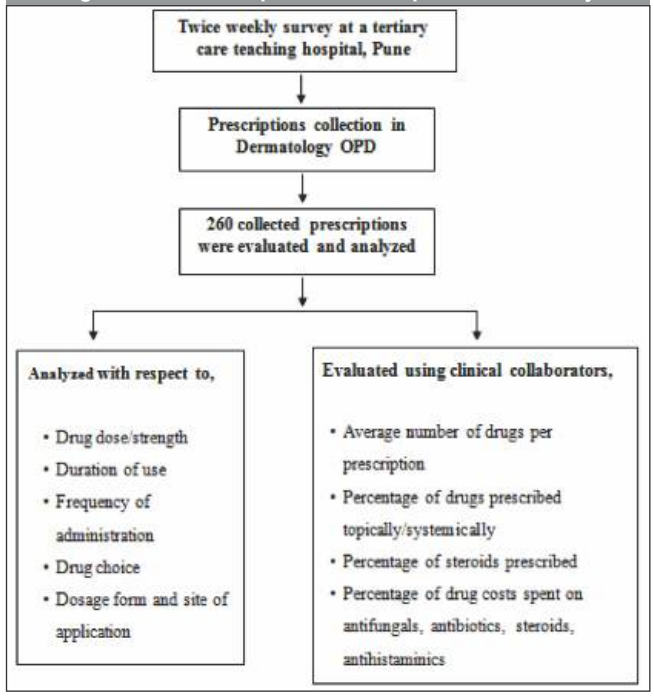
Considering the economic burden of the skin diseases cause owing to its high prevalence, it is of interest to study the drug prescribing patterns and cost effectiveness of skin diseases. Irrational prescription of drugs is a common occurrence in clinical practice.[10] The cost of such irrational drug use is enormous in developing countries in terms of both scarce resources and the adverse clinical consequences of therapies that may have real risks but no objective benefits.[11] Therefore periodic auditing of prescriptions is essential to increase the therapeutic efficacy, decrease adverse effects and provide feedback to prescribers.[12]

As per our knowledge, very few systematically analyzed data are available on the drug use pattern in dermatology in India. Hence, the present study was undertaken in patients taking treatment under the dermatology outpatient department (OPD) of the teaching hospital to generate baseline data and analyze various aspects of drug prescribing practices. This can be also used as a tool to generate the rational prescribing pattern. The primary objective of this study was to perform a periodic audit of drug prescribing for patients attending dermatology OPD for rationalizing prescribing practices while secondary objectives were to analyze the disease pattern of patients attending dermatology OPD and drug cost spent on individual drug class. This study was first of its kind in this hospital.

MATERIALS AND METHODS

Prescriptions of patients attending dermatology OPD of a tertiary care teaching hospital, Pune were collected randomly by twice weekly survey for the duration of 6 months from January 2011 to June 2011. This collected prescriptions were analyzed under the sub-heads with respect to drug choice, drug dose/strength (in case of corticosteroids, potency), duration of use, frequency of administration, dosage form and site of application. Obtained information was compiled, scored and analyzed in consultation with clinical collaborators and were subjected to critical evaluation using WHO guidelines as described in accordance with "How to investigate drug use in health facilities?"[13, 14] Disease pattern was analyzed for each patient attending dermatology OPD and classified according to dermatologic condition.[15] Average cost of drugs prescribed per prescription was calculated by analyzing unit cost of drugs prescribed to the patient. Flow of the procedure adopted for this study is shown in Fig I.

Fig 1: Flowchart of procedure adopted for the study



RESULTS

Overall 260 prescriptions were analyzed amongst 226 patients during the study period. Table I provide the age distribution of the patients. The number of males were 142 (62.83%) while number of females were 84 (37.17%) with male to female ratio of 1.69. The maximum number of patients were in the age group of adults (19 to 60 years) and minimum numbers of patients were in the age group of infants (1 month to 1 yr) that visited the OPD during the study period.

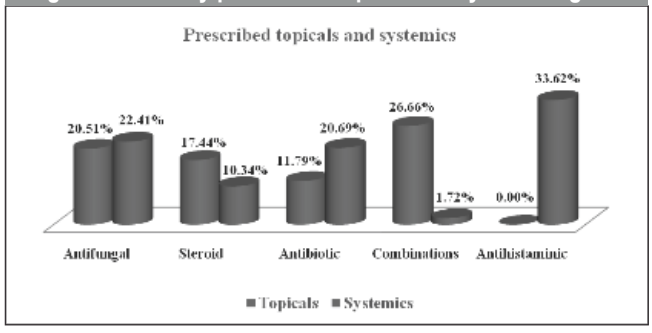
Table I: Age distribution of study population

	No. of Patients (n=226)	% of Patients
Infants (1 month - 1 yr)	2	0.88%
Children (1 yr - 11 yr)	16	7.08%
Adolescents (12 yr - 18 yr)	38	16.81%
Adults (19 yr - 60 yr)	156	69.03%
Geriatrics (> 60 yr)	14	6.19%

Average no. of drugs prescribed was 2.39/prescription which includes topical and systemic formulations. Maximum number of drugs prescribed were topicals (62.7%) compared to systemics (37.3%).

Antifungals (23.15%) were the most commonly prescribed class of drugs followed by steroids (19.61%) and antibiotics (16.72%). Commonly prescribed topical agents were combination preparations (26.66%) followed by antifungals and antibiotics alone (20.51% and 11.79% respectively) while the most commonly prescribed systemic agents were antihistaminics (33.62%) followed by antifungals (22.41%) and antibiotics (20.69%) alone as shown in Fig. 2.

Fig. 2: Commonly prescribed topical and systemic agents



Major combinations prescribed were steroids in combination with antibiotics, antifungals and keratolytics.

In about 43.47% instances high potency steroids were prescribed while steroids with mild potency were least prescribed (15.22%) (Table 2). Out of 92 steroids prescribed, 30 were in combination with antibiotics, antifungals and keratolytics

Table 2: Steroid classification on the basis of potency

	No. of Steroids Prescribed (n=92)	% of Steroids
Very potent	40	43.47%
Potent	20	21.74%
Moderately potent	18	19.57%
Mild	14	15.22%

Table 3 shows the disease pattern of patients attending dermatology OPD during the study period. The common skin conditions encountered were of fungal infections (25.26%) followed by 16.98% of sebaceous gland disorders and 13.84% cases of eczema and dermatitis.

Table 3: Disease pattern in dermatology OPD

	No. of Diagnosis (n=318)	% of Diagnosis
Fungal infection	80	25.26%
Viral infection	8	2.52%
Bacterial infection	20	6.29%
Parasitic infection	20	6.29%
Eczema and dermatitis	44	13.84%
Photosensitivity reactions	8	2.52%
Hypersensitivity reactions	20	6.29%
Papulosquamous disorders	26	8.18%
Sebaceous gland disorders	54	16.98%
Disorders of pigmentation of skin	8	2.52%
Disorders of hair	8	2.52%
Tumors of skin	6	1.88%
others	16	5.03%

Total cost of drugs prescribed was found to be 51152.4 INR. Average cost of drugs per prescription was found to be 196.74 INR. Maximum percentage drug cost spent was on antifungals (28.61%) followed by combination products (22.28%) and antibiotics (15.11%) (Table 4).

Table 4: Percentage cost incurred on drug classes

Class of Drugs	Total Cost incurred In INR (c=51152.4 INR)	% Drug Cost incurred
Antifungals	14635.22	28.61%
Antibiotics	7727.64	15.11%
Steroids	5485.52	10.72%
Antihistamines	1880.16	3.68%
Combination products	11394.52	22.28%

DISCUSSION

Average number of drugs prescribed was 2.39/prescription in our study which correlates with other two studies carried out by Sarkar C et al[9] and Narwane SP et al[16] showed average number of drugs prescribed was 2.42 and 2.7/prescription respectively. A great majority of drugs were prescribed in brand names in this study. Our study depicted slightly lower average number of drugs/ prescription compared to previous studies.

Our study finding showed antifungal as the most commonly prescribed drug class followed by steroids and antibiotics which differ from the study carried out by Narwane SP et al showing antiallergics as the most commonly prescribed drug

followed by antifungal and antibiotic.[16] Moreover, our study showed there was a correlation between classes of drug prescribed with the disease encountered. Antifungals and steroids were commonly prescribed as majority of the patients had fungal infections and inflammatory skin condition as a common disorder. In the context of antifungal agents, fluconazole was the drug most commonly prescribed systemic antifungal rather than terbinafine in this study. A study by Lesher JL showed effectiveness of oral antifulgals in fungal infections and found that tinea corporis and tinea cruris were effectively treated by 150 mg once weekly for 2 to 3 weeks and 250 mg terbinafine daily for 1 to 2 weeks while tinea pedis has been effectively treated with pulse doses of 150 mg fluconazole once weekly and with 250 mg terbinafine daily for 2 weeks.[17] However, prescribing practice of fluconazole once weekly was found to be more cost effective with lesser side effect profile than terbinafine prescribed daily.[18] We also found that antibiotics were another class of drugs commonly prescribed for the treatment of acne. Among the antibiotics clindamycin, azithromycin and minocycline were commonly prescribed, as these are the first line therapy and found to be effective for the treatment of acne.

Topicals were commonly prescribed compared to the systemic agents. Use of topicals were usually preferred for treating skin diseases as they have site specific action, less systemic absorption resulting in less side effects and convenient for patient use. Majority of topicals (27%) were prescribed in combinations. This finding was comparable with studies by Khan NA et al[5] and Sarkar C et al[9] that showed steroid and its combinations were most commonly prescribed topically. The most commonly prescribed systemic agents were antihistaminics (33.62%) in this study which correlates with the findings of above two studies.[5,9] Analysis of data showed that all the antihistaminic agents were prescribed systemically in dermatology because of disease prevalence with related symptoms of itching (associated with fungal infection, scabies, eczema and dermatitis).

Corticosteroids were among the most widely used drugs in dermatology and one has to view their usage in the light of their limitations and adverse effects.[19] Our study findings showed maximum number of steroids prescribed were of high potency (43.47%) while mild potency were least prescribed (15.22%). Findings of a study in Tamilnadu by Ashok kumar M et al showed 27.7% steroids prescribed were of very potent class while 22.3% were of potent class.[20] Major steroids were prescribed in combination containing antibiotics, antifungals and keratolytics which is comparable with the Sweileh WM study[2] on prescribing of corticosteroids showing the same combination of steroids with the antimicrobials and other agents. As a general rule, physicians should use the weakest possible corticosteroid that will treat the dermatological condition. Topical corticosteroids are mainly used for non-infective dermatologic disorders associated with inflammation such as psoriasis, atopic dermatitis, contact dermatitis, otitis externa etc.[21-26] Potent topical steroids used on areas like face and flexures or when used under occlusion may lead to cutaneous side-effects like striae, atrophy, steroid acne and hypertrichosis.[27] So, careful consideration of patient's age, potency of steroid prescribed, site of application and efficacy of prescribed corticosteroid need to be taken into consideration. However, in this study adequate prescribing information, other advices and cautions regarding corticosteroid use was maintained in majority of the prescriptions.

Vitamin A may be helpful in acne, psoriasis and icthyosis. Synthetic retinoids (isotretinoin, acitretin) are commonly used in treatment of acne and psoriasis respectively, but is a potent teratogen thus limiting its use in women with child-bearing potential.[28] The commonly prescribed retinoids found in our study were adapalene and tretinoin either alone or in combination with clindamycin as an antibiotic.

We found 21 prescriptions where multiple prescribing of antifungals was given i.e. 2 topicals, topical along with systemic and 2 systemics. In a case of polymorphous light eruption (back) + Intertrigo (right inflammatory area) fluconazole tablet given in combination with miconazole, clotrimazole topical and betamethasone as steroid. Similarly in 6 cases more than one steroid was prescribed. However, polypharmacy (2 topical + 1 systemic antifungal or 1 topical + 1 systemic antifungal/steroid together) should better be avoided.[27]

Our study findings showed most of the dermatological conditions in the OPD were of fungal infections (25.26%) followed by sebaceous gland disorders (16.98%). The common fungal infection found includes tinea cruris, tinea corporis and candidiasis and among the sebaceous gland disorder maximum number of patient was of acne (grade I, II and III) with or without Post Inflammatory Hyperpigmentation (PIH). The reason responsible for the above finding can be humid environmental condition and poor hygiene. This data differs from the study carried out in Nepal showing the cutaneous infections (40%) as the most common dermatologic condition followed by eczema (31%).[9]

Considering the economic burden and high prevalence of the skin diseases, this topic is of interest to study the drug prescribing patterns and cost effectiveness of skin diseases. In developing country like India, patient compliance is primarily

dependant on the cost of treatment.[8] Our study findings showed the average cost of 196.74 INR ($ 4.37) per prescription which was quite higher than Narwane SP et al study which reported the average cost of 135.60 INR.[16] Unit cost of drugs prescribed per patient was calculated. However actual direct costs and indirect costs were not taken into consideration for cost analysis.

Frequency and duration of administration was specified in majority of prescriptions (99%) for topical administered drugs which shows quite rational prescribing but dose/strength was specified in 54 (13.85%) prescriptions only which shows that the prescribing pattern should be improved to avoid imprecise prescription leading to the prescription errors while dispensing the medication by a pharmacist and there is a need to emphasize on rational and appropriate prescribing pattern to be followed in the OPD for better patient care. Although dose/strength for topical drugs was inadequately mentioned but chances of error were negligible as the brand had availability in single dose/strength in pharmacy.

CONCLUSION

A great majority of drugs were prescribed in brand names. Though, dose/strength for topical drugs was inadequately mentioned but chances of error were negligible as the brand had availability in single dose/strength in pharmacy. The prescription audit can be an eye opener for the prescribers. Clinical pharmacist can conduct such periodic audit to rationalize the prescription, reduce errors and suggest a cost effective management of skin diseases. The hospital administration can look into the issues in the hospital by implementing a formulary into the system so that physicians restrict their prescribing in generic names and provide a cost effective therapy to the patients as essential drugs will be incorporated in hospital pharmacy.

ACKNOWLEDGEMENTS

We thank Department of Dermatology, Bharati Hospital and Research Centre, Pune for their kind cooperation and support in conduct of the study. We would also like to extend our thanks to the postgraduate students for their support.

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Knowledge and Practices of Patent Medicine Vendors in Rivers State, Nigeria: Implications for Malaria Control in Rural and Sub-Urban Communities

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ABSTRACT

Submitted: 20/1/2012 *Accepted: 15/2/12012*

Anti-malarial drugs rank high among the drugs administered by patent medicine vendors in Nigeria. Many local inhabitants erroneously perceive these vendors as well knowledgeable on health matters and can be relied on or trusted. This study aims to highlight the knowledge and practices of patent medicine vendors in order to stimulate policy regulation of their practices for effective malaria control and accelerated attainment of the Millennium Development Goals by 2015. A cross sectional study was carried out in October 2008 among 263 patent medicine vendors operating in Rivers State, Nigeria through a two-stage sampling design. All the data generated were analyzed with Epi Info ver 6.04d Statistical Software. Significant tests were performed with confidence level set at 95%. The medicine vendors consisted of 179(68.1%) male and 84(31.9%) female. Most of them had formal education: 148(56.3%) had secondary and 101(38.4%) post secondary education. Their knowledge on the new National Malaria Treatment Policy recommending the use of artemisinin combination therapy for the treatment of uncomplicated malaria in place of monotherapies like chloroquine and sulfadoxine-pyrimethamine was however low (20.5%). Only 24(9.1%) complied with the policy. But their knowledge on use insecticide treated nets was high 250(95.1%). Although most medicine vendors possessed basic education, their knowledge with respect to change in National Malaria Treatment Policy was very low. Adequate dissemination of the new policy and training of patent medicine vendors on rational use of Artemisinin Combination Therapy are necessary to accelerate malaria control in the State and in Nigeria.

