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Patterns and Causality Assessment of Adverse Drug Reactions in Inpatients of a Tertiary Care Hospital, Nepal

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ABSTRACT

Introduction

Adverse drug reaction (ADR) is a leading cause of morbidity and mortality around the world. Causality assessment is done to establish relation of drug exposure with undesired clinical events. This study conducted in tertiary care hospital was undertaken to evaluate the patterns of ADR and causality assessment using Naranjo causality algorithm.

Methods

Data on suspected ADR cases were collected retrospectively from Medicine and Dermatology wards of Tribhuvan University Teaching Hospital, Kathmandu from April 2018 to April 2019. Naranjo causality assessment was performed. Statistical analysis was done using SPSS version 18.

Results

Of 34 suspected ADR, occurrence of ADR was more in females (18) as compared to males (16). Skin and integumentary system was the most common organ affected (35.29%). Pyrazinamide induced hepatitis was found to be the most common suspected ADR. Causality assessment was performed and ADRs were categorized as possible 17 (50%), probable 16 (47.06%) and definite 1 (2.94%).

Conclusion

The patients are commonly admitted at the hospital due to suspected ADRs. Pyrazinamide induced hepatitis was the most common suspected ADR.

Keywords

Adverse drug reaction, causality assessment, Naranjo algorithm, pharmacovigilance

INTRODUCTION

Medicines are important component of patient management in health care settings. Drug therapy initiated for patients' care have potential to cause beneficial as well as harmful effects like adverse drug reactions (ADRs) leading to significant morbidity and mortality.[1,2] An ADR is defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product".[3] Causality assessment is used to evaluate the likeliness of occurrence of the adverse event due to the suspected drug used during the treatment. Naranjo algorithm is one of the most commonly used globally.[4]

Pharmacovigilance in Nepal is still in its infancy stage. ADRs monitoring system in Nepal rely on voluntary reporting from healthcare professionals.5 This often leads to under-reporting due to issues like fear of litigation, guilt, lack of motivation, inadequate training and most importantly the workload of health-care providers.6 The study was conducted with the objective of to determine the pattern of suspected adverse drug reaction among patients admitted to medicine and dermatology ward in a tertiary care hospital of Kathmandu.

METHODS

Medical records of suspected adverse drug reactions reported from Medicine and Dermatology Departments admitted from April 2018 until April 2019 were reviewed. Data on age, sex, clinical history, suspected adverse drug reactions, suspected drug and outcome were recorded on a data collection sheet.

Causality assessment of the suspected adverse drug reaction were carried out using Naranjo algorithm. Naranjo algorithm is a set of ten questions with answers as "Yes", "No" and "Don't Know". According to the question, the responses is scored from -2 to +2. The maximum score that can be given to a suspected drug-ADR pair is 14. The causality can be labelled as definite, probable, possible and doubtful if the scores are more than or equal to 9, between 5-8, between 1-4 and less than or equal to zero respectively. In our study as well, scores were assigned to suspected drug-ADR pair and were accordingly classified as doubtful, possible, probable and definite.

Data thus collected were entered in Microsoft Excel 2019 and analysed using SPSS version 18. Ethical approval was obtained from the institutional review committee.

Based on severity scale of ADR, it is classified as minor, moderate, severe and lethal. If an ADR requires change in therapy, specific treatment or prolongs hospital stay by at least one day it is classified as moderate.7

RESULTS

There were 34 suspected ADR forms compiled in the department over the one-year duration from Medicine and Dermatology departments. The median age of cases was 49.50 years. Most of the cases were female (n=18, 52.94%). List of all the suspected drugs with their Anatomic and Therapeutic Classification (ATC) codes and suspected adverse drug reaction has been summarized in Table 1.

The most common drug-suspected ADR pair was found to be of pyrazinamide-hepatitis (8, 23.53%). Most of the patients (12, 35.29%) presented with involvement of skin and integumentary system

