Review Article

Pharmacovigilance and Adverse Drug Reactions Reporting in Bhutan: A Review of Current Status

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ABSTRACT

Bhutan is a small country located in the eastern Himalayas situated between China and India. Bhutan's road to modern health system began in 1961. Essential Drugs Program under the Ministry of Health introduced pharmacovigilance to the pharmacy professionals before the establishment of the Drug Regulatory Authority. Legislations and relevant guidelines for pharmacovigilance activities are developed and health professionals are sensitized on adverse drug reaction reporting system. Bhutan became a member to the World Health Organization Program for International Drug Monitoring in 2014. National Pharmacovigilance Center takes necessary regulatory actions based on the degree of adverse reactions reported. Pharmacovigilance centers set up in five major hospitals collect, assess and report adverse drug reactions. Currently, only healthcare professionals are involved in reporting of adverse drug reactions. Adverse drug reaction reports are assessed and uploaded through VigiFlow database. Pharmacovigilance in Bhutan is still at its nascent stage and a lot more lies ahead for improvement. More health professionals must be trained to promote adverse drug reaction reporting.

Key words: Adverse Drug Reactions, Pharmacovigilance, Drug Regulatory Authority, Pharmacovigilance centers, Bhutan.

INTRODUCTION

Bhutan is a small country located in the eastern Himalayas and landlocked between China and India. The total population of Bhutan projected for 2017 is 779, 666.[1] Bhutan's road to modern health system began in 1961.[2] Health care is provided free by the Government as guaranteed under the Constitution.[3] The 86th National Assembly of Bhutan in 2003 enacted the Medicines Act of the Kingdom of Bhutan. The Drug Regulatory Authority (DRA) was established in May 2004 to implement the Medicines Act to regulate and ensure the quality, safety and efficacy of medicinal products in the country.

Systematic international efforts to address drug safety issues did not exist until the thalidomide disaster in 1961.[4] The Sixteenth World Health Assembly resolution emphasized on the need for early action on dissemination of information on adverse drug reactions (ADRs) quickly which later led to inception of World Health Organization (WHO) Pilot Research Project for International Drug Monitoring in 1968.[5] The purpose of the project was to develop a system for detecting adverse effects of medicines. The WHO technical report 1972 was released following a consultation meeting held in 1971.[6] Since then, pharmacovigilance has remained dynamic[7] and has progressed so much over the last few decades.

Unlike the developing countries, Bhutan's pharmacovigilance is still a new concept in the Bhutanese context. ADRs were reported as early as 2004 but proper reporting procedure was instituted only after 2008. Today, DRA functions as the National Pharmacovigilance Center (NPC) for Bhutan[8] and there are five pharmacovigilance centers being set up in few major hospitals.

This article documents the existing pharmacovigilance system in Bhutan. This is the first such article on the subject and

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can serve as a basis for future research on this subject in Bhutan. Information was sourced from review records, records of minutes, Google Scholar, Ministry of Health website (http:/www.health.gov.bt/) and Drug Regulatory Authority website (http:/www.dra.gov.bt/). Medicines Act of the Kingdom of Bhutan and Bhutan Medicines Rules and Regulation were also referred.

Importance of Pharmacovigilance

The WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem."[9] Pharmacovigilance is a term that describes the processes for monitoring and evaluation of ADRs.[4] Monitoring and evaluation of drug safety forms an important component of an effective medicines regulation. The scope of pharmacovigilance is getting expanded to include herbals, traditional and complementary medicines, blood products, biological, medical devices and vaccines.[6]

During the clinical trial studies of a medicine, not much is known about the serious and rare effects of a drug. The limitations are also that only a limited number of carefully selected subjects are used for the safety and efficacy studies for most of the medicines.[4] There is a need for more information about the use of medicines in special population groups like children, pregnant women and the elderly. Post marketing surveillance is an important area but relies so much on spontaneous and voluntary reporting of ADRs by the healthcare professionals (HCPs).[10] In most cases, adverse effects of medicines are known and studied only after the medicines are put onto the market and used by the public. Pharmacovigilance is set to play a crucial role owing to the increasing numbers of medicines available in the market.[7]

Pharmacovigilance ensures that doctors have enough information to decide a medicine of choice for their patient[11] as doctors will be aware of ADRs experienced by their patient. In fact, pharmacovigilance and drug safety issues are relevant for any person who avails healthcare services in any ways.[4] Pharmacovigilance begins from the premarketing of new drugs and goes till the post marketing of drugs.[12] Hence, it is essential to have in place, mechanisms for monitoring and evaluation of ADRs to prevent or minimize harm to the patients and improve public health.

Pharmacovigilance and ADR Reporting System

Bhutan did not have proper pharmacovigilance system until the establishment of DRA in 2004. Essential Drugs Program under the Ministry of Health introduced pharmacovigilance to the pharmacy professionals through sensitization programs and workshops.[13] ADR reporting started only after the establishment of the DRA. Pharmacovigilance centers are instituted in three hospitals, Jigme Dorji Wangchuck National Referral Hospital, National Traditional Medicines Hospital and National Veterinary Hospital for allopathic, traditional and veterinary medicines respectively.

The National Pharmacovigilance Center is instituted at the Drug Regulatory Authority.[8] In December 2014, Bhutan NPC became an official member of WHO International Drug Monitoring Program.[14-15] Mongar Regional Referral Hospital and Gelephu Regional Referral Hospitals were identified as regional pharmacovigilance centers for the eastern and central regions respectively.[16] Guidelines for ADR reporting are developed. Few DRA officials availed training on pharmacovigilance conducted by WHO collaborating centers in the Region.