Keywords: Patent Medicine Vendors, Malaria Control, Rivers State, Nigeria

INTRODUCTION

More than a million people die yearly of malaria in Africa.[1] Aside from the human toll, malaria wreaks significant economic havoc, resulting in a decreased Gross Domestic Product (GDP) by as much as 1.3% in countries with high levels of transmission.[1] In Nigeria, malaria is estimated to cause about 132 billion Naira (£530 million) direct loss to the economy.[2] Malaria control relies essentially on prompt and effective management of the clinical disease, but unfortunately, most early treatments in developing countries occur through self-medication with drugs recommended or bought from patent medicine vendors.[3,4] These patent medicine vendors (PMVs) are persons without formal training in pharmacy, who sell orthodox drugs and other pharmaceutical products on a retail basis for profit.[5,6] They take advantage of the persistent shortage of health manpower and are often the primary sources of orthodox drugs for both urban and rural populations[7, 8] and cut across the various socio-economic groups. However, because of the frequent drug stock-outs in public health facilities, the services of these patent medicine vendors become inevitable. Their drugs are perceived to be cheaper, while they are said to be friendlier and approachable by the locals unlike orthodox health care practitioners. Even where there are free medical care programmes in public health facilities, people are more likely to patronize medicine vendors to avoid the travel, inconvenience and especially time wastage associated with public health services.[9] Some have however, argued that the closeness of the patent medicine sellers to homes of majority of the people than the formal sector facilities could be responsible for the relationship existing between them.[10]

Over-the-counter (OTC) drugs are the only drugs authorized to be sold by the patent medicine vendors in Nigeria, but they generally sell all types of drugs based on their financial capability[11] and customer demands. Antimalarial drugs rank high among the drugs administered by these medicine sellers in Nigeria.[7] In addition to selling drugs, they are also a major source of advice about illness and health matters.[12] Many local

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inhabitants erroneously perceive them to be well knowledgeable on health matters and can be relied on or trusted. However, with widespread resistance to chloroquine and the shift in malaria treatment policy to artemisinin-combination therapy (ACTs) there are concerns that medicine sellers may continue to sell monotherapies like artemisinin derivatives alone because they are cheaper, thus potentially jeopardizing ACT efficacy in the long-term.13 There are also concerns that PMVs are indulged in the use of counterfeit drugs, incorrect dosing and irrational prescription practices.[14]

Goal six of the Millennium Development Declaration (MDGs) addresses malaria and targets to halt it and begin to reverse its incidence by 2015.[15] Similarly, the Global National Malaria Action Plan has the target to reduce malaria deaths to near zero by 2015.[16] It has been said that by addressing the problem of malaria most of the MDGs would also have been addressed. One cannot therefore undermine the important role PMVs can play in achieving this. This study aims to highlight the knowledge and practices of patent medicine vendors with a view to stimulating policy regulation for enhancing their role towards effective malaria control in rural and sub-urban communities for the accelerated attainment of the MDGs by 2015.

MATERIALS AND METHODS

Study Area:

The study was carried out in Rivers State, Nigeria. Rivers State is one of the 36 States of the Nigerian Federation. It is located in the South-south geopolitical zone and is one of the major oil bearing states of Nigeria's Delta region. A third of the State is riverine and comprised of a mangrove and rainforest vegetations with heavy rainfall and high humidity all year round. It has a population of 5.2 million people with an annual growth rate of 3%. The most vulnerable groups for malaria in the state; children under five years of age and pregnant women constitute 20% and 2% of the population respectively. Administratively, the state is made up of three Senatorial Districts, with each comprising of 7-8 Local Government Areas (LGAs). Each LGA has between 12-19 Political Wards. Each ward is made up of 1-4 communities. Health care in the state is weak, and is provided by both by formal and informal sectors. The informal sector providers constitute the majority and comprise predominately of Patent Medicine Vendors, Alternative Care and Herbal Practitioners, and Spiritual Healers. Most of the communities are rural with little or no social amenities like good roads, health centres or schools. The predominant occupations of the people are farming, fishing and petty trading.

Study Design and Sampling:

A cross sectional study design was used to carry out the study in October 2008 among PMVs operating in Rivers State. A minimal sample size of 263 was determined using the formula for descriptive studies [17] based on 9% of PMVs who stocked artemisinin combination drugs (ACTs) for treatment of malaria in three of the six geopolitical zones of Nigeria [18] and error margin of 5%, Design Effect of =2, and attrition rate of 5%. Participants were selected through a multi-stage random sampling method. The first stage was the selection of three LGAs; one from each of the three Senatorial Districts. The second stage was the selection of a political ward from each of the selected LGAs. The third stage was the selection of communities in each political ward. Subsequently, all PMVs operating in a selected community were identified with the assistance of local guides and those who consented among them to participate in the study were interviewed using a self-administered, semi-structured questionnaire. A few illiterate PMVs had their questionnaire interviewer-administered. A total of 270 questionnaires were distributed and 263 were returned completed, giving a response rate of 97.4%. The questionnaire was in three parts: demographic profile of respondents; knowledge of respondents on malaria drugs and drug regulation; and practices of PMVs.

Data Analysis:

All the data generated were double-entered and analyzed with Epi Info ver 6.04d statistical software package. Significant tests were performed with confidence level set at 95%.

Ethical Considerations:

A verbal consent was obtained from all participants after explanation of the aim of the study and assurances of confidentiality and the right to decline participation without sanctions.

RESULTS

A total of 263 PMVs were interviewed between 16th and 30th October 2008. They consisted of 179(68.1%) male and 84(31.9%) female participants. Their mean age was 35.98±9.75. Most of them 148(56.3%) [95% CI= 50.05 – 62.35] had at least a secondary education, while only a few 6(2.3%) did not have formal education. Majority, 154 (58.5%) had practice experience of between 0-9 years (Table 1).

Knowledge of PMVs on Malaria:

The knowledge of PMVs on the new National Malaria Treatment Policy was low. Only a fifth (20.5%) had knowledge of the policy recommendation in the use of ACTs

Table 1: Demographic Characteristics of Patent Medicine Vendors

Variable	Absolute Frequency (n=263)	Relative Frequency (%)	95%CI
Age distribution n=263			
20-29	75	28.5%	23.14-34.39
30-39	101	38.4%	32.50-44.58
40-49	66	25.1%	19.97-30.79
50-59	15	5.7%	3.23-9.23
60-69	6	2.3%	0.84-4.89
Sex distribution			
Male	179	68.1%	62.06-73.65
Female	84 31.	9%	26.35-37.94
Educational level			
Non-formal education	6	2.3%	0.84-4.89
Primary	8	3.0%	1.32-5.91
Secondary	148	56.3%	50.05-62.36
Post secondary	101	38.4%	32.67-44.39
Length of experience as medicine vendor			
0-9 yrs	154	58.5%	52.34 – 64.57
10-19 yrs	83	31.6%	25.99 – 37.55
20-29 yrs	17	6.5%	3.81 – 10.15
⩾30	9	3.4%	1.58 – 6.39

in place of monotherapies like chloroquine and sulfadoxine-pyrimethamine for prompt treatment malaria in both the children and adult populations. The vast majority of the PMVs 148 (56.3%) [95% CI= 50.05 – 62.35] had no idea of the policy. However most 259 (98.5%), were aware of the regulation to stock and sell only drugs registered by the National Agency for Food and Drugs Control (NAFDAC). Also, most 265 (99.3%) [95% CI= 94.59 – 98.9] looked out for drug expiration dates before purchasing. On why some PMVs sell low quality drugs to their clients, the main reason given was to increase their profit margin (47.9%). About one-third (39.5%) however, claimed ignorance of the quality of the drugs they sell (Table 2)

Practices of PMVs and Validation of PMV Claims:

Most of the PMVs 235 (89.4%) [95% CI= 84.98 – 92.81] were found to be registered with their respective LGA authorities. Only a few, 28 (10.6%) were not registered. In the same vein, most of the available anti-malaria drugs found with PMVs had the certification/registration numbers of the National Food and Drug Administration and Control (NAFDAC), the government body that regulates and certifies drugs in Nigeria.

Table 2: Knowledge of Patent Medicine Vendors on Malaria

Variable	Absolute Frequency (n=263)	Relative Frequency (%)	95%CI
Knowledge of New National malaria treatments policy			
Good knowledge	54	20.5%	15.82 -25.92
Limited Knowledge	61	23.2%	18.23 – 28.77
No knowledge	148	56.3%	50.05 – 62.35
Awareness of importance of NAFDAC registration of drugs			
Yes	259	98.5%	96.15 – 99.58
No	4	1.5%	0.41 – 3.84
Awareness of the importance of drug expiration dates			
Yes	256	97.3%	94.59 – 98.92
No	7	2.7%	1.07 - 5.40
Awareness of the Need to check for drug expiration date			
To avoid harm to client	242	92.0%	88.05 – 94.98
To ensure that drug is safe	17	6.5%	3.81 – 10.14
Others	4	1.5%	6.87 – 14.58
Reason why some PVMs sell low quality drugs			
Ignorance	104	39.5%	33.59 – 45.53
To maximize profit	126	47.9%	41.73 – 54.13
Others	33	12.5%	8.79 – 17.16

However, most of the PMVs used monotherapies for the treatment of uncomplicated malaria instead of ACTs; (32.7%) used sulphadoxine-pyrimethamine and (25.5%) used chloroquine respectively. Only a few, (9.1%) [95% CI= 5.93 – 13.27] used artemisinin-based combination drugs (ACTs) for same reason. Similar finding was observed in the treatment of malaria among pregnant women. Majority of the PMVs 170 (64.6%) [95% CI= 58.53 – 70.41] procured their drugs from the open markets instead of from licensed pharmaceutical stores. Action taken by PMVs when clients did not respond to initial treatment with anti-malaria drugs showed that majority (67.5%) referred the patients to a health facility, while about a quarter (27.4%) prescribed other drugs (Table 3).

Knowledge about Insecticide-Treated Bed Nets:

Knowledge of Insecticide Treated Nets (ITNs) for malaria prevention was high among the PMVs 250(95.1%) [95% CI= 91.69 – 97.34]. However, only a third (35.4%) of them reported ever having received request for the purchase of ITNs from their clients. Nevertheless, most PMVs 184(70.0%) [95% CI= 64.02 – 75.44] believed that they are a potential source of ITN distribution in the communities (Table 4).

Table 3: Practice of Patent Medicine Vendors on malaria

Variable	Absolute Frequency	Relative Frequency	95%CI
Registration of drug store by LGA or other authorities			
Yes	235	89.4%	84.98 – 92.81
No	28	10.6%	7.19 – 15.02
NAFDAC Registration of available anti-malaria drugs			
All have NAFDAC Reg. no.	236	89.7%	85.41 – 93.12
Don ' t have NAFDAC Reg. no.	27	10.3%	6.87 – 14.58
Drugs used for treatment of malaria n=263			
Choroquine	67	25.5%	20.32 - 31.19
Sulphadoxine/ Pyrimethamine	86	32.7%	27.06 – 38.73
Amodiaquine	26	9.9%	6.56 – 14.15
ACT	24	9.1%	5.93 – 13.27
Artesunate only	58	22.1%	17.19 – 27.56
Others	2	0.8%	0.09 – 2.72
Drugs used for treatment of malaria in pregnant women			
Choroquine	27	10.3%	6.87 – 14.58
Sulphadoxine/ Pyrimethamine	120	45.6%	39.49 – 51.85
Amodiaquine	7	2.7%	1.07 – 5.41
ACT	11	4.2%	2.11 – 7.36
Artesunate only	17	6.5%	3.81 – 10.15
Others	3	1.1%	0.24 – 3.30
Don't Know	78	29.7%	24.20 – 35.58
Source of anti-malaria drugs			
Open market	170	64.6%	58.53 – 70.41
Pharmaceutical store	72	27.4%	22.08 – 33.19
Drug manufactures	10	3.8%	1.84 – 6.88
Others	11	4.2%	2.11 – 7.36
Action taken when clients response to anti-malaria was poor			
Change to other drugs	72	27.4%	22.08 – 33.19
Refer to Health centre	178	67.7%	61.66 – 73.29
Refer for native/ spiritual treatment	2	0.8%	0.09 – 2.72
Do nothing	1	0.4%	0.00 – 2.10
Others	10	3.8%	1.84 – 6.88

Table 4: Knowledge and use of Insecticide Treated Nets

Knowledge of ITNs			
Yes	250	95.1%	91.69 – 97.34
No	13	4.9%	2.66 – 8.30
Seen any ITNs			
Yes	240	91.3%	87.17 – 94.38
No	23	8.7%	5.62 – 12.83
Request of clients for ITNs			
Yes	93	35.4%	29.59 – 41.46
No	162	61.6%	55.42 – 67.50
Sometimes	8 3.0%	1.32 – 5.91	
PMVs as source of ITN distribution			
Yes	184	70.0%	64.02 – 75.44
No	73	27.7%	22.43 – 33.59
Others	6	2.3%	0.84 – 4.89

DISCUSSION

Although patent medicine vendors (PMVs) are individuals without formal training in pharmacy, they take advantage of the weaknesses in the health system like shortages in health manpower and frequent drug stock outs to find relevance in rural and sub-urban communities. This study revealed that most of the PMVs interviewed had at least secondary level education which was quite reassuring that they possessed the basic education that could be improved upon and harnessed for malaria control in these rural and sub-urban communities where health care centres are few or completely lacking. This notwithstanding, it was found that their knowledge regarding the change in malaria treatment policy from the use of monotherapies like chloroquine, sulfadoxine-pyrimethamine, artesunate, dihydroartemisinin to ACTs was quite low. The implication is that they have continued to deploy and use these monotherapies to treat uncomplicated malaria with the attendant risk of severe consequences like treatment failure, exacerbation of symptoms, emergence of complications such as cerebral malaria and the increased potential for parasite resistance. Similar result was also obtained by Oladepo et al[18] in the study they carried out in three of the six geo-political zones in Nigeria. They reported that despite the impressive educational background of PMVs, their use of ACTs was low, thus suggesting that such major change in malaria policy might not have been widely disseminated across to all the relevant stakeholders in the nation. The World Health organization (WHO) had recommended the use of ACTs as the best available treatment option for uncomplicated malaria to avoid these risks and accelerate the global malaria control efforts.[1,13]

Knowledge of the use of insecticide treated bed nets (ITNs) for malaria control was however high among the PMVs and this might not be unconnected with the various ITN intervention programmes such as the free net distribution campaigns in communities as well as the free antenatal care programmes for pregnant women that were ongoing in the State during the period of the study. This was however significant because PMVs are generally known to be located in communities closer to the homes of majority of the people and often act as a major source of advice about health matters to community folks.[10,12] Similarly, other studies have also revealed that these PMVs were more likely to be patronized by people who want to avoid the travels, time wastage and other beaurocratic bottle necks often associated with public health services.[10] The advantaged position of PMVs in this regard can therefore be leveraged for ITN distribution and other malaria control interventions in the communities as was even suggested by most of the PMVs themselves.

The study also revealed that a large portion of the PMVs were registered with the local LGA authorities, who were quite good in identifying and regulating their practices and could also be utilized for information sharing and capacity building. In the same vein, almost all the PMVs interviewed were aware of the National Regulation to stock and sell only drugs registered by NAFDAC and the need to check for drugs expiry dates before procurement and sale. Though impressive, this might not be unconnected with the regular media campaigns mounted by NAFDAC on the dangers of adulterated and sub-standard drugs and the need for individuals to purchase only drugs registered by it. NAFDAC had in the past several years consistently enlightened the general public on ways to identify "fake" drugs which included absence of its (NAFDAC) registration number or manufacturers' name or expiry date. However, while residents in urban areas with better access to social infrastructure and electronic media of communication might be well sensitized, those in rural and sub-urban communities with lower literacy levels and poorer amenities may not be that lucky.

