Strengthening the Pharmacovigilance Programme in Nepal

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ABSTRACT

The aims of pharmacovigilance are early recognition of previously unknown adverse drug reactions (ADRs), recognition of changes in frequency of known ADRs, identification of risk factors and mechanism of ADRs, quantitative analysis of benefit/risk ratio and dissemination of safety information for rational drug prescribing and regulation. The pharmacovigilance programme in Nepal is a recent development. The Department of Drug Administration (DDA) took the initiative to set up a pharmacovigilance program in 2002; however, it was initiated systematically only after two years. DDA acts as the National Pharmacovigilance Centre (NPC). It collects ADR case reports from the Regional Pharmacovigilance Centre (RPC). Currently there are six RPCs operating in the country. The current reporting trends suggest high under-reporting of suspected ADRs. This paper is a review of those studies which are focused on pharmacovigilance and healthcare professionals' perspectives on ADR reporting in Nepal. It also recommends the possible ways to improve the ADR reporting based on the context of Nepal.

Keywords

Adverse drug reaction; pharmacovigilance; healthcare professionals; knowledge; attitudes

Background

The thalidomide tragedy of 1960s was a disastrous incident that shed light on the lapses of drug safety assurance. It opened the eyes of drug regulators as well as other concerned bodies to establish a way to ensure drug safety, especially after the drug becomes available in the market[1, 2].

The term pharmacovigilance is a combination of the Greek word "Pharmaco" which means medicine and the Latin word "Vigilantia" which means vigilance or watchfulness[3]. Professor Bernard Begaudh as described pharmacovigilance as "a discipline involving detection, evaluation and prevention of undesirable effects of medicines"[4]. The World Health Organization (WHO) has defined pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems"[5]. Pharmacovigilance is not

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only confined to modern medicines; it also includes herbal, complementary and alternative medicines, blood products, biologicals, medical devices and vaccines[6]. Pharmacovigilance aims for early recognition of previously unknown adverse drug reactions (ADRs), recognition of changes in frequency of known ADRs, identification of risk factors and mechanism of ADRs, quantitative analysis of benefit/risk ratio and dissemination of safety information for rational drug prescription and regulation.

The specific aims of pharmacovigilance as focused by WHO are to [6]

• improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions,

•improve public health and safety in relation to the use of medicines,

•contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and

•promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

There is always insufficient drug safety assurance data generated as a part of clinical trials. It is near unattainable to be able to rule out all possible adverse effects of the drug which may occur in the real world. In most cases, it is beyond the scope of clinical trials. The major limitations of clinical trials are[7]:

•animal testing is not enough to rule out human safety,

•limitation of time frame and only selected patients are exposed, normally without any complications, and

•exposure of limited human subjects, in most of the cases less than 5000 subjects which is only favorable to detect the more common types of ADRs.

In reality, clinical trials cannot provide information on rate or very rare types of ADRs. A large sample size is required to detect such types of ADRs, which is normally calculated by "rule of 3" [8]. For example, to find out the incidence of 1 in 10,000, at least 30,000 subjects need to be treated with a drug. If we want to find out the incidence of 1 in 100,000, the sample size is almost beyond the scope of clinical trials. Therefore even well-designed clinical trials cannot provide overall drug safety information. Hence, post marketing surveillance is necessary to ensure the overall safety of the drug. Drug safety issues are dynamic; a drug that was highly beneficial in the past can develop a high potential for harm later. There are examples of many drugs withdrawn from the market because of drug safety issues. Pharmacovigilance is a critical source of information, which guides regulators on whether the drug should continue in the market, be restricted in usage, or in the worst possible scenario, withdrawn from the market. Rosiglitazone was the latest drug withdrawn from European market due to cardiovascular safety concerns; however it is still being used in US market with high restriction[9].

