

Adverse Drug Reaction (ADR) Monitoring at the Eastern Regional Pharmacovigilance Centre, Nepal

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ABSTRACT

Background

Adverse Drug Reaction is any unintended drug consequence. It is often preventable. In developed countries, it is among the top ten leading causes of morbidity and mortality. However, it's monitoring is largely unexplored in developing countries like Nepal.

Objective

To identify and characterize the pattern of Adverse Drug Reactions at BP Koirala Institute of Health Science (BPKIHS), the Eastern Regional Pharmacovigilance Centre of Nepal.

Method

It was an observational study among the patients presented to different Clinical Departments of BPKIHS. Study duration was between July 2012 to July 2015. Adverse Drug Reactions were documented in a structured questionnaire and analysis done, in the department of Clinical Pharmacology and Therapeutics, using Microsoft 2013 Excel.

Result

There were total 150 Adverse Drug Reactions documented mostly in the age range of 19-40 years (61.4%) with female preponderance (56.7%). Maximum Adverse Drug Reactions were collected from Psychiatry (60.7%) followed by Dental surgery (17.3%) and Internal Medicine (10.7%). Most frequent Adverse Drug Reactions were seen with drugs primarily affecting CNS (64.7%), followed by steroids (18.0%) and Antimicrobial drugs (12.0%). Among CNS drugs, Antidepressants (93.6%) accounted for most documentation. Weight gain (20.1%), Fatigue (12.4%), Rash (8.1%), Acid peptic disorder (7.7%), Headache (7.2%) and Puffiness of face (7.2%) were the most frequently encountered Adverse Drug Reactions.

Conclusion

Most reported Adverse Drug Reactions were from young (18-40) female presented to the department of Psychiatry. Weight gain was the most common side effect.

KEY WORDS

Adverse Drug Reaction, BP Koirala Institute of Health Science, Pharmacovigilance

INTRODUCTION

ADR (Adverse Drug Reaction) is any harmful or unpleasant response to a medicinal product such that it warrants prevention, specific treatment, alteration of dosage regimen, or even withdrawal of that product in future.¹

Though any drug is intended either to cure a condition or mitigate physical or mental suffering, it is a double-edged sword.² It could prolong hospital stay and substantially increase the health care expenditure.³ Even Permanent handicaps and deaths have been reported to be caused by drugs.⁴

Data from developed countries, show that in hospitalized patients, ADR is among top ten leading causes of morbidity and mortality.^{5,6} ADR stands among top five leading causes of death in the United States.^{7,8} Even among other developed countries, reported ADR vary from 0.7 to 35%.^{3,9} It increases hospital costs by 5-10%.¹⁰ A recent meta-analysis showed that serious ADRs and fatal ADRs among hospitalized patients, were respectively 6.70 and 0.32%.¹¹

ADR monitoring is largely unexplored in developing countries.¹²⁻¹⁵ In the neighboring India, ADR reporting rate is 1% as compared to 5% in developed country.¹⁶ Causes for under-reporting include fear of litigation, guilt, ambition, ignorance, lethargy, lack of awareness, motivation, training and most importantly, time among health-care providers.¹⁷

We still lack monitoring and reporting of ADRs in our part of the world. The information gathered is expected to help minimize preventable ADRs, make ADR reporting better and help clinicians deal with ADRs more efficiently.

The study, therefore, was carried out to identify and characterize the pattern of ADRs in the institute.

METHODS

It was an observational study of suspected ADRs. Any patient in clinical department with documented ADR within the time frame of July 1 2012 to July 31 2015, was taken as study subject. ADRs were collected in a structured ADR reporting questionnaire-forms, prepared as per the World health Organization-Uppsala Monitoring Center (WHO-UMC) guidelines. The demographic and other information relevant to drug reactions were collected. Patients having known concomitant major organ dysfunction like Liver cirrhosis, Chronic Kidney Disease, Chronic Obstructive Pulmonary Disease and those having known allergy to the given drug, were excluded from the study.

Data obtained, were entered in Excel sheet Microsoft office 2013 version 15.0.4420.1017 and later analyzed with SPSS version 21. Evaluation of the data was done for various parameters which included patient demographics, drugs involved in ADR, organ system involved in ADR, department where ADR was documented and type of ADRs.

However, Causality (Naranjo's algorithm), Severity and Preventability assessments were not done.^{18,19}

RESULTS

Total 150 ADR cases were documented in the scheduled study period. All age groups exhibited adverse drug reaction. The youngest patient was a newborn female and the oldest, was a 83-year-old male. Most documented cases were in the age range of 19-40 years (61.4%) followed by 41-60 years (21.4%). ADRs were more frequently seen among females (56.7%; Table 1).