The study further showed that while most of the PMVs sold antimalarials with NAFDAC number/certification, some PMVs were found with antimalarials without NAFDAC certification, thus suggesting that such drugs might be counterfeit drugs unless proven otherwise. The consequences of the use of such drugs might spell doom for malaria control in the State if unchecked. The major motivation for buying and selling counterfeited drugs was said to be profit maximization since such drugs were usually cheaper and are freely sourced in the open markets.[14,19] Given that PMVs are said to be the foremost source of antimalaria and other drugs for many rural and sub-urban communities in developing countries, including Nigeria, their role therefore in malaria control should not be overlooked.[20,21]

CONCLUSION

While most of the PMVs operating in rural and sub-urban communities of Rivers State, Nigeria possess adequate basic education, their knowledge with respect to the change in National Malaria Treatment Policy from the use of monotherapies such as chloroquine and others to ACTs was found to be very low. Wider dissemination of the policy to all relevant stakeholders and the training of PMVs on the rational use of ACTs as well as their inclusion into the State and National Malaria control strategies are advocated to accelerate malaria control in the State and to speed up the attainment of the MDGs by 2015.

ACKNOWLEDGEMENTS

We acknowledge with gratitude the funding support for the study provided by the Rivers State Ministry of Health and also Dr. Seye Babatunde who helped with data analysis.

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Pattern of prescribing at a paediatric outpatient setting in northern India

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Submitted: 22/1/2012 *Accepted: 13/2/2012*

ABSTRACT

Introduction Drug prescribing is a skill that needs to be refined on a continuing basis. It reflects physician's skills and attitude toward diagnosis of an ailment and selection of appropriate treatment. In view of this, it is important to do study the pattern of prescribing in paediatric patients on continuous basis. The aim of this study was to analyze the prescribing pattern in a paediatric outpatient setting.

Methods: A drug utilization study was carried out in a paediatric outpatient setting in northern India for period of 4 months, on a pilot basis. The study is continuing. The prescriptions of children up to 18 years approaching the clinic were studied and the data was captured from the "Wise-kid" software. The data was analysed to determine WHO recommended prescribing indicators and three complementary indicators for cost.

Results: The data were collected from 436 prescriptions and it was found that upper respiratory tract illness is the most common illness (31%). The average number of drugs prescribed was 3.2±0.06, while drugs prescribed by generic name were 3.8%. Percentage of encounter with injection and antimicrobials prescribed were found to be 0.9% and 18% respectively. The prescribing from National List of Essential Medicine (NLEM-2011) was found to be 39.6%. The median cost of drug per encounter was INR132, while cost spent on injection and antimicrobials were 0.3% and 7%, respectively.

Conclusion: The prescribing pattern in private paediatric outpatient setting were found to be rational as less number of antimicrobial drugs and injections were use in the practice. A very fair number of medicines were prescribed from the National List of Essential medicine (NLEM-2011).

Keywords- Prescribing pattern, Drug utilization, Pediatrics, Out-patients, India

INTRODUCTION

WHO defines rational use of drugs when "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community".[1] The irrational use of drugs is known to lead to an increase in the cost of treatment, incidence of ADR and development of resistance against antimicrobials.[2] Various examples of irrational drug use are poly-pharmacy, inappropriate use of antimicrobials (often in inadequate dosage) for non-bacterial infections; over use of injections when oral formulations would be more appropriate, failure to prescribe in accordance with clinical guidelines, inappropriate self-medication (often of prescription only medicine), and non-adherence to dosing regimens.[1]

There is enough evidence to demonstrate that prescribing of drugs has shifted from generics to branded and prescribing out of NLEM.[3-5]The rational prescribing can be assessed with the help of conducting prescription audit on continuous basis. The results of such studies help policy makers to develop policy regarding quality of rational drug use in a health facility.[6-8] The presence of vast number of brands of the same drug affects the choice of prescribing a medicine.

A meticulous perusal of the literature reveals that paediatric population faces improper use of medicines and subsequent ADR events.[3-5,9] Since paediatric patients are more sensitive toward drugs and ADR. Irrational use of drug can't be tolerated in this age group of population. For that reason drug utilization study on continuous bases must be performed to expose and eliminate such events as much as possible. The prescribing pattern was found with the help of various prescribing and complimentary indicators. The present piece of study was started with the aim to find out the prescribing pattern in a paediatric outpatient setting and is an ongoing study.

METHODS

A drug utilization study was carried out in a paediatric outpatient setting in northern India for a period of 4 months, on a pilot basis. The prescriptions of children up to 18 years approaching to clinic were captured from the "Wise-kid"

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software. The information such as case ID, age, sex, weight, date of consultation, diagnosis, antimicrobial drugs (AMD) and all other drugs prescribed and their doses, dosage form and route of administration, total duration of AMD and other drugs received, total dose of antimicrobials and other drugs administered was recorded in a spreadsheet. Vaccination and other procedures like suturing etc. at the clinic were excluded from the study.

The data so obtained was analyzed for WHO recommended prescribing indicators and three complementary indicators for cost.[10]

1. Average number of drugs prescribed
2. Percentage of drugs prescribed by their generic name
3. Level of adherence in prescribing of drugs from the National List of Essential Medicines (NLEM–2011)[11]
4. Percentage of the prescribed AMD.
5. Percentage of prescriptions with injections.

The determination of cost was performed using the following points:

1. Only the direct cost in terms of Maximum Retail Price (MRP) of drugs in the prescription was calculated. MRP as mentioned in the current issue of the CIMS (Current Index of Medical Specialities) was used.

2. The cost of the prescribed brand was calculated, wherever applicable. In case of drugs prescribed by the generic name, the highest cost was considered.

3. All the estimations for cost were done for the total duration of therapy prescribed.

The cost of drugs per prescription was also computed. In addition, prescriptions were also analysed for morbidity pattern, utilization of different dosage forms, route of administration and antimicrobials. The indicators were represented as average±SEM (Standard error of mean) or percentages, as applicable.

RESULTS

A total of 436 prescriptions were analysed and drug utilization pattern was reviewed with special emphasis on the antimicrobial drugs. The population consisted of 260 male and 176 female patients. The average age of patients was 52.2±2.2 months.

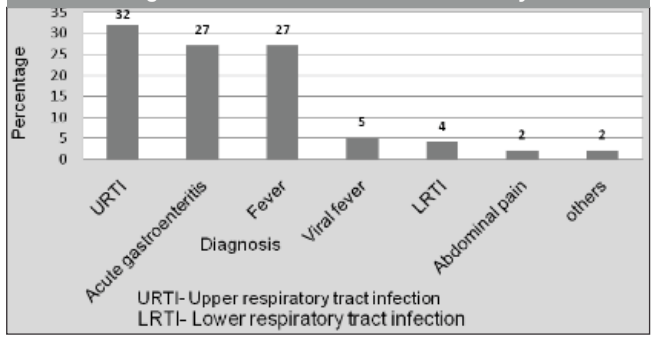
All the patients were divided according to "American Academy of paediatrics" in different age groups (table 1).[12]

Table 1: Age wise profile of patients

Age group	Patients
1-12 Months, Infants	98(22%)
1-12 Year, children	305(70%)
13-18 year, adolescents	33(8%) Total 436

The most common diagnosis in the patients was infection of the upper respiratory tract (31%) followed by fever (27%) and acute gastroenteritis (27%).WHO has recommended five

Fig. 1: Profile on the basis of morbidity



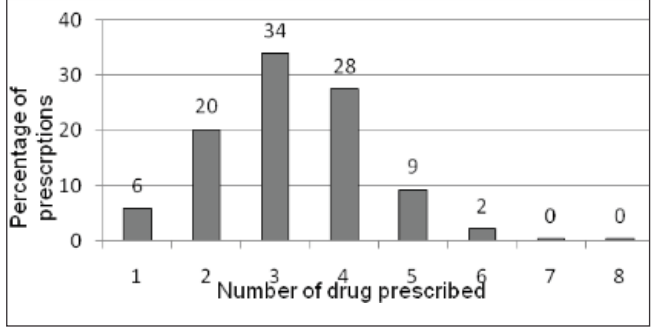
prescribing indicators i.e average number of drug per encounter, medicine prescribed from NLEM, medicine from generics, Injection prescribed, AMD prescribed.

Table 2: WHO recommended Prescribing Indicators

Indicator	Value
Average number of drugs per encounter	3.2(±0.06)
Percentage of drugs prescribed from NLEM-2011	39.6
Percentage of drugs prescribed by generic name	3.8
Percentage of encounters with an injection prescribed	0.9
Percentage of encounters with an AMD prescribed	18

The average number of drug per encounter was found to be 3.2, with a minimum of 1 and maximum of 8 drugs. The proportion of patients receiving 3 drugs per prescription,4 drugs and two drugs was 34%, 28% &20%, respectively.

Fig .3: Profile of drugs prescribed



Of the total 1331 drugs prescribed, 527 drugs belonged to the NLEM-2011. Of all the drug prescribed, only 50were prescribed by generic name (3.8%). Only 79 drugs, of 1331, were antimicrobials (6%). The rank order of prescribed antimicrobials was cephalosporin (33%) > penicillin (20%) > macrolide (14%) = fluoroquinolones (14%). The other antimicrobials were antifungals, aminoglycosides and chloramphenicol

Table 3: Pattern of antimicrobial prescribing

Antimicrobial classes	Number
Cephalosporin	26(33%)
Penicillin	16(20%)
Macrolide	11(14%)
Fluoroquinolones	11(14%)
Antifungal	9(11%)
Aminoglycosides	5(6%)
Chloramphenicol	2(3%)

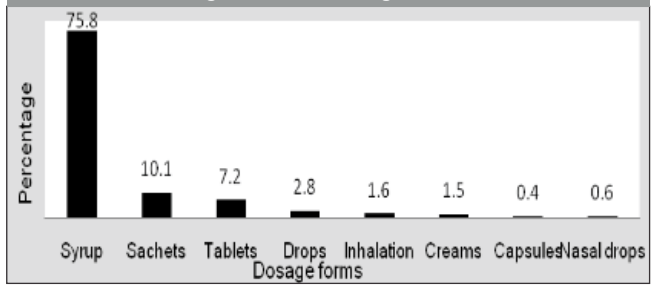
This study also focused on the complimentary Indicators. The cost of drugs was calculated from the CIMS online portal and from the label of drug at the pharmacy. The various complimentary indicators are shown in table 4.

Table 4: Complimentary Indicators

Indicator	Cost (in INR)
Average cost of drug per encounter	210.4±10.6
Median Cost	132
Cost spent on AMD (% of total)	6123 (7%) C
ost spent on Injection (% of total)	228(0.3%)

Average cost of prescribed drugs was found to be INR 210. Nearly 7% of the cost spent on the antimicrobials costing 6123INR.Out of the total drug prescribed, 90% were administered by oral route, followed by topical (7%) and inhalation (3%).Over 75% of the prescribed dosage forms were syrups followed by the sachets(10%), tablets(7.2%), drops(2.8%), inhalation(1.6%), creams (1.5%), capsules(0.4%) and nasal drops(0.6%;fig 3)

Fig .3: Use of dosage forms



DISCUSSION

The results of the present study are based on the data obtained from 436 patients. The male to female ratio reflected a higher number of male patients who were visiting the clinic compared to female patients. One probable reason for this may be the skewed gender profile in northern part of India.[13]

Upper respiratory tract infection (31%) was the most common infection followed by the fever and acute gastroenteritis. Reactive airway diseases were more common among the children which may be due to cold weather during the period of study. The finding of the present study is in concurrence with the results of Mohanty et al, where the upper respiratory tract infection (39%) were shown to be the most common infection.[14]

The average number of drug prescribed increased with increase in number of diagnosis. In this study the average number of drugs prescribed was 3.2. The rational use of drugs demands that the number of drugs prescribed is as small as possible not only to reduce the cost of treatment but also reduce the chances of drug interaction and adverse effects. The results of studies in paediatric outpatient setting by Dimri et. al..and.Mohajer et. al. have reported the average number of drugs prescribed to be 2.31 and 2.81, respectively.[15,16]

In the present study, only 3.9% of the medicines were prescribed by generic names. Other studies conducted by Mohanty et. al. in southern India found this as 1.42% and Dimri et. al. in Chandigarh reported this as 5.8%.[14,15] The results of Dimri and co-workers are based on patient data from public hospital. However, this study has been conducted in a private setting and this may have an influence on the prescribing by generic names. The possible reasons for less prescribing by generic drugs could be prescribers' doubt about the bioavailability and efficacy of generic formulations, prescribers' ignorance about the price variations between generic and branded and the lack of information on the availability of various generic formulations. Another possible reason could be that the branded drugs are easily available, names are easy to recall for the prescriber and dispenser.

Additionally, the pharmaceutical companies thrive upon the advantage a brand name offers to the business.

A very fair number of drugs were prescribed from the National List of Essential Medicine-2011 (39.6%). There seems to be a scope to improve this indicator. Prescribing from the NLEM in various studies conducted all over India were Dimri et. al., Mohanty et. al., Adebyo et. al., Bharty et. al. were to the tune of 68%, 45%, 6.4% & 58%, respectively. The prescribing from the NLEM should be promoted for optimal use of financial resources and to satisfy the health care needs of the majority of the population safely.[14,15,17,18]

The parental dosage forms are expensive and cause pain due to the prick. WHO recommends lesser use of injection as it helpful in reducing the cost of treatment and eliminate the pain to patient. There are certain factors which lead to increase in injection usage drug available in injection form only and some patients who think that injection could treat their illness faster compare to oral medicine. In present study only 0.9% injection were used. It is found comparable with studies conducted by Dimri et. al., Kumari et. al. (1.18%, 1.17% respectively).[15,19]

Overprescribing with antibiotics increased with overestimation of illness by physicians. Parents intend to see rapid symptomatic relief of disease and often put pressure on the prescriber to prescribe a "strong medicine" i.e. an antibiotic for relief. The overuse of antibiotic is known to cause drug resistance, increased side effects and make the treatment expensive. In this study, only 18% of antimicrobial drugs were prescribed. Other results have reported between 18.5-29% of antimicrobial drugs being prescribed.[15,16] On comparison with results available in literature, it was found that the antimicrobial use in the present study was rational.

To 34% of the patients, three drugs were prescribed. This has to be viewed with the fact that the most common diagnosis was URTI. For treatment of URTI, an analgesic, cough syrups, saline drops were prescribed with or without antibiotics. This is comparable with the results of Kshirsagar et al. in which two and three drugs were prescribed to 37 and 32% of patients, respectively.[20]

Cephalosporin and Penicillin were found to be the most commonly prescribed antibiotic (33%, 20% respectively). Acute respiratory tract infections were found to be most commonly infection and the appropriate antibiotic for treating are Penicillin, Cephalosporin and Macrolide. The findings of study conducted by Khaled et al. has shown that Penicillin prescribed maximum number of time (52%) followed by cephalosporin (32%).[16]

In this study, the median cost of drugs per encounter was found to be INR132. The prescribing of antimicrobials and the injections was rational in this study, and therefore the cost of the prescription is not very high. The cost of prescription increased as the number of injection and antimicrobial drug prescribed increased. It indicates that the prescribing of antimicrobial drugs and injections determine the cost of prescription.

The most commonly used dosage form was syrup. Children are comfortable with the dosage form like syrups and drops compared to tablets and capsules and this finding is well taken. Younger children find tablets and capsules difficult to swallow and the taste is also an issue for compliance. The administration of liquids can be a major contributing error in dosing in the children. The use of different size of spoons may lead to underdosing and overdosing of medication.[21] As syrup were found to be maximally prescribed, therefore it is advised to use graduated caps for accurate measurement of syrup.

The results of this study have provided strong evidence for the rational use of antibiotics. This is an encouraging finding, especially when the prescribers and the policy makers are concerned about issues like antimicrobial resistance and NDM-1.

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Knowledge, Attitude and Skills of Nurses of Delhi towards Adverse Drug Reaction Reporting

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Submitted: 19/12/2011 *Accepted: 4/1/2012*

ABSTRACT

This study was aimed to determine the awareness of nurses of Delhi (India) about Adverse drug reaction (ADR) reporting and their involvement in activities related to pharmacovigilance.