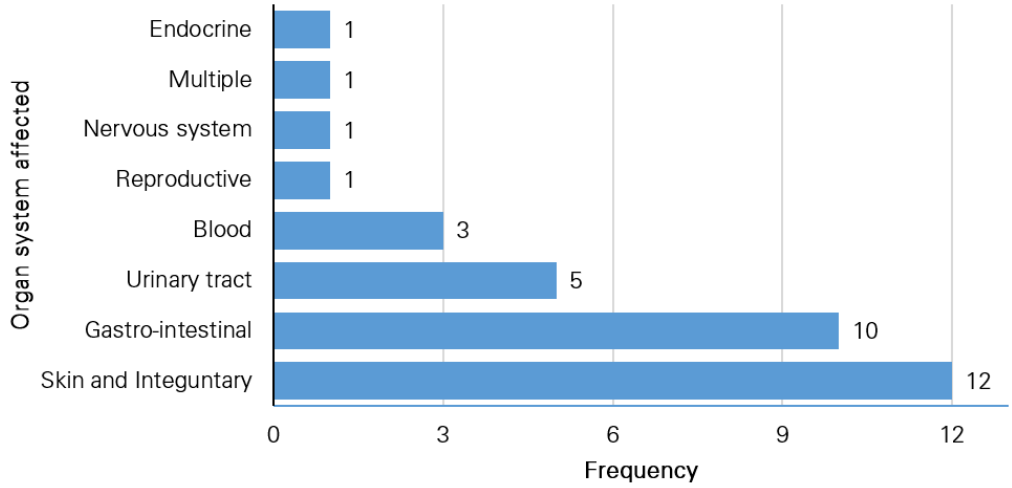

Fig 1. Likely organ system affected due to suspected adverse drug reactions

Table 1. List of drug-suspected adverse drug reaction pair seen during the study and assessed using Naranjo algorithm

Suspected Drug	ATC code	Suspected adverse drug reactions	Frequency
Allopurinol	M04AA01	Steven Johnson Syndrome	1
Aspirin	B01AC06	UGI bleed	1
Carbamazepine	N03AF01	Steven Johnson Syndrome	2
	N03AF01	DRESS Syndrome	2
	N03AF01	Erythroderma	1
Cefixime	J01DD08	Steven Johnson Syndrome	1
Dapsone*		Methaemoglobinemia	1
	J04BA02	Hypersensitivity reaction	1
Etoricoxib	M01AH05	Steven Johnson Syndrome	1
Ibuprofen	M01AE01	Gastritis	1
	N02BE51	DRESS syndrome	1
	N02BE51	Acute Kidney Injury	1
Indomethacin	M01AB01	Acute Kidney Injury	1
Isoniazid	J04AM06	Peripheral neuropathy	1
Methotrexate	L04AX03	Mucositis with Extramucosal involvement (Pancytopenia)	1
Nimesulide	M01AX17	Acute Kidney Injury	3
	M01AX17	Steven Johnson Syndrome	2
Phenytoin	N03AB02	DRESS Syndrome	1
Prednisolone	H02AB06	Hyperglycemia	1
Pyrazinamide	J04AM06	Hepatitis	8
Spironolactone	C03DA01	Gynecomastia	1
Warfarin	B01AA03	Coagulopathy	1
		Total	34

** ATC code has not been assigned to Dapsone for systemic use in bullous pemphigoid.*

(drug induced rash, Steven Johnson Syndrome, erythroderma) followed by patients with gastro-intestinal system being affected (10, 29.41%) as shown in figure 1.

When causality assessment was conducted for the suspected ADR-drug pair using Naranjo algorithm, it was seen that most of the drug-suspected ADR pair scored 5 out of 13 (13, 38.24%). However, when categorising the scores, scores of most of the drug-suspected ADRs were between 1-4, and hence were classified as possible (17, 50.00%) as summarised in table 2.

Table 2. Score and category of causality assessment using Naranjo algorithm

Score	Frequency (%)	Category (n, %)
1	2 (5.88)	Possible (17, 50.00%)
2	3 (8.82)	
4	12 (35.29)	
5	13 (38.24)	Probable (16, 47.06%)
6	2 (5.88)	
7	1 (2.94)	
9	1 (2.94)	Definite (1, 2.94%)
Total	34	

It was seen that most of the patients (20, 58.82%) had recovered by the time of discharge followed by patients recovering from suspected ADR at the time of discharge (12, 35.29%). In one patient outcome was not known and was not recovered in one patient.

DISCUSSION

It was seen that there were 34 cases of suspected ADR over one-year duration collected by Department of Clinical Pharmacology. Adverse drug reactions (ADRs) are inevitable consequences of drug therapy and is significant cause of morbidity and mortality worldwide. A systematic review including studies from different parts of the world stated that studies have reported median

prevalence of ADR admissions to be 5.3% and ranging between 0.16-15.7%.[8] Multiple studies from developed countries reported ADRs to be among the top six causes of death in hospital settings.[9,10] A study from eastern India reported an incidence of 0.41% of ADRs, of which 0.19% occurred during the hospital stay.[2] Similar number of cases have been reported by another study conducted previously.[11] Study reporting higher number of suspected ADR cases are present.[12] In a study from Sweden, it was reported that 40% of patients admitted in emergency medical ward has at least one possible ADR.13 Higher rate of suspected ADRs could have been reported due to involvement of multiple clinical departments in the previous studies.[10] This emphasizes the need to incorporate pharmacovigilance activities in different hospital services.

Female preponderance in suspected ADRs was observed in our study. Study with similar[12] as well as male preponderance in suspected ADRs are existent.[11,14] This could have been prevented by optimal counselling regarding right dose, frequency and duration of treatment by different healthcare professionals as depicted using "Swiss cheese" model of medication error.[15] Skin and integumentary system(7, 38.89%) was most commonly affected in females with suspected ADRs in our study. These adverse effects were due to anti-epileptic agents (5, 14.71%) and non-steroidal anti-inflammatory medicines (NSAIMs) (2, 5.88%). Factors like drug-food interactions, use of over-the-counter drugs, irrational use, etc. could have caused adverse effects in these females as anti-epileptics have narrow therapeutic range.