In any research involving human subjects, research ethics have to be taken into account. Research ethics highlight the core values of the "Declaration of Helsinki" and the "Common Rule", which basically focuses on individual autonomy, well-being of individual research subject, distribution and equality of opportunity and burdens in any conduct of research[10]. The protection prioritizations under the Common Rule are provision of an Institutional Review Board (IRB) to review research protocols and informed consent of each individual research subject. The guidelines issued by Council for International Organizations of Medical Sciences (CIOMS) for epidemiological studies also highlight the requirement for voluntary informed consent[11]. But in case of pharmacovigilance research, obtaining informed consent is often difficult. An individual research subject may not be available because of death or discharge from hospital. In the case of sourcing a hospital database, large populations would have to be asked for informed consent, which makes research expensive. So, strict requirement of informed consent in case of pharmacovigilance research may lead to selection bias and reduced response rates, which ultimately leads to invalid results.

Methods

We conducted a search on the Pubmed database and Google Scholar using search terms such as pharmacovigilance, adverse drug reaction, adverse drug reaction monitoring combined with programmes in Nepal. The references which were most relevant to this review were scanned. Any other relevant references cited within the obtained articles were also scanned.

Data abstraction and analysis

We attempted to collect as many published articles as possible related to pharmacovigilance and/or adverse drug reaction monitoring program in Nepal. Pharmacovigilance, adverse drug reaction, adverse drug reaction monitoring, pharmacovigilance programme, knowledge, attitudes, practice, healthcare professionals, doctor, nurse, pharmacist, Nepal etc. were the key words used to search the database. Only the articles which were published online and/or available online in Pubmed database were included for this review preparation.

Pharmacovigilance programme in Nepal

In Nepal, drug retailers are often the first contact point of people seeking solutions for mild to moderate health

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problems. This is because of low patient to doctor ratio and easy accessibility to retailers. This contributes to high dependence on self- medication[12]. Self-medication may lead to incidence of ADRs either by prescribed drugs or by interaction with already prescribed drugs[13]. Besides, there is also evidence that some drug retailers even examine and prescribe drugs to general public seeking medical solution[14]. The use of traditional herbal medicines is also high in Nepal. Due to inadequate coverage of modern healthcare system in Nepal, in most rural areas, people depend on traditional herbal medicines as a primary means of healthcare[15]. Even in urban areas, people use traditional herbal medicines along with modern medicine. Considering these circumstances, implementation of an effective ADR monitoring programme in Nepal is urgently required in order to safeguard public health and harmonize national practices to international practices. The Department of Drug Administration (DDA), the national drug regulatory authority in Nepal, was established in 1979 to enforce the Drug Act of 1978. After its establishment, it had banned several medicines and drug combinations on the grounds of irrational combination, potential toxicity, doubtful efficacy, and potential for irrational use[16]. Though the need of pharmacovigilance was identified as early as those days, a stricter practice was put in practice only several years after its establishment. The DDA took up the initiatives to set up a pharmacovigilance program in 2002; however, it started systematically only after two years. In 2004, the Ministry of Health and Population (MoHP) designated DDA as the National Pharmacovigilance Centre (NPC) for ADR monitoring programme in Nepal. Nepal became a full member of the WHO collaborating Centre for International Drug Monitoring in July 2006. As a national centre for ADR monitoring, DDA facilitated the ADR monitoring in the country.

There are currently six RPCs operating in the country. In the year 2004, DDA recognized Manipal Teaching Hospital (MTH), Pokhara as a first Regional Pharmacovigilance Centre (RPC). This hospital started ADR monitoring in coordination with Drug Information Centre of the hospital. Based on the experience gained by this RPC, DDA recognized Tribhuvan University Teaching Hospital (TUTH), Kathmandu as a second RPC in 2006. Subsequently, it appointed two RPCs located at Nepal Medical College Hospital (NMCH), Kathmandu and KIST Medical College Hospital (KISTMCH), Lalitpur in the year 2007 and 2008. Recently, it appointed B.P. Koirala Institute of Health Science (BPKISH), Dharan and Civil Service Hospital (CSH), Kathmandu as the fifth and sixth RPCs in the county. The RPCs report the ADR to the national centre via a web based system for ADR management called 'Vigiflow'. These centers are all hospital based and are involved in collecting the ADR cases occurring in the hospitals. The reporting system is based on spontaneous reporting by healthcare professionals working in those hospitals. The revised National Medicine Policy 2009 has also recognized the need for pharmacovigilance programmes in Nepal[17]. It aims to implement agendas for effective post marketing surveillance (PMS) and ADR reporting to ensure safety and ongoing assessment of drug. In mid-2010, the NPC had about 323 ADR reports reported by RPCs since its establishment[18]. The highest number of ADRs was reported by MTH while the NMCH reported the least, only about 11 ADR reports so far.