A questionnaire was distributed and then collected from the nurses serving in Delhi. The response rate of the survey was 65%. The meaning of term pharmacovigilance was known to 68.27% of nurses. Surprisingly, only 51.92% of nurses understood the correct meaning of the term ADR. None of the nurses knew about the pharmacovigilance centers of India. Only 7.69% nurses knew the reporting centers of Delhi while just 2.88% nurses had their phone number, address. Nurses (93.27%) inform patients about the expected therapeutic effects of the prescribed drugs. Their interaction with the patients regarding side effects was significant. Nurses (90.38 %) said that they report observed ADRs. Majority of the nurses reported the ADRs to the physicians or hospital pharmacy. Nurses felt that, they need not report ADR either because ADR is well known (40.38%) or due to uncertainty about the causal drug (49.04%). About half of the nurses (47.12%) informed that they have existence of set procedure of reporting ADR in their organization. Most (75%) of the nurses did not have ADR reporting forms. Remaining 25% nurses had only localized ADR reporting forms.

Thus, we can conclude that nurses are not reporting ADRs to ADR monitoring centers of Central Drugs Standard Control Organization (CDSCO), New Delhi. Education and training is essential for enhancing ADR reporting by nurses to the ADR monitoring centers.

Keywords: ADR, ADR reporting, pharmacovigilance, nurses.

INTRODUCTION

Pharmacovigilance (PV) is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem" [1]. Adverse drug reaction is a response to a medicine which is noxious and unintended and which occurs at a dose used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions [2]. ADRs are global problems because they have a significant pessimistic impact on both health and healthcare costs [3]ADRs are cause for a substantial proportion of hospital admissions. ADRs account for 6.5% of all hospital admissions in the UK .[4] The percentage of adverse drug reactions leading to hospitalization in general population is 1.8% in the Netherlands [5]. ADRs are a cause of 6.89% of total admissions at medical emergency department of KEM hospital, Mumbai, India [6]. The economic burden of ADRs is massive. Data provided by Pirmohamed M. suggests that admissions related to ADRs cost up to £466m annually to National Health Service in UK [4]. For patients suffering from ADRs, total medical costs have been increased by an average of 19.86%[1].

Need of pharmacovigilance in India: India is the second most populous country in the world with over 1.21 billion people (2011 census) [8]and is now becoming favorable destination for conduct of clinical trials by various pharmaceutical companies. After successful clinical trials and permission from drug authorities, these drugs are launched into the market. Even after stringent scrutiny before launching, some drugs need to be withdrawn from the market due to ADRs. Hypoglycemic drug, Rimonabant is withdrawn from Indian market in 2008, due to serious side effects like depression, suicidal tendencies and seizures [9]. Rofecoxib, an analgesic, was withdrawn in 2004 due to high risk of myocardial infarction [9]. It is essential to recognize adverse drug reactions as soon as possible and prevent them if possible, to ensure the well-being of the patient. Up to 72% of the ADRs are avoidable [4] Spontaneous reporting by healthcare professionals is critical for curtailing the ADRs. ADR reporting rate in India is below 1% as compared to the world

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rate of 5% [10] and therefore it is the need of the hour to improve the awareness of healthcare providers regarding PV and ADR monitoring.

Pharmacovigilance program of India: National Pharmacovigilance Program (NPP) is revived by the Ministry of Health and Family Welfare in July 2010[11,12] and it is overseen by CDSCO, New Delhi. The program is envisaged to be rolled out in three phases:

Phase I plans to include 40 ADR monitoring centers (AMCs).

Phase II plans to include 140 MCI recognized medical colleges by end of 2011.

Phase III would ultimately cover the total healthcare system by 2013.

ADR reports collected at the AMCs will be dispatched to the national co-ordinating centre. The coordinating centre will conduct causality assessment and upload the reports into the pharmacovigilance software. Lastly, the integrated ADR data will be transmitted through vigiflow software interface into the Uppsala Monitoring Center's ADR database where signal processing can be carried out[12].

Nurses and Pharmacovigilance: Nurses are the bedside caregivers. They can play a key role in ADR reporting because they can observe the adverse drug reactions first hand. It is important to motivate nurses to understand their role and responsibility in the detection, management, documentation, and reporting of ADRs, which are essential activities for optimizing patient safety.

The goal of our study was to determine the level of awareness of nurses regarding ADRs,their reporting and the extent of their involvement in pharmacovigilance activities.

MATERIALS AND METHODS

Research Design: This was a questionnaire based study involving nurses. A self prepared questionnaire was distributed to nurses working in various hospitals and clinics of Delhi, the National Capital of India. The prospective study was conducted, over a period of 10 months from December 2009 to September 2010. Entire area of Delhi was covered, which included North, West, South and Central zones of Delhi. We personally presented the questionnaire to the nurses and collected the duly filled questionnaire on the same day.

Material used: A questionnaire containing 23 questions was formulated to assess the knowledge, attitude and skills of the nurses regarding pharmacovigilance and ADR reporting. The questionnaire contained 7 questions related to knowledge, 6 questions related each to attitude and skills. The remaining 4 questions were designed to generate demographic data like name, qualification, sector and experience.

Subjects: The study included 160 nurses practicing in various government or private sector hospitals/clinics of Delhi.

Study setting: The study covered 8 government hospitals, 4 government dispensaries, 10 private hospitals and 3 private clinics of Delhi, namely

Government sector hospitals

1. Safdarjung Hospital (SJH).
2. Guru Gobind Singh Government Hospital (GGSGH).
3. Charak Palika Hospital (CPH), Moti Bagh.
4. Lok Nayak Jaiprakash Hospital (LNJP).
5. Deen Dayal Upadhaya Government Hospital (DDU).
6. Pt. Madan Mohan Malaviya Hospital, Malviya Nagar.
7. Primary Health Centre (PHC), Mehrauli.
8. ESI Hospital, Rohini.

Government sector Dispensaries

1. C.G.H.S Dispensary, R.K.Puram.
2. MCD Dispensary, Ber Sarai.
3. Delhi Government Dispensary, Khanpur.
4. Delhi Government Dispensary, Raghubir Nagar.

Private sector hospitals

1. Park Hospital, khyala.
2. Batra Hospital and Medical Research Centre, Tughlakabad.
3. Yogmaya Hospital, Mehrauli.
4. Neelu Angels Hospital, Saket.
5. Vikas Hospital, Mehrauli.
6. Bhagwati Hospital, Mehrauli.
7. Sitaram Bhartiya Hospital, Qutab Institutional Area.
8. Majeedia Hospital, Tughlakabad.
9. Rockland Hospital, Katwaria Sarai.
10. G M Modi Hospital, Saket.

Private clinics

1. Tayal Nursing Home, Mehrauli.
2. Bakaya Clinic, Mehrauli.
3. Sanjivani Nursing Home, Kamla Nagar.

RESULTS

Out of 160 nurses approached to participate in study, 104 nurses responded, giving response rate of 65%. The demographic profile of respondents is presented in Table 1. Maximum participation was from the nurses (24.04%) working in Safdarjung Hospital, New Delhi.

Table 1: Demographic profile of respondents.

DEMOGRAPHICS	NUMBER	PERCENTAGE
Qualification		
Diploma	73	70.19
B. Sc nursing	20	19.23
Un-qualified	11	10.58
Gender		
Male	02	1.92
Female	102	98.08
Sector		
Government	56	53.85
Private	48	46.15
Experience		
0-5 yrs.	52	50
5-15 yrs.	33	31.73
15-25 yrs.	11	10.58
25 or more	8	7.69

Assessment of Knowledge:

Out of the 104 nurses, 71 (68.27%) were aware of the term pharmacovigilance, 26 (25%) nurses did not know the term pharmacovigilance and 7 (6.73%) nurses did not respond, indicating that total, 26+7 =33 (31.73%) nurses did not know the term pharmacovigilance. Majority (92.31%) of the nurses were aware of the expected therapeutic effects of the prescribed drugs, 3 (2.88%) nurses did not know and 5 (4.81%) nurses did not respond to this query. The correct meaning of the term ADR was known to about half of the nurses (54, 51.92%). Thirty four (32.69%) nurses had hazy idea of the term ADR while 16 (15.38%) nurses did not respond. This shows that total 50 (48.08%) nurses, did not know the correct meaning of the term ADR. Most of the nurses (91.35%) said that they were aware about possible side effects of the drugs, 8 (7.69%) nurses responded negatively, one (0.96%) nurse did not respond.

None of the nurses had idea that reporting can be done at National Monitoring Center (NMC) and/or Regional monitoring centers (RMC).They responded that ADRs can be reported to physicians (79.81%), hospital pharmacy (7.69%), Director of health services (0.96%), Senior supervisor (0.96%), Pharmacy in-charge and Director medical services (0.96%). Six (5.77%) nurses gave mixed response and four (3.85%) nurses did not respond. Total eight nurses (7.69%) knew correct reporting centers of Delhi. Out of these eight nurses, four voted for All India Institute of Medical Sciences, two voted for DGHS (Ministry of health and Family welfare), one each for Lady Hardinge Medical College and Maulana Azad Medical College, as reporting centers of Delhi. Only 3 (2.88%) nurses had the phone number and address of the reporting centers. This indicates that 101 (97.12%) nurses report ADRs at places other than official ADR monitoring centers designated by CDSCO.

Assessment of Skill:

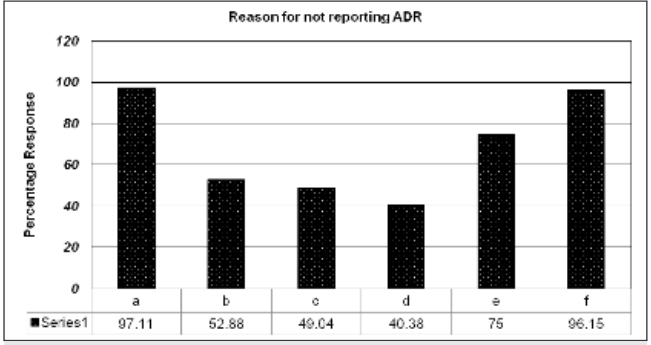
Majority of nurses 97(93.27%) said that they inform the patients about the expected therapeutic effects of the prescribed drugs while 7(6.73%) nurses did not inform. Significant number of nurses 95(91.35%) inform patients about the possible side effects, while 9(8.65%) nurses did not tell about possible side effects. Ninety three (89.42%) nurses responded that patients inform them about the discomfort experienced by them during or after the drug treatment, 7(6.73%) nurses responded negatively and 4(3.85%) nurses did not respond. Ninety four (90.38%) nurses said that they report ADR while 7(6.73%) did not report ADR and 3(2.88%) did not respond. Thus, 7+3= 10 (9.61%) nurses did not report the ADRs. Forty nine (47.12%) nurses reported to have set procedure of reporting ADRs in their organization. Forty three (41.35%) nurses agreed that their organization does not have set procedure of reporting ADR while 5 (4.81%) nurses said that they did not know answer to this question and 7 (6.73%) nurses did not respond. So, it shows that 5+7=12 (11.54%) nurses were doubtful about the existence of set procedure for ADR reporting in their organization. Surprisingly, 67 (64.42%) nurses said they do not have ADR reporting forms and 11 (10.58%) nurses did not respond. Thus total, 78 (75%) nurses did not have either hospital generated ADR reporting form or CDSCO prescribed ADR reporting form. Only 26 (25%) nurses had ADR reporting form. Out of these 26 (25%) nurses, 22 (84.61%) nurses had their in-built organizational ADR reporting form and 4 (15.38%) nurses were unwilling to show the form.

Assessment of Attitude:

One hundred one (97.11%) nurses felt that ADR monitoring is essential. One (0.96%) nurse responded negatively and 2 (1.92%) nurses did not respond. The reasons of not reporting ADRs given by nurses were – uncertainty about causal drug (49.04%), ADR is well known (40.38%), unawareness of ADR reporting centers (83.65%).

Fifty seven (54.81%) nurses undergo continuing education program, 38 (36.54%) nurses did not undergo education program and 9 (8.65%) nurses did not respond to this question. Large number of nurses 96 (92.31%) were of the opinion that education and training is essential for increasing the ADR reporting rate while 1 (0.96%) nurse disapproved and 7 (6.73%) nurses did not respond. The overall reasons for not reporting ADRs are presented in Figure 1.

Fig. 1: Reasons for not reporting the ADRs by nurses.

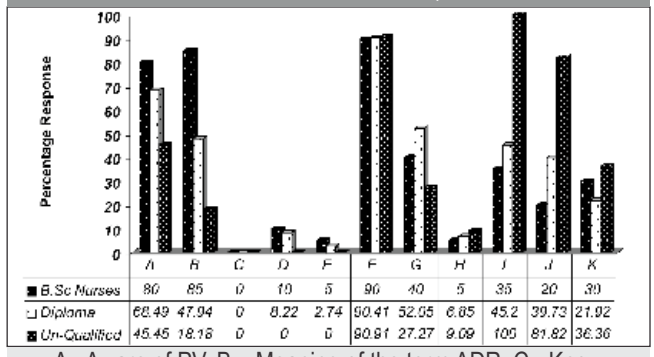


a = not aware of correct reporting centers, b = did not have set procedure of ADR reporting in their organization, c = was not sure about the drug causing it, d = as ADR was well known, e = did not have ADR reporting form, f = did not have ADR reporting form of CDSCO.

Correlation between knowledge, attitude and skills of nurses with their qualification (Figure 2):

The knowledge of Pharmacovigilance was better in Graduate nurses (80%) than Diploma nurses (68.49%). Graduate nurses (85%) had better understanding of the term ADR as compared to Diploma nurses (47.94%). Graduate nurses (10%) were more aware of the ADR reporting centers of Delhi as compared to Diploma nurses (8.22%). Awareness of the phone number and address of these reporting centers was more of Graduate nurses (5%) than Diploma nurses (2.74%). Uncertainty about the drug causing ADR and the feeling that ADRs need not be reported as they are well known was maximum among un-qualified nurses (100%, 81.82%) followed by Diploma nurses (45.20%, 39.73%) and then Graduate nurses (35%, 20%). No association was observed between qualification and extent of ADR reporting.

Fig. 2: Correlation between knowledge, attitude and skills of nurses with their Qualification



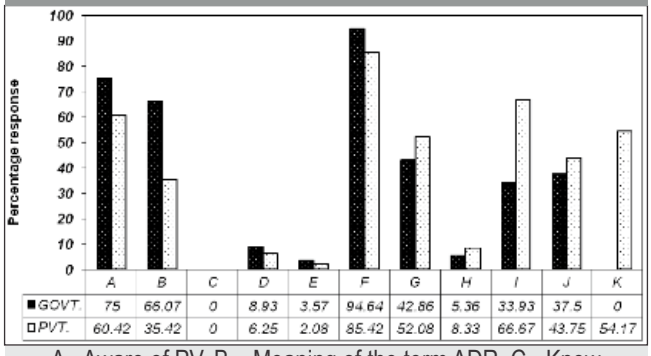
A - Aware of PV, B – Meaning of the term ADR, C - Knew NMC/RMC as reporting centers, D - Aware of ADR reporting centers of Delhi, E - Have phone no. and address of NPP reporting center, F - Report observed ADR, G - Have set procedure of ADR reporting in their organization, H - Non-reporting due to lack of knowledge about center, I - Uncertain of drug causing ADR, J - Feel all ADRs are well known, k- Have ADR reporting form.

Correlation between knowledge, attitude and skills of nurses with their sector (Figure 3):

The nurses were grouped as per their sector of working as: Government sector nurses (53.85%) and Private sector nurses (46.15%). Awareness about Pharmacovigilance and ADR was better of the nurses from government sector (75%, 66.07%) as compared to private sector (60.42%, 35.42%). Knowledge of phone number and address of pharmacovigilance centers of Delhi was poor among both government sector nurses (3.57%) and private sector nurses (2.08%). Reporting by nurses from government sector (94.64%) was better than private sector (85.42%) nurses but none of the government nurses had ADR reporting form. Twenty six (25%) Private sector nurses had either organizational or CDSCO prescribed ADR reporting form.