Table 1. Age and sex-wise distribution of ADR (N=150)

Age group	Male (%)	Female (%)
<18 years	9 (6)	8 (5.3)
19-40 years	37(24.7)	55(36.7)
41-60 years	16 (10.7)	16 (10.7)
>60 years	3(2.0)	6 (4.0)
Total	65 (43.3)	85 (56.7)

Maximum ADRs were collected from Psychiatry department (60.7%) followed by Dental surgery (17.3%) and Internal Medicine department (10.67%; Table 2). Most frequent ADRs were seen with drugs primarily affecting CNS (64.7%), followed by steroids (18.0%) and Antimicrobial Agents (12.0%; Table 3).

Table 2. ADRs Seen in Different Clinical departments (N=150)

Department	Number of patients with ADR (%)
Psychiatry	91 (60.7)
Dental surgery	26 (17.3)
Internal Medicine	16 (10.7)
Pediatrics and Adolescents Medicine	10 (6.7)
Others*	7 (4.7)

*Surgery-4, Obstetrics-2, Dermatology-1

Table 3. Ranking of Drug groups based on ADR frequency (N=150)

Drug group's Rank	Drug group	ADR frequency (%)
1	Drugs Affecting CNS*	94 (62.7)
2	Steroids**	27 (18.0)
3	AMA [†]	18 (12.0)
4	NSAIDs ^{††}	4 (2.7)
5	Drugs Affecting other system [#]	7 (4.7)

*Escitalopram, Fluoxetine, Sertraline, Risperidone, Phenytoin, Lithium, Lorazepam, Carbamazepine

**Prednisolone, Medroxyprogesterone Acetate

[†]Amphotericin B, Ceftriaxone, Metronidazole, Sulfasalazine, Vancomycin, Amikacin, Ampicillin, Sulbactam, Clofazimine, Rifampicin, Diethylcarbamazine, Ciprofloxacin, Gancyclovir

^{††}Paracetamol, Nimusulide

[#]Lactulose, Metazone, Metoprolol, Cyclophosphamide, Salbutamol, BCG Vaccine

Among CNS drugs, Antidepressants (93.6%) accounted for the most ADRs. Others were Risperidone (2.1%), Phenytoin (1.1%), Lithium (1.1%), Lorazepam (1.1%), Carbamazepine (1.1%). Among all drugs, Escitalopram accounted for maximum reported ADRs (28%) followed by Prednisolone (17.3%) Fluoxetine (16%) and Sertraline (14.7%).

These antidepressants frequently showed Fatigue, Sexual dysfunction, Paraesthesia, Confusion, Weight gain, Headache, Sweating, Dryness of mouth, Itching, Tremor etc.

Among steroids, Prednisolone (96.3%) and Medroxyprogesterone Acetate (3.7%) were identified (Table-3). Prednisolone mainly caused Headache, Insomnia, Puffiness of face, Acid peptic disorder and Oral Candidiasis.

Similarly, various AMAs were implicated in suspected ADRs. In descending order, they were Amphotericin B (22.2%), Ceftriaxone (16.7%), Metronidazole (11.1%), Sulfasalazine (5.6%), Vancomycin (5.6%), Amikacin (5.6%), Ampicillin+Sulbactam (5.6%), Clofazimine (5.6%) Rifampicin (5.6%), Diethylcarbamazine (5.6%), Ciprofloxacin (5.6%) Gancyclovir (5.6%). They mainly caused dermatological and GI related ADRs.

Table 4. Ranking of ADRs (N=209) based on frequency

Ranking	ADRs documented	Frequency encountered (%)
1	Weight gain	42 (20.1)
2	Fatigue	26(12.4)
3	Rash	17(8.1)
4	Acid peptic disorder	16(7.7)
5	Headache	15(7.2)
6	Puffiness of face	15(7.2)
7	Other CNS related ADRs*	33(15.8)
8	Other GI related ADR**	21(10.0)
9	Sexual dysfunction	9 (4.3)
10	Other Dermatological ADR ⁺	11(5.3)
11	Other ADR ⁺⁺	4 (1.9)

*Paraesthesia, Tremor, Fever, Insomnia, Agitation, Confusion, Dizziness, Altered sensorium, Irritability, Peripheral Neuropathy, Delirium

**Dryness of mouth, Anorexia, Diarrhea, Metallic taste, Nausea or vomiting, Black stool, Epigastric Pain, Polydipsia, Polyuria, Jaundice

⁺Sweating, Itching, Alopecia, Oral Candidiasis, Redman syndrome

⁺⁺Bradycardia, Dyspnea, Megaloblastic anemia, Muscle weakness

Next, in NSAID group, Paracetamol (75%), Nimusulide (25%) were found causing mainly GI intolerance and rash (Table-3).