Knowledge, attitudes and practices among healthcare professionals in Nepal

Knowledge and attitudes towards ADR and ADR reporting among healthcare professionals play an essential role in reporting any cases of ADR. There are a few studies focused on pharmacovigilance and healthcare professionals' perspectives in Nepal[19, 20, 21]. A study was carried out to investigate the knowledge, attitude and practice (KAP) of healthcare professionals regarding ADRs and pharmacovigilance at MTH in Nepal[19]. This study was based on the KAP questionnaire survey. Among 24 respondents, the mean KAP score was 13.6 $\pm$3.7 for doctors, 11.3 $\pm$4.1 for nurses, and 13.0 $\pm$7.1 for pharmacists out of maximum possible score of 25. It showed that healthcare professionals had low score of KAP regarding ADRs and pharmacovigilance. It recommended educational and managerial intervention to improve KAP and awareness among healthcare professionals. The study was based on only one regional center and was conducted on a low sample size. However, it provided an overview of the prevailing situation of healthcare professionals towards ADR reporting.

A study was conducted by Subish and colleagues to investigate the knowledge, attitudes and practice of the community pharmacists to ADR and pharmacovigilance in Nepal[20]. Out of 116 respondents, the mean KAP score was 31.25$\pm$ 2.37 (knowledge 14.04 $\pm$ 1.92, attitude 9.77 $\pm$ 0.60 and practice 7.39 $\pm$ 0.89) with maximum possible score of 40 (knowledge 22, attitude 10 and practice 8). In Nepal, at the moment, community pharmacies are run not only by assistant pharmacists or pharmacists. Among the respondents, 42 were Community Medical Assistants (CMA), 12 were professional persons recognized by DDA to sell drugs, 3 were assistant pharmacists, 3 were pharmacists, and 68 had other qualifications. It showed that the current mix of personnel involved in community pharmacies had poor knowledge about ADR and pharmacovigilance; however, they had positive attitudes and practice. It concluded that training is necessary to improve awareness.

A study conducted by Jha and colleagues to investigate the prevalence of ADRs in five different hospitals in Nepal found a 0.86% prevalence rate of ADR[21]. It also found that females experienced more ADRs compare to males. A higher percentage (40.5%) of ADRs was reported in the elderly. Authors have highlighted the need of RPC in Midwestern

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region of Nepal[22]. Nepangunj Medical College Teaching Hospital (NGMCTH), Kohalpur—is a tertiary care teaching hospital providing healthcare facilities to the Midwestern and Far western region of Nepal. It has introduced the ADR reporting form as suggested by DDA and also has a functional Drug and Therapeutic Committee (DTC). However, it is not recognized as RPC yet.

Several strategies for healthcare professionals such as awareness, training programmes, incorporating pharmacovigilance in their curricula and expanding pharmacovigilance to the community level are also recommended to strengthen the pharmacovigilance activity in Nepal[18].

Recommendations

Intervention through education is the most effective way to improve the rate and quality of ADR reporting among healthcare professionals[23, 24, 25, 26]. Inclusion of drug safety issues in the secondary level curriculum may cultivate concern about the drug and ADRs. However, the effect of educational intervention on healthcare professionals is temporary. The effect of periodic renewal of educational interventions with or without continuous education modules is still unknown[24, 25].