Further the nurses were probed sector wise for reasons of underreporting. Major reasons for underreporting in private sector were lack of knowledge about centers of Delhi (93.75%), uncertainty about the drug causing ADR (66.67%), lack of set procedure of ADR reporting (47.92%), non availability of reporting form (45.83%), feeling that ADRs are well known and hence need not be reported (43.75%). Underreporting in Government sector was mainly due to non availability of reporting form (100%), lack of knowledge about centers of Delhi (91.07%) , lack of set procedure of ADR reporting (57.14%), feeling that ADRs are well known hence need not be reported (37.5%) and uncertainty about the drug causing ADR (33.93%).

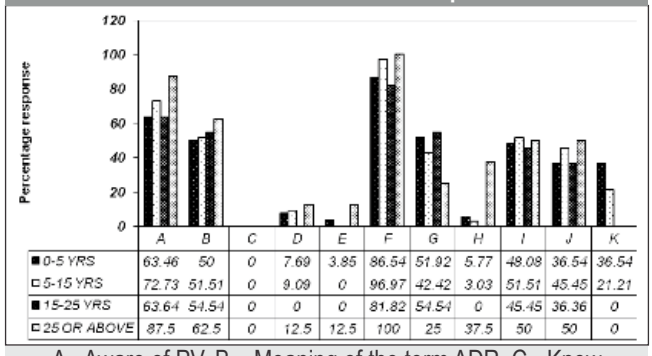
Fig. 3: Correlation between knowledge, attitude and skills of nurses with their Sector.



	A	B	C	D	E	F	G	H	I	J	K
GOVT.	75	66.07	0	8.93	3.57	94.64	42.86	5.36	33.93	37.5	0
PVT.	60.42	35.42	0	6.25	2.08	85.42	52.08	8.33	66.67	43.75	54.17

A - Aware of PV, B – Meaning of the term ADR, C - Knew NMC/RMC as reporting centers, D - Aware of ADR reporting centers of Delhi, E - Have phone no. and address of NPP reporting center, F - Report observed ADR, G - Have set procedure of ADR reporting in their organization, H - Non-reporting due to lack of knowledge about center, I - Uncertain of drug causing ADR, J - Feel all ADRs are well known, k- Have ADR reporting form.

Fig. 4: Correlation between knowledge, attitude and skills of nurses with their Experience.



	A	B	C	D	E	F	G	H	I	J	K
0-5 YRS	63.46	50	0	7.69	3.85	86.54	51.92	5.77	48.08	36.54	36.54
5-15 YRS	72.73	51.51	0	9.09	0	96.97	42.42	3.03	51.51	45.45	21.21
15-25 YRS	63.64	54.54	0	0	0	81.82	54.54	0	45.45	36.36	0
25 OR ABOVE	87.5	62.5	0	12.5	12.5	100	25	37.5	50	50	0

A - Aware of PV, B – Meaning of the term ADR, C - Knew NMC/RMC as reporting centers, D - Aware of ADR reporting centers of Delhi, E - Have phone no. and address of NPP reporting center, F - Report observed ADR, G - Have set procedure of ADR reporting in their organization, H - Non-reporting due to lack of knowledge about center, I - Uncertain of drug causing ADR, J - Feel all ADRs are well known, k- Have ADR reporting form.

Correlation between knowledge, attitude and skills of nurses with their experience (Figure 4):

The nurses were grouped as per their experience as: Junior (0-5 years, 50%), Middle (5-15years, 31.73%), Senior (15-25years, 10.58%) and senior most (more than 25 years, 7.69%). Senior most nurses were found to be most aware of pharmacovigilance (87.5%) and ADR (62.5%). ADR reporting forms were not available with senior and senior most nurses. The availability of ADR reporting forms was found to be maximum (36.54%) with junior nurses. Senior most nurses were most aware about reporting centers in Delhi (12.5%) and their phone number and address (12.5%). Reporting of observed ADRs was best by senior most nurses (100%). This indicates that reporting is done orally, within the organization. Non-reporting of ADRs due to lack of knowledge of reporting centers (37.5%) as well as due to the feeling that ADRs are well known and need not be reported (50%) was maximum in senior-most nurses. The uncertainty about the drug causing the ADR was highest in middle nurses (51.51%).

DISCUSSION

For seeking health care facilities, majority of the Indian population favors government hospitals. This means a good ADR database can be generated from these hospitals. The daunting task is to foster a culture of ADR reporting among nurses who are in constant contact with hospitalized patients. Reasons for the low level of ADR reporting include lack of awareness, training and low understanding of significance of reporting.

An additional factor is that the government has not made it mandatory for health care providers to report ADRs unlike some countries such as Spain and Sweden [13]. Hence, there is definite need for spontaneous ADR reporting from the nurses in addition to physicians and pharmacists. Moreover, only few studies have been conducted on ADR reporting by nurses. Therefore this study was conducted to ascertain the actual participation of nurses of Delhi in ADR reporting to ADR monitoring centers.

The response rate of our survey was 65% against the 36% response rate of a study conducted in Iran [14]. In our study about half of the nurses (51.92%) knew the correct meaning of the term ADR. The knowledge of ADR was found to be much higher (75%) in a study conducted by Giti Hazebi in Iran[14] while the finding of Li Q in china shows that only 1.6% of the nurses correctly define the term ADR [15]. Most of the nurses (91.35%) said that they were aware about possible side effects of the drugs. It seems that nurses were more familiar with the word side effect rather than adverse drug reaction. Possibly, there is lack of clarity in their knowledge regarding ADR and side effect.

In our study, nurse's proficiency in informing patients about expected side effects (91.35%) and therapeutic effects (93.27%) was very good. Nurses (89.42%) said that patients freely communicate the discomfort experienced by them. It indicates that the interaction of nurses with patients and vice versa was good. Nurses shared the relevant drug related information with patients. Eight respondents (7.69%) knew

correct reporting centers of Delhi which is much lower than an Iranian study, which states that 48% nurses were aware of ADR center. But study of Li Q in china observed that just 2.2% nurses knew the correct reporting center [15]. In our study, only 2.88% nurses had the phone number address of the reporting centers. Similar observations were found in studies conducted in Iran and China. Only 3.4% nurses of Iran and 2.9% nurses of China knew the phone number and address of the ADR reporting centers of their countries.

According to our study, 90.38% nurses report ADR, analogous to 92% reporting in case of a study in Iran[14]. National Pharmacovigilance program (NPP) of India states that ADR should be reported to ADR monitoring centers [11,12]. But our nurses report ADRs mainly to the physicians (79.81%) and hospital pharmacy (7.69%) which is in congruence with the study in Iran indicating nurses report to physicians in the ward (56%), head nurse (26%), and pharmacy (13%) [14]. Hospital pharmacies, pharmaceutical companies and drug centers within the area are the responses given by nurses of a study in China as the main places for reporting ADRs [15].

As per our study, total 75% nurses reported that they did not have ADR reporting form. Out of remaining 26 (25%) nurses, 22 (84.61%) nurses had in-built organizational ADR reporting form and 4 (15.38%) nurses were unwilling to show the form. These nurses were unqualified and thus it seems that they have given fake response regarding availability of the form. Thus we can say, none of the nurses had CDSCO ADR form. Moreover, the results show that nurses were devoid of the knowledge about the reporting centers in Delhi as well as India which confirms that reporting by nurses is not reaching the AMCs. The reason may be that nurses consider that once they report the ADR to physician or Pharmacy, their duty is completed. This restricts ADR reporting to their organization without further communication to ADR monitoring centers for the larger benefit of the society.

Essentiality of education and training, for increasing the ADR reporting rate, was expressed vehemently by nurses. Our study shows, 92.31% of nurses strongly felt that education and training is important for enhancing ADR reporting rate by nurses. It has been shown in the studies of Sweis [16] and Green [17] conducted in UK and study of I. Ribeiro Vaz [18] in Portugal, that education and/or training improves ADR reporting.

Suggestions for Improvement in ADR Reporting:

1. Each hospital should establish local 'Pharmacovigilance Unit' for disbursement and collection of ADR reporting forms.
2. Conducting pharmacovigilance workshops to provide guidance to nurses for recognizing and reporting ADRs.
3. Providing a separate space for ADR reporting in patient chart.
4. Associate ADR reporting with rewards.25. Felicitation of nurses for maximum ADR reporting in a year.
6. Periodical meetings of experts from NPP with nurses should be arranged to boost reporting.
7. The NPP should periodically collect ADR forms from hospitals by sending representatives.
8. ADR drop boxes should be introduced at strategic sites in hospitals.
9. Facilitate ADR reporting by e-mail, fax and phone.
10. Incorporation of pharmacovigilance in the nursing syllabus.
11. Assurance of non-involvement in legal matters, if they arise.
12. Making ADR reporting mandatory for nurses.
13. Each hospital should have data-base on ADRs, easily accessible by nurses.
14. Periodic meetings between nurses, physicians and pharmacists for effective co-ordination.
15. Positively changing the mindset, so that ADR reporting becomes an accepted and understood routine.

CONCLUSIONS

Even though all nurses felt ADR monitoring to be essential and are willing to report, they are unaware about the national pharmacovigilance program. They lack the knowledge of ADR reporting centers. The availability of CDSCO ADR reporting forms and reporting to ADR monitoring centers of Delhi was extremely poor. None of the hospitals had effective set procedure of ADR reporting. Education and training regarding noticing, reporting of ADRs to nurses is essential. ADR reporting by nurses would significantly improve after implementing the suggestions. Proactive participation of nurses would certainly enhance spontaneous reporting of ADRs to ADR monitoring centers.

ACKNOWLEDGEMENTS

The authors wish to thank all the nurses who participated in the study.

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Indian Journal of Pharmacy Practice | Association of Pharmaceutical Teachers of India

Prescribing Pattern of Antiepileptic Drugs in Adults in a South Indian Tertiary care Hospital

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ABSTRACT

Submitted: 13/1/2012 *Accepted: 129/1/2012*

Our study describes the antiepileptic drugs (AEDs) utilization patterns in Kempegowda Institute of Medical Sciences (KIMS) Hospital and Research Center during January 2008 to May 2011. More research studies are required in this area due to lack of well-defined studies in India to conclude which is the most frequent class of epilepsy seen with the AED's used. We retrieved prescription data from patient profile forms and medical record department. We documented essential data in a Patient Profile Form, specifically designed for our study. A total of 108 patients data were recorded in the study. In our study we found that percentage of men suffering from epilepsy was 61.11% (66 nos.) and percentage of females was 38.88%. Our data shows that most of the patients 33 (30.55%) were from the age group of 40-50 years; followed by 28 (25.92%) of patients in the age group of 29-39 years and 16 (14.81%) patients were in the each age group of 18-28 years and 51-61 years. The most common epilepsy was Generalized Tonic-Clonic seizure 68 (62.96%) followed by Simple Partial Seizures 11 (10.18%) and Myoclonic Seizures 8 (7.40%) respectively. Most commonly prescribed drug concluded by our study is Phenobarbitone which accounts for 61 (56.41%) in both the genders, followed by Phenytoin 38 (35.18%) and Valproic acid (VA) usage was 24 (22.22%). Monotherapy is the type of therapy most frequently used in all types of seizures. The selection of AEDs is based on the efficacy for specific seizures. The most frequently prescribed AED in our study was Phenobarbital followed by Phenytoin, VA, Carbamazepine, and Lamotrigine due to the minimal adverse drug reaction of Phenobarbital in comparison with the other AEDs. We had found that as age progressed incidence of epilepsy increased.

INTRODUCTION

An epileptic seizure is a transient paroxysms of uncontrolled discharges in neurons causing an event that is discernible by the person experiencing the seizure and /or observer.[1] Epilepsy is a medical condition with recurrent, unprovoked seizures.[2,3,4] Epileptic seizures have many causes, including a genetic predisposition for certain seizures, head trauma, stroke, brain tumors, alcohol or drug withdrawal, and other conditions.[3,4] Epileptic seizures are divided into two main pathophysiologic groups—partial seizures and generalized seizures—by EEG recordings and clinical symptomatology.[5] It is estimated that there are 55, 00,000 persons with epilepsy in India, 20, 00,000 in USA and 3, 00,000 in UK.[6,7] A recent study in Bangalore, India, reported that the problem is nearly two and half times higher in rural areas as compared to urban areas, where they are not receiving any treatment.[6,8-17] Monotherapy is the usual dictum, but polytherapy is needed for patients with multiple seizure types or refractory disease.[18]Many controlled clinical trials have tested the efficacy of the older Anti-Epileptic Drugs (AEDs), (such as Phenobarbital and Phenytoin) and newer AEDs (such as Carbamazepine and Valproic acid) in controlling seizure frequency and their safety when prescribed in monotherapy or in combination. The interest in drug utilization studies began in the early 1960s, and its importance has increased since then because of increase in marketing of new drugs, wide variation in the pattern of drug prescribing and consumption, growing concern about delayed adverse effects and the increasing concern regarding the cost of drugs. [18] Hence we have made an attempt to study the prescribing pattern of AEDs in the treatment of different types of epilepsy in Medicine department in KIMS Hospital.

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METHODOLOGY

Study Site: This study was conducted in KIMS Hospital, Bangalore. It is a 1,000-bedded Tertiary Care Superspeciality Hospital, providing specialized health care services to all strata of people in and around Bangalore and also the rural population.

Study Design: This was a hospital based prospective and retrospective observational study conducted on in-patients to review the current prescribing pattern of antiepileptic drugs in patients with epilepsy admitted to medicine wards.

Sample Size: A total of 108 In-patients from different units of medicine department, who were on AEDs and fulfilled the inclusion criteria were selected and the rest of the patients were excluded from the study, and the data were collected in a well designed performa.

Study period: The retrospective study was conducted for a period of 36 months from January 2008 to December 2010. The prospective study was conducted for a period of six months from January 2011 to May 2011.

Study Criteria:

1) Inclusion Criteria All adult In-patients who were treated with AEDs admitted in different units of Medicine Department.

2) Exclusion Criteria All pregnant women who are on AEDs.

3) Source of Data: Data was collected using a well-designed patient data collection form.

1. By reviewing the patient's treatment chart, case sheets of the patients.

2. From the Medical Record Department of KIMS Hospital and Research Centre.

Preparation of data collection form: Information extracted from the case files will include: Demographic data, chief complaint, If he/she is a known case of epilepsy and etiology of seizure, habits (Smoker/Alcoholic/food habits), adverse effects, past medical history and past medication history, family history, laboratory details, diagnosis (provisional or confirmatory). Treatment: AEDs prescribed and prescription of the AEDs by generic names. The recommended dosages of the AEDs were obtained from the patient case files and discharge summary

(ii) Statistical method.

The data of each case file was collected and analyzed by a percentage method.

4) Study procedure: After the Institutional Ethics Committee approval a prospective and retrospective study was conducted in KIMS Hospital and research centre to study the prescribing patterns of AEDs in the treatment of epilepsy.

RESULTS

A retrospective and prospective study 108 epileptic patients was undertaken to study the prescribing pattern of AED.

The study included 108 epileptic patients on antiepileptics among whom 66 (61.1%) patients were found to be male and 42 (38.9%) patients were females.

Majority of the patients 33 (30.55%) were in the age group of 40-50 years, followed by 28 (25.92%) of 29-39 years and 16 (14.81%) patients were in both age group of 18-28 years and 51-61 years. About 15 (13.88%) patients were in the age group of 62 years and above. Our data shows that most of the patients were from the age group of 40-50 years and majority of the enrolled patients were male as in the other studies.

Fig. 1: Graphical representation of the distribution of 108 epileptic patients based on the gender.

