

Comparison of days lost due to disability and Karnofsky performance status in burden of diclofenac induced adverse drug reactions

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ABSTRACT

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Basic objective of this study was to find out the benefit of Days Lost due to Disability (DLD) over Karnofsky Performance Status (KPS) in detecting the burden of Adverse Drug Reactions (ADRs) of diclofenac tablet in clinically recovered male and female groups. This was a cohort study done in 1000 prescriptions of diclofenac tablets to find out the burden of its ADRs in a popular pharmacy in Kasaragod District, Kerala, India. Stratified randomized sampling was done to male and female strata to compare DLD and QoL using KPS. DLD considers incidence and duration of ADRs in addition to the QoL component, disability weight to give a more complete burden of disease score. For cutaneous reaction, female scored 61 DLD over 26 in male. For peptic ulcer female scored 40 over 37 in male, even though males had higher incidence. Female suffered from higher DLD in other ADRs too. DLD was found to be more complete and sensitive tool than KPS QoL tool in calculating the burden of ADRs due to diclofenac tablet. Female gender is a contributing factor of increased burden of ADRs.

Keywords: peptic ulcer, diclofenac, ADR, female

INTRODUCTION

Burden of disease or illness could be effectively calculated by disability adjusted life years (DALY) or quality of life (QoL) tools. DALY has two components i.e., years of life lost (YLL) and years lost due to disability (YLD). YLD assess burden of disease or illness in survived casualties. While studying burden of illness in clinically recovered cases of adverse drug reactions (ADRs), most of the times the suffering of ADRs lasts few days. So rather than calculating it for years, as it is in YLD, it could be calculated in days, thus becoming days lost due to disability (DLD). In this study we plan to assess the sensitivity of DLD by comparing with Karnofsky performance status (KPS) in gender variation in the burden of ADRs caused by diclofenac tablet.

Burden of ADRs were commonly assessed by the decrease in quality of life. Days Lost due to Disability (DLD) which is part disability adjusted life years is a more advanced tool to calculate burden of ADRs than Karnofsky Performance Status. DLD is a new tool introduced by the authors. It could be calculated for 100 or 1000 population. The key limitation is that it could be calculated only for clinically recovered ADRs.

QoL or performance status is one of the commonly used clinical outcome research tools in many of the illness. There are general QoL tools and disease specific tools. Compromise in QoL is used to measure the influence of disease on health when a medical (mainly pharmaceutical) and/or surgical intervention is used, improvement in QoL could be measured to study the influence of treatment of disease. At the same time the medicines also could cause ADR and compromise further on QoL. Practically it becomes very difficult to separate the compromise on health happened due to disease and ADR on an observational study.¹

DLD is a more complete tool to assess burden of disease or ADRs by calculating the incidence, duration and disability weight (DW). DLD have a component of QoL in the form of DW.² DW could be measured in a scale between 0 to 1, where 0 becomes perfect health and 1 becomes the worst.³ KPS is a widely used QoL or performance status tool for many decades in different disease settings. KPS is a very structured questionnaire scoring 0 to 100, where 0 becomes death and 100 becomes perfect health.⁴ KPS results could be easily converted to the scale of 0 to 1 and then 1 - KPS gives DW. DW also could be measured in an analogue scale.

While measuring QoL, we had experienced that subjective measures dominate over objective measures. Perception of the patients on their health is an important factor of their QoL. Generally females consider ill health more importantly than males. They shall be more cautious in prevention and

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management of ADRs. This could be one of the reasons when an ADR happens, it shall subjectively affect the quality of life to a higher extent in female.⁴

In addition to the QoL component i.e., DW, DLD measures the incidence rate and duration of illness/ADR in the cohort. Thus, the usefulness of DLD over QoL in assessing the burden of ADRs could be measured with an example of gender influence in ADRs of diclofenac tablet.³ If DLD is found to be more sensitive in than QoL, it could be further studied in future in comparison with other QoL tools, epidemiologically different study groups and different ADRs of different medicines. The findings will have anticipated generalizability to use DLD in more clinical settings. And NSAIDs including diclofenac is one of the top groups of medicines to cause ADRs.⁵⁻⁶ DLD is a new tool which was not used previously to measure the burden of ADRs in clinically recovered patients. DALY was commonly used by World Health Organization in calculating the burden of diseases or illness. DLD evolved with minor changes in one of the component of DALY. And it is a new discovery of a valuable tool in pharmacovigilance and drug safety to quantify the burden of ADRs which was difficult to be studied by the otherwise commonly used QoL tools.

METHODS

The study was done in a popular pharmacy in Kasaragod District, Kerala, India. Stratified random sampling was used to male and female groups who consume diclofenac tablets. Equal number of males & females (500 each) were enrolled in the study strata (groups) based on a total of 1000 prescriptions of diclofenac. ADRs were reported based on the diagnosis of the doctor, Naranjo Algorithm for causality assessment and finally filling out the ADR reporting form by Central Drugs Standards Control Organization, India. Our study focused on the influence of gender on ADRs, not on the ailments required to be treated with NSAIDs. The differences obtained in each ADRs in QoL and DLD was compared numerically in male and female groups. Ethical committee approval was taken and confidentiality of the subjects maintained.