Educational outreach programs can be an effective intervention to improve ADR reporting by physicians[23]. Studies have shown that there was a tenfold increase in the reporting rate by the implementation of just a one hour long educational intervention. The effect was optimally retained for the first 4 months and remained significant for one year. It also found that there was an improvement in the quality of ADR reports and increased the reporting rate for serious, high causality, unexpected, and new drug related ADRs. A study conducted by Bracchi and colleagues to investigate the effect of distance learning packages on the rate and quality of ADR reporting by general practitioner and pharmacist in UK found that there were significant improvements on the rate and quality of ADR reports; however, the effect was short term[24]. Another study found that educational interventions can improve reporting rates in complementary and alternative medicine (CAM) up to as high as 148% and the impact remained significant for 16 months of intervention[25]. Continuous intervention of spontaneous reporting systems within a hospital resulted in very high number of ADR reports. A study conducted in Spain showed that ADR reports increased from 2 reports to 236 reports which required hospitalization, and 99 reports to 277 reports of ADRs among hospital in-patient[26].

Pharmacovigilance is often difficult to apply in rational and irrational combinations, nutraceuticals, herbal combinations etc. for causality assessments because the causative agent is quite difficult to identify and availability of safety information on those types of products are very limited. However, effective pharmacovigilance programmes can help in generating warnings on those types of products.

To counter the under-reporting of ADRs, different measures should be taken simultaneously such as educational intervention to upgrade the knowledge and attitudes of healthcare professionals, compulsory ADR reporting, easy access to ADR databases and issuing guidelines or codes related to ADR reporting. The Intensive Medicines Monitoring Programme (IMMP) in New Zealand uses a simple methodology introduced by Prof. Ivor Ralph Edwards to reduce the administrative work of ADR reporting by prescribers who used special prescriptions which allowed them to record if an ADR had occurred or not with no other detail. The ADR was followed up without the need for repeating details of the patient, reports or drugs that were already available from the prescription. The increase in reporting rate was 14-fold when it was introduced and compliance during follow up was greater than 80%[27, 28, 29].

Recommended ways to improve ADR reporting

There are different approaches recommended to improve the under reporting by healthcare professionals. Those are contextual and many not be fitting in all situations. Even a single approach may not be result oriented. ADR reporting as a professional obligation is one suggested way to counter under-reporting[30,31]. Involvement of pharmacists in ADR reporting has shown a positive impact on the reporting of ADR. This has also resulted in improving the number and quality of ADR reports along with substantial roles in maintenance of drug safety monitoring programme[32,33,34]. Feedback from the national pharmacovigilance programme also has a positive impact on reporting rate. In Sweden, feedback letters along with result of causality assessment of the reported ADR is sent to the reporter concerned[35].

In the context of the situation in Nepal, the following recommendations can be implemented to improve the ADR reporting.

•Take immediate action to improve the knowledge about ADR reporting among healthcare professionals preferably by awareness, training and collaboration.

•Design appropriate training tools to enhance knowledge of ADR reporting among healthcare professionals. It would be better to design at least two levels of training courses to healthcare professionals based on their role and responsibility to ADR reporting.

•Expand the current ADR monitoring program to cover the whole country by increasing the number of potential RPCs.

•Establish a functional pharmacovigilance advisory committee to take any technical decision related to ADR monitoring and ADR reports and also to establish communication strategy.

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•Encourage reporting by doctors, nurses and pharmacists working at any health institutions.

•Involve pharmacists in ADR reporting and causality assessment in collaboration with other healthcare professionals.

•Incorporate current awareness in drug safety, information on new ADR and international drug safety regularly on the Drug Bulletin of Nepal (DBN).

•Encourage universities and other professional organizations to design and administer continuing medical education (CMEs) focusing on ADR and ADR reporting.

•Encourage RPCs to conduct continuous awareness programmes and regular training for healthcare professionals to improve ADR and ADR reporting.

•Collaborate with universities, professional organizations and RPCs to strengthen ADR monitoring program in Nepal.

•Set appropriate means of feedback from national centre to the active ADR reports.

Conclusion

ADR reporting has been recently implemented in Nepal. Available studies suggest that there is a high rate of under-reporting of suspected ADR cases by RPCs. The coverage of RPCs throughout the country is inadequate and awareness about the ADR reporting among healthcare professionals is low. In these circumstances, there is an urgent need to develop programmes and improve the situation by NPCs in collaboration with RPCs and other stakeholders as recommended by the authors above. This will ensure the safe use of drug for the better therapeutic as well as economic outcome.

Conflict of interest

The authors do not have any conflict of interest to declare.

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