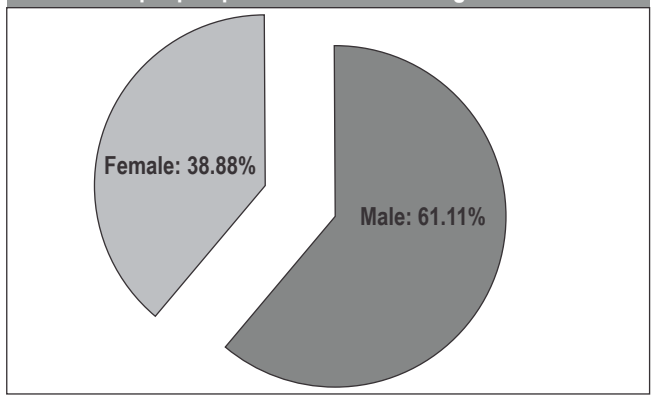
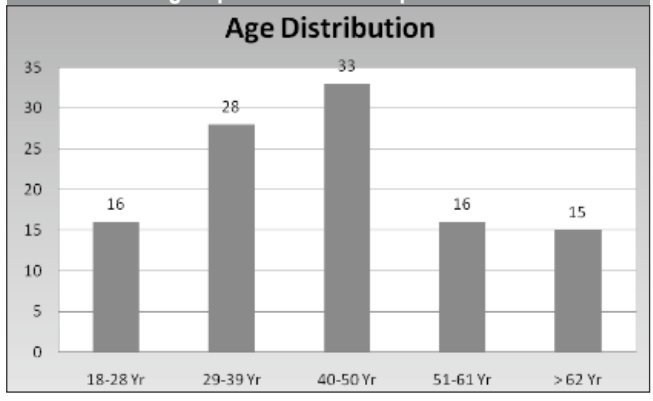


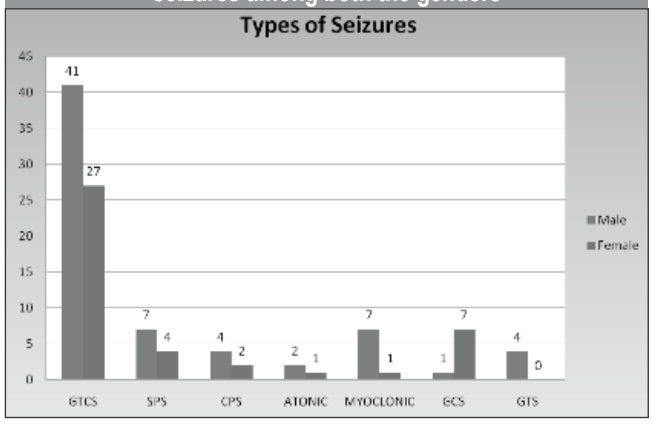
Fig. 2: Graphical representation of distribution of age group with number of patients.



Generalized Tonic-Clonic Seizures was found to be more prevalent 68 (62.96%) patients out of which 41 were males and 27 were female, followed by Simple Partial Seizures 11 (10.18%), 07 were males and 04 were females. Total numbers of Myoclonic Seizures were 08 (7.40%) of which 07 males and 01 female. Generalized Clonic Seizures 08 (7.40%) of which 01 was male and 07 female. In Complex Partial Seizures 06 (5.55%), 04 were male and 02 were female. Generalized Tonic Seizures of 04 (3.70%) patients, there were only male patients. In Atonic Seizures, a total of 03 (2.77%) patients of which 02 male and 01 female.

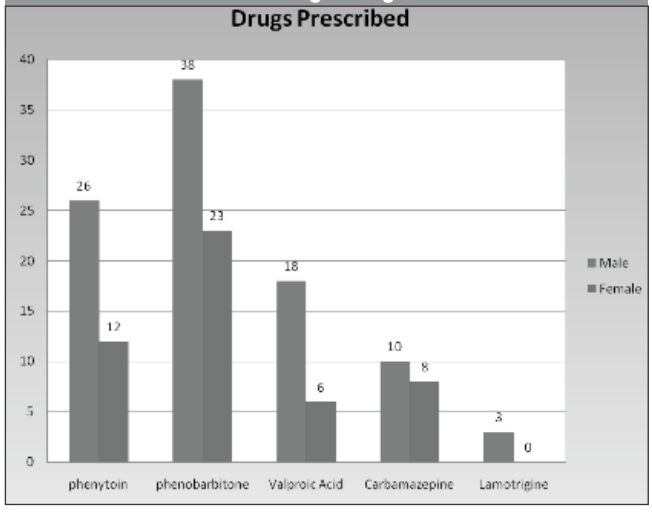
Among all the prescriptions including drugs given individually, and in combinations, the usage of Phenobarbitone accounts for 61 (56.41%) patients of which

Fig. 3: Graphical representation of distribution of types of seizures among both the genders



38 were male patients and 23 were female patients, followed by phenytoin 38 (35.18%) patients of whom 26 were male patients and 12 were females. VA usage was 24 (22.22%) patients of which 18 were males and 08 were females.

Fig. 4: Graphical representation of prescribing pattern of AEDs among both genders



Carbamazepine usage was 18 (16.85 %) patients of which, 10 were males and 08 were females. 03 (3%) of Lamotrigine, 03 patients were males and we did not have any female patients recorded.

Age distribution of the patients with Generalized Tonic Clonic Seizures among both the genders**:** Out of 68 patients of Generalized Tonic Clonic Seizures majority were in the age group of 29-39 years, 18 (26.47%) patients, 11 were males and 07 were females. 15 (22.05%) patients were in the age group of 40-50 years, 13 were males and 02 were females. 14 (20.58%) patients were in the age group of 18-28 years, 07 were males and 07 were females.11 (16.17%) patients were in the age group of 62 years and above, of which 04 were males and 07 were females. 10 (14.70%) were in the age group of 51-61 years, 06 were males and 04 females.

Age distribution of the patients with Simple Partial Seizures among both the genders: Out of 11 patients with simple partial seizures 04 (36.36%) patients were in the age group of 29-39 years and 51-61 years, followed by 03 (27.27%) patients were in the age group of 40-50years.

Age distribution of the patients with Complex Partial Seizures among both the genders: Out of 06 patients with complex seizures 03 (50%) patients were in the age group of 40-50 years, of which 02 were females and 01 was male, followed by 02 (33.33%) and 01 (16.66%) patient were in the age group of 29-39 years and 62 years and above respectively.

Age distribution of the patients with Atonic Seizures among both the genders: Out of 03 patients with 02 (66.66%) patients were in the age group of 40-50 years, followed by 01 (33.33%) patient was in the age group of 29-39 years.

Age distribution of the patients with Myoclonic Seizures among both the genders: Out of 8 patients with Myoclonic Seizures 04 (50%) patients were in the age group of 29-39 years, followed by 02 (25%) patients were in the age group of 40-50 years, 01 (12.5%) patient each were in the age group of 18-28 years and 51-61 years.

Age distribution of the patients with Generalized Clonic Seizures among both the genders: Out of 08 patients with Generalized Clonic Seizures 03 (37.5%) patients were in each of the age groups of 40-50years, and 62years above, followed by 01 (12.50%) patient each in the age group of 18-28 years, and 51-61 years.

Age distribution of the patients with Generalized Tonic Seizures among both the genders: Out of 04 patients with Generalized Tonic Seizures 03 (75%) patients were in the age group of 40-50 years, followed by 01(25%) patient was in the age group of 18-28 years.

DISCUSSION

With the rise in the incidence of epilepsy over the past years developments of newer AEDs have entered into the current scenario. The advances in the therapeutical aspects of epilepsy and the efficacy of monotherapy versus combination therapy have not been extensively studied. The beneficial effects of second generation drugs can also be studied conduction Drug utilization studies in this area. In our study we were able to make inferences with regard to the most commonly prescribed AED's, most common types epilepsy, the different age group distribution, and the gender most likely affected. A total of 108 epileptic patients were included. The incidence of epilepsy was found to be higher in male than in females and also the incidence of epilepsy increases with an

increase in age. This inference was supported by a study in London conducted by Aidan Neligan.[28] Another finding we observed in our study was that Phenobarbital was the most frequently prescribed drug followed by Phenytoin and VA. This drug utilization finding was supported by two other studies conducted by Radhakrishnan K., Nayak S.D. et al. in Kerala and a study conducted by R.K Gupta and Pooja S. Reddy. [29-30] The above studies justified the use of Phenobarbital because it was the equally effective as other AEDs when used in monotherapy, very less incidences of adverse drug reactions (ADR) and also the cost was least when pharmacoeconomics evaluation (Cost Minimization Analysis) was conducted. Our study had certain limitation, as our center is not a referral center for neurology; hence we had limited number of sample size for our study. Our study embarks to conduct a prospective study for about two years to access the quality of life of the epileptic patients, along with this we can also include monitoring of adverse effects of all AED's, long term medication adherence and thereby control of seizures, pharmacoeconomics evaluations and repeated hospitalization due to recurrent episodes of epilepsy.

CONCLUSION

Monotherapy is the type of therapy most frequently used in all types of seizures. The selection of AEDs is based on efficacy for specific seizure types and epileptic syndromes. Most commonly prescribed drug concluded by our study is Phenobarbitone followed by Phenytoin and VA usage We observed that most of the patients had Generalized Tonic Clonic Seizures followed by Simple Partial Seizures and Myoclonic Seizures. The percentage of men suffering from epilepsy was higher than females. Our data shows that most of the patients were from the age group of 40-50 years.

ACKNOWLEDGMENTS

The authors wish to thank all the faculty members of medicine department, KIMS Hospital and Research Centre, the Medical Record Department (MRD) staff, KIMS hospital and Research Centre for their kind cooperation in issuing the medical reports. We also extend our sincere gratitude to all the faculty of Department of Clinical Practice, V.I.P.S for her valuable guidance. We extend our heartfelt thankfulness to the Principal, V.I.P.S for this timely support to complete this work.

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Five year screening on occurrence of vaccine-preventable diseases in rural Anantapur

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ABSTRACT

Objective: The main objective of the study was to screen the occurrence of Vaccine- preventable disease (VPD) in the rural Anantapur area in South India by reviewing the diseases treated in the most popular referral hospital in the area.

Methods: Screening of patients' records of five year period (2006-2010) was done to find the occurrence of VPDs. Significance of gender variation on occurrence of measles was assessed by paired t-test. Microsoft Excel was used for tabulation and graphs.

Results & Discussion: All the children born in the hospital had 100% adherence to first schedule of the vaccination. The complete schedule for the vaccination of children up to 5 years is given free of cost, but still there were no full adherence to vaccination because of reasons such as unawareness, relocating from the mother's house to father's house after delivery and following the vaccination in other health care facilities etc. There was no gender discrimination in the access to vaccines. Eighty two cases of VPD were reported in the hospital from 2006-2010. On an average 16 VPD were observed per year. Among them most commonly observed diseases, measles accounts for 56 cases in five years.

Conclusion: Adherence to vaccination was high for the first schedule. Measles was the most common VPD observed in rural Anantapur region. There were no cases of polio, diphtheria and tetanus reported in the period of 2006-2010. The limitations of the study include not identifying the occurrence of hepatitis B infection due to lack of information about type of hepatitis. It was also not sure that the patients with VPDs were properly vaccinated or not due to unavailability of their vaccination cards.

Keywords: Immunization, DPT, OPV, BCG, hepatitis B, occurrence.

INTRODUCTION

The induction of immune response by the deliberate inoculation of appropriate immunogen(s) in the form of a vaccine is termed as vaccination.[1] The immunization of children in India has resulted in a significant reduction in morbidity and mortality. The current immunization schedule protects against poliomyelitis, diphtheria, tetanus, pertussis, measles, and tuberculosis. The Government of India (GOI) established its Expanded Programme on immunization (EPI) in January 1978. Initially the EPI offered free immunization to every child against tuberculosis, poliomyelitis, diphtheria, tetanus and pertussis. In 1985, the EPI was modified as the Universal Immunization Programme (UIP) with inclusion of the Measles vaccine and increasing the target of immunization coverage from 80 to 100%.[2]

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Immunization forms the major focus of child survival programmes throughout the world. Roughly 3 million children die each year of VPDs with a disproportionate number of these children residing in developing countries. Recent estimates suggest that approximately 34 million children are not completely immunized and almost 98 % of them residing in developing countries.[3] Prevention is better than cure, especially when there is an effective vaccine.

A study at Bellary in 2011 shows that on analyzing information in cards, complete immunization was found to be 96%, whereas on the basis of parents recall alone, the coverage of complete immunization was 87%.[4]

The immunization status needs to be improved by education, increasing awareness, and counseling of parents and caregivers regarding immunizations and associated misconceptions. The most common reasons for partial or non-immunization were: inadequate knowledge about immunization or subsequent dose; belief that vaccine has side-effects; lack of faith in immunization; or oral polio vaccine is the only vaccine required.[5]

A study at Bareily in 2010, states that Immunization coverage was high for BCG (92.86%) and lowest for measles (62.38%). Most common reason (50%) for partial and non immunization of children was found to be ignorance on the part of parents. Religion, education of both mother and father was found to be significantly associated with immunization status. The need of the hour is to make routine immunization a "felt need" of the community. Increasing the knowledge and understanding of the caretakers of the young children about the essentiality and benefits of routine immunization would be a strong step forward in achieving the goals.[6]

According to World health organization number of vaccine preventable cases reported are as follows;

Table 1: WHO Vaccine preventable disease

VPD	1980	1985	1990	1995	2000	2005	2010
Diphtheria	39,231	15,685	8,425	2,123	5,125	10,231	6,081
Measles	114,036	161,216	89,612	37,494	38,835	52,454	48,181
Pertussis	320,109	184,368	112,416	4,073	31,431	13,955	44,180
Polio	18,975	22,570	10,408	3,263	265	66	559
Tetanus(neonatal)	-	-	9,313	1,783	3,287	891	811
Tetanus(total)	45,948	37,647	23,356	-	8,997	3,543	3,714

Courtesy: WHO vaccine-preventable diseases: monitoring system 2010 global summary.

Quality of record keeping is very important for effective implementation of immunization schedule. [7] The failure in immunization of rural areas was mainly due to unawareness of need for immunization, mother too busy, place and time not known, place for immunization too far, each for unaware of need to return for subsequent dose.[8] Proper maintenance of immunization cards and ensuring the availability of them with mothers for inspection are recommended for obtaining accurate estimation of vaccine coverages.[9] Strengthening of health education activities can definitely improve the awareness and thereby improve the immunization coverage.[10]

Main aim of the study is to collect information on the vaccination, adherence and adverse events if any. The objectives include;

- To assess occurrence of vaccine preventable infections reported to the hospital.
- To check the adherence to vaccination schedule.

METHODOLOGY

Study settings: The samples for the study were children born in a rural secondary level care referral hospital in Anantapur district, A.P. There were mothers from various places of Anantapur district. The hospital is serving the health care needs of the public of Anantapur and it is one of the first choices for majority of the population.

There was same vaccination schedule provided by the hospital for the past 8 years. In order to screen the number of patients treated in the hospital due to VPD was taken from the medical records. Data was collected from 2006 to 2010 and the age group selected was 1-8 years. Microsoft excel was used to tabulate the results and preparing graphs.

Results

The hospital provides vaccination free of cost to the children born in the hospital or not. On a pilot evaluation of six months, 84 children were found to be fully immunized, including one dose of BCG vaccine, 4 doses of oral polio vaccine, two doses of DPT and Hepatitis B vaccines. Among the children who got immunization completely for six months were 44 male children and 40 female children. Table 2 & 3 are giving the details of vaccinations given in the hospital for the first six months.