It was seen that majority of the patients in this study belonged to age group of 26-50 and 51-75 years, with a median 49.50 years. Other studies reporting higher proportion of elderly patients with suspected ADRs are common.[11,12,14] This could have occurred due to multiple factors like co-morbidities, polypharmacy, general health status of the patients.

It was seen that pyrazinamide induced hepatitis (8, 23.53%) was the most common suspected drug-ADR pair in our study. The indication of pyrazinamide was tuberculosis and was prescribed in combination with other three first line anti-tubercular therapy (ATT) drugs. Patients on ATT are commonly associated (5-28%) with hepatotoxicity resulting in drug discontinuation in 11% patients.[16] Though isoniazid, rifampicin and pyrazinamide are known to cause hepatotoxicity, the most common drug implicated for causing hepatotoxicity among the four drugs is isoniazid.[16] A study from India also reported that antimicrobials were the commonest group of drugs responsible for ADR.[17] Another study from Western Odisha reported that ATT were responsible for 2.52% of the ADRs studied and one of the ADR to be due to combination of rifampicin and pyrazinamide.[18] Contrary to our finding, Bajracharya et al reported that 20% of ADRs were due to isoniazid induced hepatotoxicity.[11] A study conducted by Yee et al also reported that incidence of pyrazinamide induced hepatotoxicity was higher than with the other first line ATT drugs. The study added that frequency of pyrazinamide-hepatotoxicity was higher than previously recognized.[19] We considered pyrazinamide to be the drug causing hepatitis because all the cases showed improved liver function on discontinuation of pyrazinamide. Additionally, in one case, hepatitis was found to re-appear when pyrazinamide was re-introduced to the regimen. It would however be desirable to rule out isoniazid as the cause of hepatotoxicity with the availability of genetic tests. Active pharmacovigilance activities at directly observed treatment short-course (DOTS) clinic could play pivotal role to detect these adverse effects early and decrease the morbidity or hospitalization.

In our study, ADRs related to skin and integumentary system was found to be commonest organ system affected (12, 35.29%), however, hepatitis was the most common ADR (8, 23.53%). Skin and integumentary system was also reported to be most commonly affected organ system by different studies conducted in India and Nepal.[14,17,18] Easy noticeability of the lesions could have resulted in the frequent presentation of the ADR to the hospital where as life-threatening nature of the ADR could have caused increased hospitalization of these patients. Similar to our study, Bajracharya et.al. also reported hepatotoxicity to be the most common ADR in their study.[11]

Causality assessment is used to evaluate the relationship between the occurrence of the adverse event and the suspected drug used during the treatment and plays an important role in better management of the adverse reactions. Of the several tools used to assess the causality, Naranjo algorithm is one of the most commonly used globally.[3,4]

Causality assessment using Naranjo algorithm in our study resulted majority of the suspected ADRs to be classified as possible (17, 50.00%). One case of pyrazinamide induced hepatitis scored 9 out of 14 in Naranjo algorithm and was categorised as definite in this study. A higher proportion of ADRs were categorised as possible in another studies conducted previously.[11,14] As Naranjo algorithm considers factors like re-challenge, challenge with placebo, measurement of drug levels in body fluid (therapeutic drug monitoring), change in response with dose modification, and these factors are not commonly assessable, these could have led to most of the suspected ADRs to be classified as possible or probable. Patients cannot be rechallenged with

the suspected drug for the purpose of causality assessment and doing so is unethical and not acceptable. This could also have resulted in a smaller number of suspected ADRs in definitive category. It is therefore required that therapeutic drug monitoring services are strengthened that would play supportive role in proper management of the suspected ADR patients.

Causality assessment can also be conducted using World Health Organisation-Uppasala Monitoring Center (WHO-UMC) algorithm as done by Behra et.al. in 2018.[18] The agreement on causality assessment using WHO-UMC and Naranjo was reported to be poor and Naranjo algorithm was also found to be more time consuming.[20] Due to its simplicity, Naranjo algorithm can easily be adopted by clinicians in their patient management protocol for suspected ADR patients.[11] Besides these two algorithm, Spanish Pharmacovigilance system has developed a seven question causality assessment algorithm that can also be used for causality assessment.[4]

As the study was retrospective in nature, there were instances where required information for causality assessment was missing in medical records. This could have resulted in most of the suspected ADR to be classified as probable or possible. The number of cases enrolled in the study were also small.

CONCLUSION

It was thus seen that patients are commonly admitted at the hospital due to suspected ADRs. Pyrazinamide induced hepatitis was the most common suspected drug-ADR pair in our study. Most of the suspected ADRs were categorized as possible on causality assessment using Naranjo algorithm. Pharmacovigilance activities needs to be strengthened, incorporated into different departments as well as vertical programmes like DOTS clinic and causality assessment needs to be carried out frequently.

CONFLICT OF INTEREST

None declared.

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