Pharmacovigilance centers collect, assess ADR reports and upload in the VigiFlow, a database managed by WHO Uppsala Monitoring Center. Serious ADR reports are sent to NPC. NPC creates awareness on medicines safety and disseminate information about benefit, harm and risk of medicines to practitioners, patients and the public besides taking necessary regulatory measures to prevent and reduce ADRs. National Pharmacovigilance Committee reviews standards and procedures for pharmacovigilance activities and recommend regulatory measures. However, there is no national data base for ADR reports.

DRA has created a separate Division responsible for all pharmacovigilance activities in the country. Increasing support from the government and external donor agencies underscored the importance of pharmacovigilance and drug safety. Bhutan currently focuses on training ofHCPs to promote ADR reporting as several studies[17-18] reported that education and training is crucial in improving ADR reporting. The attitude of HCPs towards ADR reporting is critically important.[17] First ever workshop on veterinary pharmacovigilance was conducted in 2018. Pharmacovigilance guidelines for different categories of medicines are being developed and relevant personnel involved trained and sensitized. ADR reporting in Bhutan has improved over the years as HCPs are trained on ADRs and reporting.

Trends of ADR Reporting

ADR reporting is central to effective pharmacovigilance system for any medicines regulatory authorities. The spontaneous reporting of ADRs is considered as the foundation of post marketing surveillance of drug safety.

The main aim of spontaneous reporting is the early detection of signals of new, rare and serious ADRs.[19] Currently, ADRs are reported only by the HCPs in Bhutan.

The process of ADR reporting is shown in the Figure 1. ADR reports are crucial in preventing and reducing harm to the patients but under-reporting is an existing problem in all the countries worldwide.[20] About 5% of all hospital admissions have occurred due to ADRs[18, 21-23] and ADRs are reported as the top 10 leading causes of mortality in some nations.[4] Even in Bhutan, under-reporting of ADRs is a challenge.[15] There are also differences in the knowledge about ADRs among the HCPs in Bhutan. A study conducted in Bhutan reported that Bhutanese doctors and pharmacists have better knowledge of ADRs than nurses and traditional medicine practitioners, while the knowledge of ADR reporting is low for all healthcare professionals.[15]

Jigme Dorji Wangchuck National Referral Hospital was the first hospital to report ADR in 2007 and has reported the highest number of ADRs from 2012-2017. ADR reporting has increased starting 2012 with many hospitals contributing in ADR reporting (Table 1).

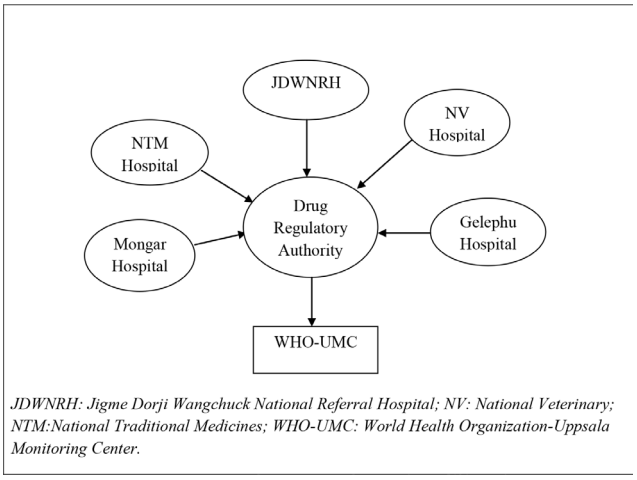
Table 1: ADR Reporting by Hospitals.

	Year						
Name of Hospital	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
Bumthang Hospital	0	0	0	0	1	6	7
Gelephu Hospital	0	0	0	4	14	33	51
JDWNRH*	3	2	3	13	34	30	85
Lheuntse Hospital	0	0	0	0	2	3	5
Monggar	0	1	0	6	41	30	78
Phuntsholing Hospital	0	0	0	2	1	3	6
Paro Hospital	0	0	1	0	2	5	8

*Jigme Dorji Wangchuck National Referral Hospital.

CONCLUSION

Pharmacovigilance is essential for any medicines regulatory system to ensure safety and efficacy of medicines for public health yet pharmacovigilance in Bhutan is still at its nascent stage. Pharmacovigilance system should be strengthened and ADR reporting improved to detect even the rarest adverse drug reactions. Technical capacity of the pharmacovigilance centers must be developed. HCPs especially the new ones must be trained on ADR reporting. Relevant authorities must explore to include curriculum on pharmacovigilance in the medical and allied health science courses.



JDWNRH: Jigme Dorji Wangchuck National Referral Hospital; NV: National Veterinary; NTM:National Traditional Medicines; WHO-UMC: World Health Organization-Uppsala Monitoring Center.

Figure 1: ADR reporting structure

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ABBREVIATIONS

DRA: Drug Regulatory Authority; ADR(s): Adverse Drug Reaction(s); **WHO:** World Health Organization; **NPC:** National Pharmacovigilance Center; **HCPs:** Healthcare Professionals

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUMMARY

Essential Drugs Program under the Ministry of Health looked after the pharmacovigilance program until the establishment of the DRA in 2004. Today, legislations and guidelines are available for ADR reporting and health professionals periodically trained on ADR reporting system. Bhutan is a member to the World Health Organization Program for International Drug Monitoring and ADR reports are uploaded in the VigiFlow database. Pharmacovigilance centers based in hospitals collect, assess ADRs and report to NPCs. NPCs disseminates information on drug safety to the prescribers, patients and public besides taking necessary regulatory measures based on the degree of adverse reactions reported. Although the healthcare professionals are only the one reporting ADRs currently, the number of ADRs reported has

increased over the years. However, pharmacovigilance in Bhutan is need to be strengthened and more number of health professionals must be trained to encourage ADR reporting.

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