Table 2: Total number of BCG vaccines given from January2011- June 2011

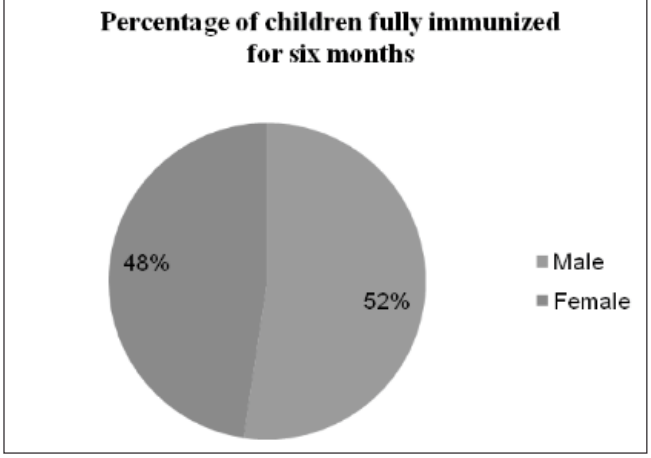
MONTH	BCG	OPV	GENEVAC	TOTAL
JANUARY	424	423	420	1267
FEBRUARY	334	336	328	998
MARCH	454	454	448	1356
APRIL	490	491	490	1471
MAY	530	531	532	1593
JUNE	530	530	532	1592

Table 3: Total number of Non BCG vaccines given from January2011- June 2011							
MONTH	**OPV**	**DPT**	**MEASLES**	**MMR**	**GENEVAC**	**Q.VAC**	**TOTAL**
JANUARY	523	242	64	67	52	182	1130
FEBRUARY	478	228	53	54	49	153	1015
MARCH	540	371	66	79	189	40	1285
APRIL	484	384	52	82	251	-	1263
MAY	527	384	56	62	254	02	1285
JUNE	616	481	70	66	289	01	1523

Table : 4. List of total vaccine preventable disease occurred from 2006-2010.						
VPD	**2006**	**2007**	**2008**	**2009**	**2010**	**Total**
Diphtheria	00	00	00	00	00	00
Measles	07	20	07	12	10	56
Pertussis	00	00	01	00	00	01
Polio	00	00	00	00	00	00
Tetanus	00	00	00	00	00	00
Tuberculosis	01	01	00	02	01	05
Hepatitis*	-	-	-	-	-	-
Mumps	00	02	01	01	00	04

*Few cases of viral hepatitis were reported in the hospital, but as it was not classified as A, B, C or D (due to lack of this information, it was excluded from the results)

Graph 1: Percentage of children fully immunized for six months



The most commonly observed VPD was measles which accounts for 56. Male children are affected more in number with measles with a *P*-value of 0.05.

DISCUSSION

In this present study the immunization coverage given to the children born in the hospital was found to be 100%. It was also observed that nearly 450-500 children were who were born in the hospital per month are immunized completely with BCG, OPV and Hepatitis B. Immunization from the second round of schedule were found to be less. Reason for decrease in the immunization coverage is generally mothers will be delivered in their mother house and later they will be vaccinating their child in their place of original residence. The study was carried out in rural place at Anantapur where many of the parents and the other care takers of the children were illiterate. Coverage of immunization in the hospital was less due to the reason that GOI also provides immunization at free of cost at every primary health care centre. Other factors could be place for immunization is too far, unaware of need to return for subsequent dose, negligence, busy in their work, lazy, forgetfulness.

For measuring the better outcome of immunization coverage in large countries like India a centralized database should be maintained in which all the data should be entered regarding the vaccines administered as per the schedule. This will prevent the fractionation in immunizing children of India. Many of the developed countries have such system. After completion of the immunization schedule for an individual child the immunization card should be maintained in the hospital and a medical certificate should be given that the child has completed the whole immunization schedule.

CONCLUSION

There was 100% adherence for BCG vaccine, OPV and hepatitis B vaccine in the first vaccination schedule of all children born in the hospital. All vaccinations are given for

free of cost for complete schedule. But the adherence rate observed from the second round of vaccination schedule was found to be less. The major reason shall be unawareness of parents or use of different health care facility for continuation of immunization. Measles was the most common VPD observed in the Anantapur region. Male children were affected more in number with measles with a *P*-value of 0.05. There were no cases of polio, diphtheria and tetanus reported in the period of 2006-2010. The limitations of the study include not identifying the occurrence of hepatitis B infection due to lack of information about type of hepatitis. It was also not sure that the patients with VPDs were properly vaccinated or not due to unavailability of their vaccination cards. Further long term field studies are needed to evaluate the reasons of occurrence of VPDs in the region.

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Comparison of the Quality of Life of Type 2 Diabetes Mellitus Patients Treated with Biguanides, Thiazolidinediones and Sulphonyl ureas

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ABSTRACT

Submitted: 17/10/2011 *Accepted: 5/11/2011*

Currently, more than 250 million people are suffering from diabetes mellitus (DM) worldwide. The purpose of this paper was to determine and compare the impact of the drug induced adverse drug reactions (ADRs) caused by biguanides, thiazolidinediones and sulfonylureas on the Health-Related-Quality-of-Life (HRQoL) in the T2DM patients. Using PubMed MeSH terms, comprehensive drug induced ADRs profiles of biguanides, thiazolidinediones and sulfonylureas were developed, separately. Furthermore, health utility values associated with each of the ADRs were determined using literature search. Quality-Adjusted-Life-Years (QALY's) measure was used to calculate and compare the impact of drug induced ADRs on HRQoL of the patients. Overall, we found that, followed by sulfonylureas and thiazolidinediones, metformin induced ADRs cause maximum decrement in the HRQoL of T2DM patients. We further found existence of both between group and within drug group differences between the magnitudes of the impact of different drug induced ADRs on the HRQoL of patients.

Keywords: Biguanides, Thiazolidinediones, Sulfonylureas, quality of life, adverse drug reactions, type 2 diabetes mellitus, quality-adjusted-life-years

INTRODUCTION AND BACKGROUND

Currently, in India, 50.8 million people are suffering from diabetes mellitus (DM).[1] By the end of the year 2030, including in India, the global prevalence of DM is expected to increase by 151%, i.e. from 171 million persons in 2000 to 336 million people in 2030.[2] This substantial increase can be largely attributed to factors such as the population growth and ageing, increased obesity and physical inactivity, and increased lifeexpectancy of people with diabetes.[3-5] Additionally, the World Health Organization (WHO) estimates that, in India, between the years 2006 and 2015, the total loss of national income from DM will be 336.6 billion International Dollars.[6]

Diabetes Mellitus is of three main types: type 1 DM (insulin-dependent diabetes), type 2 DM (non-insulin dependent diabetes), and gestational diabetes mellitus.[7] About 90-95% of all the DM patients are of the type 2 diabetes mellitus (T2DM).[7] It is a progressive disorder with an insidious onset.

The most common precipitating cause of T2DM is the beta-cell dysfunction.[8] The other metabolic disorders associated with T2DM are: chronic hyperglycemia, hepatic glucose production in the prandial state, and insulin insensitivity in fat and muscle cells.[9,11] The common risk factors of T2DM are: impaired glucose intolerance, age over 45 years, family history of diabetes, polycystic ovarian syndrome, high blood pressure, obesity, physical inactivity, low high-density lipids or high triglycerides levels, being of certain racial and ethnic groups, and women who had gestational diabetes.[12,13] Furthermore, T2DM can lead to several macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy).[14,15]

A range of classes of oral therapeutic agents exists for the treatment of T2DM, including biguanides, sulfonylureas, and thiazolidinediones. Numerous clinical trials have demonstrated that biguanides, thiazolidinediones and sulfonylureas increase the health related quality of life (HRQoL) of the T2DM patients. However, each of these therapies causes several adverse drug reactions (ADRs). These ADRs reduces HRQoL of the patients. Nonetheless, the ADRs associated with each of these drugs are of different types and occur at different rates.Therefore, in order to understand the effect of each ADRs on the HRQoL of the T2DM patients, the purpose of this paper is to determine and compare the impact of the ADRs on the HRQoL in the T2DM patients, caused by biguanides, thiazolidinediones and sulfonylureas.

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MATERIALS AND METHODS

Literature Review:

The types and rates of ADRs caused by biguanides, thiazolidinediones, and sulfonylureas were determined using the published literature. Separately, comprehensive profiles of drug induced ADRs were developed for biguanides, thiazolidinediones, and sulfonylureas. For this purpose, using the Boolean indicators "AND" and/or "NOT" in separate searches, PubMed was searched for the following MeSH terms: biguanides, metformin, thiazolidinediones, rosiglitazone, pioglitazone, sulfonylureas, glyburide, and glibenclamide. Only randomized clinical trials in English language were included. All the references cited in the above retrieved articles were also reviewed for relevance and their full-text was obtained when applicable.

Determination of Impact of ADRs on Quality of Life:

The impact of ADRs on patients HRQoL was determined using the Quality-Adjusted-Life-Year's (QALY's) measure.[16] It takes into account both the quantity and quality of life generated by any healthcare intervention. One healthcare intervention might help to increase the lifespan, nonetheless, it might also have serious adverse effects. Whereas, another healthcare intervention might not be as effective as the first one in increasing the life-span, but it might have lesser adverse effects caused by it and can therefore provide better HRQoL while the patients are alive.

While calculating QALY's, the amount of time spend in a health state is weighted by the utility score given to that health state. The utility scores can vary from 0 to 1, with 0 being worst possible health state or death and 1 being perfect health. To gain one full QALY, it takes on year of perfect health. Thus, an intervention that generates ten additional years in a health state valued at 0.50 will generate 5 QALY's.

Using QALY's, to measure the impact of ADRs on the HRQoL of T2DM patients, the rates of incidences of each of the ADRs were multiplied by 100,000 to determine the incidence of ADRs per 100,000 persons. Separately, the values of these incidences were multiplied by the respective health utility weights associated with that condition to determine the QALY's gained in that particular health condition per 100,000 persons in one year. The QALY's gained in that health condition were then subtracted from 100,000 which is the QALY's gained by 100,000 persons in one year of perfect health. The values obtained are QALY's lost due to that particular ADRs per 100,000 persons in one year. These QALY's lost per 100,000 persons in one year due to any ADR shows the impact of ADRs on the HRQoL of T2DM patients.

RESULTS AND DISCUSSION

We found several ADRs caused by biguanides, sulfonylureas, and thiazolidinediones. Based on the review, we divided these ADRs into four main categories: body as a whole events, digestive system events, cardiovascular events, and all other events (Table 2). Some ADRs, such as headache, musculoskeletal pain, and upper respiratory tract infection were common across all the drugs. On the other hand, other ADRs were limited to either one or two drug classes. For instance, hyperglycemia was limited to thiazolidinediones and cardiovascular deaths were limited to sulfonylureas and thiazolidinediones classes of drugs. Furthermore, all the ADRs were found to have different incidence rates for biguanides, sulfonylureas, and thiazolidinediones (Table 1).

Additionally, each drug induced ADR was found to have different health utilities decrements caused by them in T2DM patients (Table 2), some higher others not. For example, infections caused substantial lowering of the quality-of-life (health utility decrement=0.05(17)), whereas weight gain/loss did not had much impact on the quality-of-life of the patients (health utility decrement =0.910.[18]

Table 2: Qaly Decrements Caused by the ADRs

Health States	Health Utility weights
Body as a whole	
Accidental Injury	0.52(29)
Headache	0.77(30)
Infection	0.05(17)
Musculoskeletal/Back pain	0.70(31)
Fatigue	0.75(30)
Anemia	0.56(32)
Edema	0.99(33)
Fracture	0.34(34)
Digestive system Events	
Diarrhea	0.32(35)
Dyspepsia/Indigestion	0.54(36)
Nausea/vomiting	0.32(35)
Flatulence	0.82(37)
Abdominal Discomfort	0.82(37)
Cardiovascular Events	
Myocardial Infarction	0.64(38)
Stroke	0.50(39)
Cardiovascular deaths	0.50(40)
Other Events	
Weight gain/loss	0.91(18)
Hypoglycemia	0.55(41)
Upper Respiratory Tract infections	0.63(42)
Hyperglycemia	0.55(41)

Table 1. Incidences of ADRS from Different Therapies.

Adverse Drug Reactions	Metformin	Glyburide	Thiazolidinediones
Body as a whole			
Accidental Injury	7.3%(19)	-	7.6%(22)
Headache	4.9%(23)	8.5%(24)	10%(21)
Infection	20.5%(19)	-	5.0%(22)
Musculoskeletal/Back pain	7.2%(24)	9.8%(24)	5.5%(25)
Fatigue	5.9%(24)	5.5%(24)	3.6%(22)
Anemia	2.2%(19)	0.6%(20)	1.9%(22)
Edema	2.2%(19)	1.0%(20)	26.7%(25)
Fracture	5.1%(19)	3.5%(20)	9.3%(22)
Digestive System Events			
Diarrhea	24.8%(24)	6.1%(24)	7%(21)
Dyspepsia	7.1%(19)	4%(20)	9%(21)
Nausea/vomiting	10.4%(23)	6.6%(23)	8%(21)
Flatulence	12.1%(19)	2%(20)	-
Abdominal Discomfort	6.4%(19)	4%(23)	0.3%(26)
Cardiovascular			
Events Myocardial Infarction	-	-	8.1%(25)
Stroke	-	-	2.9%(25)
Cardiovascular deaths	-	2.3%(25)	1.9%(25)
Other Events			
Weight gain/loss	3.4%(19)	4.9%(27)	2.6%(25)
Upper Respiratory Tract infections	16.3%(28)	17.6%(28)	4.3%(22)
Hyperglycemia	-	-	3.9%(22)
Hypoglycemia	3.4%(22)	43.4%(27)	9.8%(26)

Overall, the ADRs caused by the administration of Metformin to the T2DM patients were found to have highest total decrease in HRQoL of these patients (i.e. metformin induced ADRs caused loss of 69,312 QALY's per 100,000 persons in one year) followed by thiazolidinediones (i.e. loss of 47,124 QALY's per 100,000 persons in one year) and glyburide (i.e. loss of 46,982 QALY's per 100,000 persons in one year). The details are displayed in Table 3.

In addition, each drug induced ADR impacted HRQoL differently among the three drug groups, i.e. biguanides, sulfonylureas, and thiazolidinediones. For example, the decrease in HRQoL of patients was highest due to upper respiratory tract infections induced by glyburide (i.e. loss of 6,348 QALY's per 100,000 persons in one year) followed by metformin (i.e. loss of 5,880 QALY's per 100,000 persons in one year) and thiazolidinediones (i.e. loss of 1,551 QALY's per 100,000 persons in one year).

Furthermore, we found within group differences on the impact of ADRs on HRQoL of patients within drug group. For example, incomparison to metformin induced anemia, metformin induced diarrhea caused significantly higher reduction in the HRQoL of patients, i.e. loss of 950 and 19,309 QALY's per 100,000 persons in one year, respectively.

The primary reasons for the differences in the impacts on the HRQoL due to different drugs were the differences among the ADRs incidence rates between drugs and differences in health utilities decrements due to each ADR (Table 2). For example, due to difference in rates of dyspepsia between the three drugs (i.e. metformin, glyburide, and thiazolidinediones causing dyspepsia with rates 7.1%,[19] 4%,[20] and 9%,[21] respectively), the impact on the HRQoL of patients was different, i.e. 3205, 1805, and 4062 QALY's lost per 100,000 persons in one year due to biguanides, sulfonylureas, and thiazolidinediones, respectively.

Overall, we found that, when administered, metformin induced ADRs cause maximum decrement in the HRQoL of T2DM patients. We further found existence of both between group and within drug group differences between the magnitudes of the impact of different drug ADRs on the HRQoL of patients. Nonetheless, this study has several

*TABLE 3. QALY's Gained and Lost due to Different Drugs and ADRs.