Calculation of DLD

$$DLD = I \times DW \times L$$

I is the number of incidences of disease or injury (ADR)

DW is the disability weight and L is the average duration of disease or injury in days up to clinical recovery or death. (In case of YLD it is years instead of days).²

Inclusion criteria

Patients taking diclofenac tablets were selected to the male and female groups.

Patients in the age range of 18 to 64 were included in the study.

Patients with possible, probable, or definite causalities with ADRs of diclofenac were selected for calculation of DLD.

Exclusion criteria

Those who were prescribed with different NSAIDs, corticosteroids or other potential ulcerogenic medications in the past one month were excluded.

Those who smoke on an average 10 or more cigarettes per day or consume on an average 2 or more alcoholic drinks per day were excluded.

Unrecovered, and irreversible organ failure patients from their ADRs were excluded.

Rare ADRs are excluded as they were not enough in number to compare between groups.

Geriatric, pediatric, pregnant and breastfeeding population were excluded.

Patients who were unwilling or unable to understand the study questions and/or those who are not in a position (mentally or socially compromised) to provided competent answers were excluded.

RESULTS & DISCUSSION

It was found in many studies that females have more incidences of ADRs compared to males. But diclofenac induced peptic ulcer disease (PUD) was an exemption. Incidence of diclofenac induced PUD was slightly higher in males than females. But the difference was not statistically significant ($p > 0.05$). (Table 1)

Many of the literature suggest that PUD is higher in males than females. The major reason could be smoking. Just being male was not found to be a significant factor in the study population who develop diclofenac induced PUD. Female gender could be a contributing factor of increased burden of ADRs ($p < 0.05$). There are many suggestions why females suffer more with ADRs. There are suggestions about the lower mean body weight when compared to males, hormonal and physiological influences etc. In the case of diclofenac, one of the major reasons shall be increased incidence of arthritis and other inflammatory conditions in females.⁷ (Table 2)

QoL was not showing a significant difference in male and female groups. But while calculating DLD, the burden on health by many of the ADRs where showing statistically and clinically significant differences between male and female groups. The study results reinforce many of the past research findings that female gender is a contributing factor to the burden of ADRs. Additionally here we could state that DLD is a more complete and sensitive tool than KPS QoL to measure burden due to ADRs. Even though there were higher incidences of PUD ADRs in males, females scored a higher

Table 1: DLDs in diclofenac tablet induced ADRs in males and females

	I (Incidence)	L (Disability Weight)	DW (Duration)	DLD	I (IxLxDW)	L	DW	DLD
Rash, urticaria, dermatitis	32	3.9	0.21	26	46	5.3	0.25	61
Peptic ulcer	18	6.9	0.3	37	16	7.8	0.32	40
Dizziness, drowsiness, depression, insomnia, anxiety	19	2.6	0.07	04	32	3.8	0.12	15
Oliguria, protienuria	16	3.9	0.06	04	21	4.2	0.06	05
Edema, hypertension	15	4.6	0.1	20	822	5.4	0.17	20

I is the number of incidences of disease or injury (ADR), DW is the disability weight and L is the average duration of disease or injury in days up to clinical recovery or death.

Table 2: KPS QoLs in diclofenac tablet induced ADRs in males and females

ADRs	QoL	
	Males	Females
Rash,urticaria, dermatitis	79	75
Peptic ulcer	70	68
Dizziness, drowsiness, depression, insomnia, anxiety	93	88
Oliguria, protienuria	94	94
Edema, hypertension	88	83

DLD due to longer duration and higher DW with the ADR. This example further shows the advantage of DLD over QoL.

Incidence and burden of ADRs are generally high in females as per most of the literature. Our study findings are consistent with the knowledge that women suffer more with ADRs. Diclofenac induced peptic ulcer disease was an exception, as the incidence was higher in males (not statistically significant) but burden of it on health was higher in females due to longer duration and higher disability weight.

Limitations of the study include that, the pharmacy was busy most of the times and there were limited private counseling facilities/opportunities to discuss with patients in full confidence. Also we doubt the completeness of the study population to represent the people of the community, as many of the patients who consume diclofenac tablets were not physically available or not cooperating; we couldn't also claim to cover all patients presented to pharmacy were screened for the study. So the incidence of ADRs reported in the study lacks precision and the skills of pharmacists in identifying ADRs could be used efficiently preferably with the help of a doctor, in community pharmacy there is less

scope for making a consensus decision. These factors shall decrease the number of ADRs reported. But this study strongly points out the advantage of DLD over KPS QoL (which is one of the most convenient one) in measuring the burden of ADRs of diclofenac.

CONCLUSION

As a matter of fact, female suffer from ADRs more than male. This statement was supported by our findings on increased DLD on ADRs of diclofenac in female. While considering the QoL, the KPS tool was not as sensitive as DLD in finding the gender variation in the burden of ADRs. There could be other QoL tools which are more specific and more sensitive. But it is interesting to notice that DLD is an advanced tool which additionally considers the incidence and duration with the QoL component (DW). So DLD gives a more complete measure of burden of ADRs due to diclofenac tablet. In evaluating the burden of clinically recovered ADRs it is more complete and sensitive tool for the purpose.

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