

Original Article

Cutaneous adverse drug reactions to modern medicines and initial experiences from a Spontaneous adverse drug reaction reporting program in a tertiary care teaching hospital of Western Nepal

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Abstract *Background* Cutaneous adverse drug reactions (ADRs) affect 2-3% of hospitalized patients; most are usually mild and respond to topical drugs. These reactions can arise as a result of immunologic or non-immunologic mechanisms. Extremes of age, female sex, previous history of ADRs and environmental factors are the major risk factors. The Naranjo algorithm is widely used to determine the causality of an ADR.

Objective To share the authors' experience of spontaneous adverse drug reaction reporting program Nepal.

Patients and methods During a period from September, 2004 to March, 2005, any patient who experienced a dermatological ADR were asked to report the Pharmacovigilance Cell of the Manipal Teaching Hospital, Pokhara, Nepal. Morphology of the eruption was recorded.

Results A total of 45 cutaneous ADRs were reported during the study period. Maculopapular rash (15 reports) was the most common, followed by contact dermatitis (7 reports), fixed drug eruptions (6 reports) and erythema (4 reports).

Conclusion Considering its effectiveness, the pharmacovigilance program in Manipal Teaching Hospital should be strengthened and transformed to a full-fledged active reporting program. The nationwide extension of this program would be beneficial.

Key words Contact dermatitis, cutaneous adverse drug reactions, Naranjo algorithm, maculopapular rash, pharmacovigilance.

Introduction

Drugs can be remarkably beneficial,

lengthen life and improve its quality by reducing symptoms and improving well-being. However, all drugs have adverse effects and carry the potential of causing injury, even if used properly. Well-gathered, highly representative data about the adverse effects of drugs help physicians to use drugs balancing the benefits and hazards. An

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adverse drug reaction (ADR) has been defined by the WHO as “An effect which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis and therapy”.¹ The skin and the mucosa are the commonest sites for initial presentation of many ADRs. Although the rate of acute severe adverse cutaneous reactions to medication is low, these reactions can affect anyone who takes medications and can result in death or disability.²

Cutaneous ADRs affect 2-3% of hospitalized patients.³ Many commonly used drugs cause ADRs in more than 1% of hospitalized patients.^{3,4} Fortunately, most cutaneous adverse reactions are not severe and few are fatal.^{2,3} Since most cutaneous ADRs are usually mild and respond to topical drugs, they are usually ignored. In addition to their human costs, ADRs are expensive to the health-care system. Two studies conducted independently arrived at estimates of about \$2000 per event. Preventable events were even more costly, approximately \$4500 per event.^{5,6}

Studies on the incidence of cutaneous ADRs in Nepal are lacking. In this article, the authors share the experience of cutaneous ADRs in the Manipal Teaching Hospital (MTH); a 520 bedded tertiary care teaching hospital in Western Nepal.

Patients and methods

The Spontaneous ADR Reporting Program in MTH was started on September 17, 2004. The ADR reporting forms were placed in the wards, outpatient departments (OPDs), pharmacy and pharmacovigilance cell of the hospital. On occurrence of an ADR, the doctors, pharmacists and nurses reported the

ADRs by filling the ADR reporting form. The reports were received by the cell and necessary drug information was given to the reporters upon request. The causality of the particular ADR was carried out as per Naranjo algorithm.

Recognizing adverse drug reactions

For estimating the probability that a specific drug is responsible for an ADR, several scales have been developed.^{7,8,9} The most widely used is the Naranjo algorithm.⁹ (**Appendix 1**). It has good internal reliability and assessment can be carried out quickly; it consists of ten questions about the probability that an ADR has occurred. A score of 1 to 4 points indicates that an ADR is considered possible, 5 to 8 probable, and 9 or more definite. The criteria proposed to consider in diagnosing severe cutaneous adverse reactions and their causes are as follows.²

1. Alternative causes should be excluded, especially infections, since many infectious illnesses are difficult to distinguish clinically from the adverse effects of drugs used to treat infections.
2. The interval between the introduction of a drug and the onset of a reaction should be examined.
3. Any improvement after drug withdrawal should be noted.
4. The physician should determine whether similar reactions have been reported with the same compounds.
5. Any reactions on re-administration of the drug should be noted.

Appendix 1 Naranjo algorithm

S. No.	Question	Yes	No	Don't Know	Score obtained
1	Are there previous conclusive reports on this reaction?	+1	0	0	
2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4	Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	
5	Are there alternative causes (other than the drug) that could solely have caused the reaction?	-1	+2	0	
6	Did the reaction reappear when a placebo was given?	-1	+1	0	
7	Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0	
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9	Did the patient have a similar reaction to the same or similar drugs on previous exposure?	+1	0	0	
10	Was the adverse event confirmed by objective evidence?	+1	0	0	

Total score: _____

Results

Since its inception in September, 2004, a total of 45 cutaneous ADRs were reported. Different morphological patterns and their frequencies are enlisted in **Table 1**. Similarly, **Figures 1-3** show the morphology of the three common types encountered.

Discussion

Pharmacoepidemiology i.e. the epidemiological assessment of adverse effects and pharmacovigilance, the process of identifying and responding to the safety issues about marketed drugs are often neglected in the developing world. Information from clinical trials, spontaneous reporting systems, specialty-based reporting systems, case series, cohort studies, population-based registries using computerized material and special surveillance programs can be used for this purpose. The Spontaneous ADR Reporting

Table 1 Different morphological types of drug eruptions and their frequency.

Sr. No.	Type of reaction	n (%)
1	Maculopapular rash	15 (33.3)
2	Urticaria and angioedema	9 (20.1)
8	Contact dermatitis	7 (15.6)
3	Fixed drug eruption	6 (13.3)
4	Erythema multiforme	4 (8.9)
6	Cellulitis-like erythema	1 (2.2)
7	Acneiform drug eruption and diffuse alopecia	1 (2.2)
10	Pityriasisiform drug eruption	1 (2.2)
11	Phototoxic drug eruption	1 (2.2)

Program is the pioneer in this regard in Nepal.

Certain inferences can be drawn from our study. First the Naranjo algorithm is an effective index in the diagnosis of cutaneous drug eruptions. Many studies testify the sensitivity and specificity of Naranjo algorithm.^{10,11,12} This is also a user-friendly and time saving questionnaire making it feasible even in busy practice.



Figure 1 Maculopapular rash due to carbamazepine



Figure 2 Allergic contact dermatitis due to vitamin K injection.



Figure 3 Fixed drug eruption due to oral paracetamol.

Secondly, the frequency of different morphological patterns was similar to that described in earlier studies.^{13,14,15} The maculopapular exanthema was the most common morphological type followed by urticaria, contact dermatitis, fixed drug eruption and erythema multiforme.

Thirdly, the experience at MTH supports the success of this ADR monitoring program.

Every year many drugs are added to the medical arsenal. Besides efficacy, safety is an important concern. WHO launched its International Monitoring Program in 1968 to promote drug safety and currently 86 countries are participating in this program.^{16,17,18} The future of global drug safety very much depends on countries' ability to build up local systems for drug monitoring. Such systems are already well-established in the developed countries but the third world countries are still lacking such ADRs-monitoring systems. We can use our experience at MTH to set up regional centres. The information gathered will be exchanged amongst health professionals and other stakeholders like drug regulatory authorities and pharmaceutical industry. Similarly, the information can be transferred to WHO and other global monitoring agencies.

Conclusion

Considering the encouraging results, the pharmacovigilance program in Manipal Teaching Hospital should be strengthened and transformed to a full-fledged active reporting program.

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