	Metformin			Glyburide			Thiazolidinediones		
Adverse Drug Reactions	**QALY's gained in ADR**	**Possible QALY's when no ADR occur**	**QALY's Lost due to ADR**	**QALY's gained in ADR**	**Possible QALY's when no ADR occur**	**QALY's Lost due to ADR**	**QALY's gained in ADR**	**Possible QALY's when no ADR occur**	**QALY's Lost due to ADR**
QALY'sBody as a whole Accidental									
Injury	3853	7300	3447	-	-	-	4012	7600	3588
Headache	3812	4900	1088	6613	8500	1887	7780	10000	2220
Infection	1191	20500	19309	-	-	-	291	5000	4710
Musculoskeletal/Back pain	5099	7200	2101	6940	9800	2860	3895	5500	1605
Fatigue	4472	5900	1428	4169	5500	1331	2729	3600	871
Anemia	1250	2200	950	341	600	259	1080	1900	820
Edema	2196	2200	4	998	1000	2	26657	26700	43
Fracture	1777	5100	3323	1220	3500	2280	3241	9300	6059
Digestive System Events									
Diarrhea	8149	24800	16651	2004	6100	4096	2300	7000	4700
Dyspepsia	3895	7100	3205	2195	4000	1805	4938	9000	4062
Nausea/vomiting	3417	10400	6983	2169	6600	4431	2629	8000	5371
Flatulence	10028	12100	2072	1658	2000	342	-	-	-
Abdominal Discomfort	5304	6400	1096	3315	4000	685	249	300	51
Cardiovascular Events									
Myocardial Infarction	-	-	-	-	-	-	5256	8100	2844
Stroke	-	-	-	-	-	-	1453	2900	1447
Cardiovascular deaths	-	-	-	1171	2300	1129	967	1900	933
Other Events									
Weight gain/loss	3124	3400	276	4504	4900	396	2390	2600	210
Upper Respiratory Tract infections	10420	16300	5880	11252	17600	6348	2749	4300	1551
Hyperglycemia	-	-	-	-	-	-	2181	3900	1719
Hypoglycemia	1901	3400	1499	24269	43400	19131	5480	9800	4320
TOTAL	**69888**	**139200**	**69312**	**72818**	**119800**	**46982**	**80277**	**127400**	**47124**

=*All QALY ' s gained or lost are per 100,000 persons in one year

limitations. First, in our results, we did not include the improvements in the HRQoL of patients due to administration of biguanides, thiazolidinediones, or sulfonylureas. The primary reason for this is that the purpose of our study was to determine the impact of drug induced ADRs on the HRQoL of patients, not to determine the overall impact on the HRQoL. Second, our study is limited to biguanides, thiazolidinediones, and sulfonylureas. In our analysis, we did not include other T2DM therapeutic agents such as, diphenyl peptidyl-4 (DPP-4) inhibitors, glucagon like peptides-1 analogues, and acarbose. Third, the results of this study are based on published literature review, not primary data. These studies were conducted in different settings, like in different countries and on different populations, and, therefore, pooling of results of such studies can lead to uncertainty in the results.

CONCLUSION

We compared the impact of biguanides, thiazolidinediones, or sulfonylureas induced ADRs on the HRQoL of T2DM patients. We conducted a systematic literature review and developed the drug induced ADRs profiles of biguanides, thiazolidinediones, and sulfonylureas. We further determined the health utility decrements caused by these ADRs. Furthermore, the results of this study show that metformin induced ADRs cause maximum reduction in the HRQoL of T2DM patients. This was found to be followed by thaizolidinediones, and glyburide induced ADRs.We further found both between group and within group differences in the impact of drug induced ADRs on the HRQoL of T2DM patients for biguanides, sulfonylureas, and thiazolidinediones.

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Occurrence of fixed Drug Eruptions in a Tertiary Care Hospital: Case Reports

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Submitted: 10/1/2012 *Accepted: 3/2/2012*

ABSTRACT

Fixed drug eruption (FDE) is a unique pattern of cutaneous drug reaction, characterized by skin lesions that recur at the same site or sites each time the drug is administered. Acute lesions appear as round or oval, sharply marginated, erythmateous plaques that sometimes develop central bullae. They are generally under reported with different rates in different health care systems. The present case studies were carried out in the department of dermatology in a multidisciplinary tertiary care government hospital for one month from June 12th to July 12th, 2011 by the Department of Pharmacy Practice. The cases were recorded and subjected to descriptive analysis. We observed four cases with FDE possibly induced by Isoniazid, Diclofenac, Primaquine, Ciprofloxacin and Carbamazepine. Clinical patterns and drug causing cutaneous ADRs are similar to other researchers. The case studies highlighted that above medications belongs to the group of drugs that can induce fixed drug eruption.

Keywords: Fixed Drug Eruptions, Skin rashes, Pruritus, and Hypersensitivity

INTRODUCTION

Fixed drug eruption (FDE) is a unique pattern of cutaneous drug reaction, characterized by skin lesions that recur at the same site or sites each time the drug is administered. Acute lesions appear as round or oval, sharply marginated erythmateous plaques that sometimes develop central bullae .The lesions are usually found on the lips and genitalia, although any skin or mucosal surface may be involved.[1,2] The eruption usually occurs within hours of administration of the offending agent and resolves spontaneously without scarring after few weeks of onset, usually with residual post inflammatory pigmentation. The most frequently implicated drugs are sulphonamides, tetracycline, salicylates and barbiturates.[3] It is of utmost importance to recognize drugs that induce these severe reactions and to identify the early symptoms signalling such a reaction, because prompt withdrawal might decrease mortality.[4] The present case studies were carried out in the department of dermatology in a multidisciplinary tertiary care government hospital for one month from June 12th to July 12th, 2011 by the Department of Pharmacy Practice.

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CASE REPORT 1

A 25-year-old woman was admitted to the hospital complaining of skin rashes. The patient was a known case of epilepsy disorder for which medications (CBZ 200mg) were being used. Unfortunately, she noticed to develop skin rashes in lower and upper extremities as shown in the figure 1. The rash was associated with round lesions with blisters in thigh and lumbar region. The patient was found to be suffering with low grade fever. The laboratory investigations showed: Haemoglobin 9 g/dL, platelet count 120,000/cmm, and WBC 4,000/cmm. Neutrophil 62%, lymphocyte 14%, and serum electrolytes-normal, serum creatinine 165 µmol/L, serum albumin 2 g/dL; serum calcium and serum magnesium were normal. Urine culture showed no growth. Reticulocyte count was 12%. After admission in the hospital CBZ 200 mg BD was replaced by prescribing phenytoin 150mg OD, (cause for FDE) in addition to it, hydrocortisone 75mg/topical TID, chlorpheniramine maleate 5mg/OD/bed time, paracetamol 500mg/TID and emollient cream were prescribed. I.V fluids were given as a supportive therapy. After 3weeks of the treatment, skin lesions started fading, patient's general well-being was improved with no fever, relief of body pain. She was discharged on medication and asked to consult the physician regularly till she becomes normal without any manifestations of FDE.

CASE REPORT 2

A 33-year-old woman presented with malaria and erythematous rashes over the face as shown in figure 2. She had experienced sore throat, and skin lesions appeared on cheeks and nose. The preceding day, she had been diagnosed with high fever and body pain and was administered with IV diclofenac 50 mg BD and Primaquine 15mg/day. She did not take any other medication, or nutritional supplement before being treated with antimalarial drug. On repeated 3days of administration of primaquine, she developed erythematous macules with darker purpuric centers over which flaccid blisters and a sheet-like epidermal detachment had developed, especially on her face and nose regions. Because a severe form of drug eruption was strongly suspected, the patient was hospitalized on the same day. After admission, the erythema and blisters further increased and extended rapidly over the whole body, involving >20% of the body surface area, allowing definitive diagnosis of FDE. The center of each erythema became dark red in color, followed by blister formation. The patient's temperature was high, but other vital signs were stable. Laboratory findings were normal upon admission, except for elevated erythrocyte sedimentation rate (ESR) (48 mm/h; reference range 0–15), Urine, blood, and throat cultures were negative. Electrocardiogram, abdomen ultrasonographic examination, and chest X-rays were normal. Oral prednisolone 60 mg daily, arsenuate 100 mg BD and supportive topical therapy were given. Ringer's lactate infusion of 2000 mL/day, parenteral nutrition were also started. During the first week of the therapy, few new lesions continued to appear. The signs and symptoms of FDE progressively resolved in 10 days, after which prednisolone dose was gradually tapered to discontinuation. Following discharge, there was no recurrence of the symptoms, and the skin lesions healed without any scars.

CASE REPORT 3

A 40 year old woman was admitted to the hospital with skin rashes all over the body ruptured leaving raw area like erosion and ulceration as depicted in figure 3. Patient was a known case of tuberculosis and had suffered with cough and fever for 7 days and she was administered with anti-tuberculosis drug and paracetamol 500mg (OTC drugs) for 7 days. Upon investigation, the patient's condition was confirmed to be isoniazid induced fixed drug eruption. Laboratory investigations revealed elevated WBC count and ESR. The patient's condition improved with antihistamine drugs, systemic steroids and supportive medications.

CASE REPORT 4

A severe form of eruptions over the trunk with pigmented lesions and rashes was presented in a female patient of age 21 years as shown in the figure 4, who was regularly on anti-tubercular drugs for one month, prescribed by a pulmonologist. Her laboratory results showed: RBC 3.4K/cmm, Hb 10g/dl, HCT 32%, erythrocyte sedimentation rate (ESR) 11 mm/hour. She was admitted to the hospital and treated with hydrocortisone 75mg/topical TID, chlorpheniramine maleate 5mg/OD/bed time, and IV fluids were given as supportive therapy. An extensive literature search revealed few earlier reports of Isoniazid induced FDE.

DISCUSSION

ADRs are a threat to patient's health and quality of life, and they can cause significant affect to the healthcare systems in developing and developed countries. Recently, the incidence of ADRs has increased significantly and the importance of this phenomenon will obviously vary in different healthcare system.[6,7] The present study examined ADRs in the department of dermatology in a tertiary care government hospital which is attached to medical college. FDE is characterised by sudden onset of round and/or oval, oedematous dusty-red macules and plaques on the skin and/or itching and the re-appearance of the lesions over the previously affected area when the offending agent is reused.[8,9] Histologically, there is basal hydropic degeneration, pigmentary incontinence, upper epidermal keratinocyte necrosis, dermal oedema, vasodilatation and perivascular inflammatory cells (lymphocytes, neutrophils, histocytes, mast cells).[10-14] The observations of the present study implicated Primaquine, Isoniazid, Carbamezepine and NSAIDS. As FDE are sometimes confused with multiple venereal diseases, it is of utmost importance for all the medical specialists to identify FDE clinically by doing the provocation test so that these cases are not missed.[15] Eariler studies reported that fixed drug eruptions seen, mostly due to NSAIDS,[16] Co-trimoxazole,[17] Cephalosporin, Carbamazepine and oral amoxicillin.[18] In our present study, we found isoniazid induced fixed drug eruption. Our results were similar with the study conducted by Noel M.V, et al[19] who reported that drugs such as anti-epileptics mainly phenytoin and carbamazepine were responsible for the majority (44%) of the ADRs which strengthens our study findings in case of carbamazepine.

Fig.1: Erythematous round lesions of reddish, featuring blisters on thigh and back

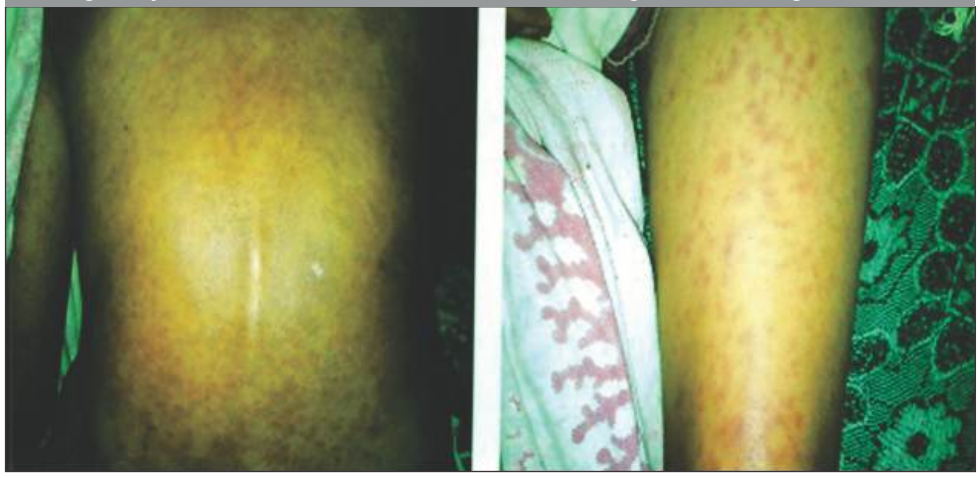


Fig.2: Round, black lesion on hand

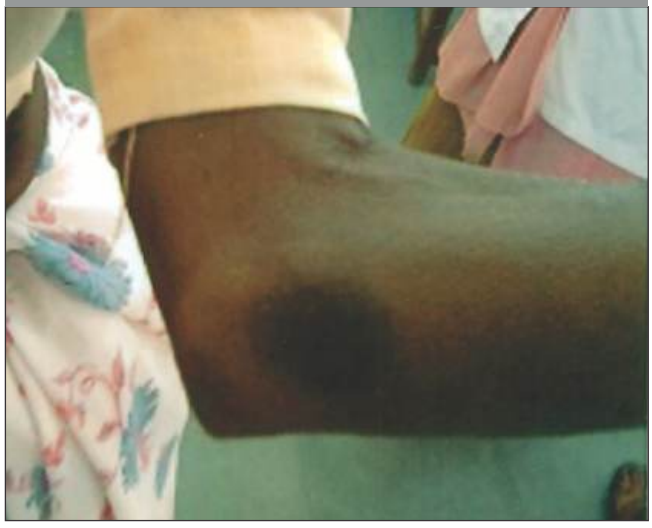


Fig.3: erosion and ulceration

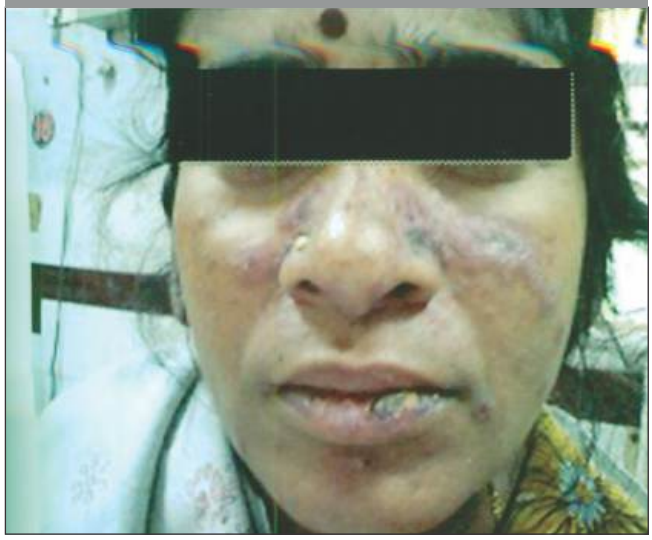
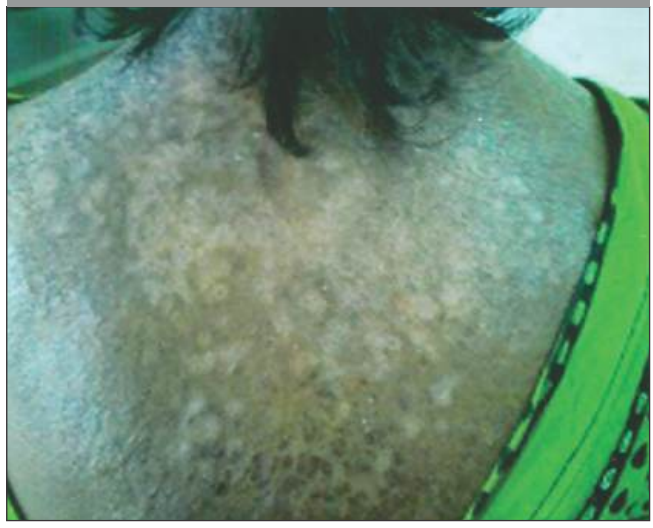


Fig.4: Pigmented lesions over the trunk



CONCLUSION

It can be concluded that the clinical patterns and the drugs causing fixed drug eruptions are remarkably similar to those observed in other countries except with minor variations.

ACKNOWLEDGEMENTS

We are grateful to Dr. E. Ashok kumar Ex. Superintendent KMC/ MGM hospital, Warangal without whose inspiration and support this work would not have been possible.

The authors are very much thankful to the patients for their co-operation to carry out this study and take the photographs of their manifestations. We also extend our thanks to Principal, Vaagdevi College of Pharmacy, Warangal, for their kind support.

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