Lastly 'other' group comprised of Lactulose (28.6%), Metazone (14.3%), Metoprolol (14.3%), Cyclophosphamide (14.3%), Salbutamol (14.3%) and BCG Vaccine (14.3%). They were causing diverse ADRs namely Lactulose-excessive diarrhea, Metazone-rash, Metoprolol-bradycardia, Cyclophosphamide-Alopecia, Salbutamol-Tremor and BCG Vaccine-dysnoea and fever (Table 3).

Weight gain (20.1%), Fatigue (12.4%), Rash (8.1%), Acid peptic disorder (7.7%), Headache (7.2%) and Puffiness of face (7.2%) were the most frequently documented ADRs seen (Table-4).

It was followed by other CNS related ADR. They were Paraesthesia (4.3%), Tremor (2.8%), Fever (2.4%), Insomnia (1.4%), Agitation (0.9%), Confusion (0.9%), Dizziness (0.9%), Altered sensorium (0.5%), Irritability (0.5%), Peripheral Neuropathy (0.5%), Delirium (0.5%). Next it was followed by GI related ADRs viz., Dryness of mouth (1.9%), Nausea/vomiting (1.9%), Diarrhea (1.9%), Anorexia (0.9%), Metallic taste (0.9%), Black stool (0.5%), Epigastric Pain (0.5%), Polydipsia (0.5%), Polyuria (0.5%), Jaundice (0.5%). Dermatological ADRs then follow like Sweating (2.4%), Itching-3, Alopecia (0.5%), Oral Candidiasis (0.5%), Redman syndrome (0.5%). Lastly, few other ADRs also documented like Bradycardia (0.5%), Dyspnea (0.5%), Megaloblastic anemia (0.5%), Muscle weakness (0.5%) (Table-4).

DISCUSSION

In our study, ADRs were observed among all age groups, in all Clinical departments. They were more common among females, male:female ratio being 1/1.31. Sex-ratio was similar to other studies.²⁰⁻²²

In our study, most frequent age-group was young between 19-40. Past pilot study from the same institute also reported maximum ADRs in the same age-range.²³

Depression was the single most common diagnosis in our case which is the most common women's mental health problem.²⁴ Moreover, inherently ADRs are 1.5- to 1.7 fold more common among female. Lean body mass, reduced hepatic clearance, differences in activity of cytochrome CYP P450 are among the myriad of causes. In addition different other immunological and hormonal factors synergize to bring these differences in ADR frequency.²⁵⁻²⁷

An observational study demonstrated that Adolescence was the most common age group affected.⁵ However, in our study, under 18 (pediatric and adolescents) contributed only 10% of the total ADRs. It may be because incidentally, the burden of mental disorders is maximal in young (20-40) adults.²⁸

In our study, maximum ADRs were from Psychiatry. Psychiatric disease is emerging global pandemic.²⁹ Needless to say more disease means more drugs and more drugs means more ADRs. Treatment response and the incidence of adverse effects to antidepressant have significant link with genetic makeup of the population, therefore, the possibility that difference might be related to pharmacogenetics of Nepalese population cannot be negated.^{30,31}

Rehan et al. reported most ADRs in the department of Internal Medicine.²¹ Pathak AK reported maximum ADRs in department of Skin and Veneral Disease.⁵ A Nepalese study

reported maximum ADRs in the department of Skin and Veneral Disease skin (35.1%).²⁰ However, in the design of that Nepalese study, the investigators did not include the department of Psychiatry.

Our study pointed that anti-depressant caused most ADRs. Noel et al., however, reported that anti-epileptics showed most ADRs.³² Much of the similar studies showed AMAs to be the most common cause of ADRs.^{5,20,33-36} Most of these studies recruited high proportion of patients from the department of internal medicine where AMAs are one of the top-prescribed drug class.³⁷ Again, as aforementioned, one study did not include department of Psychiatry at all. In our case, most documented ADRs were from Department of Psychiatry where AMAs are very infrequently prescribed.

In our study, weight gain was the single most common ADR seen. In most other studies, dermatological ADRs were more commonly seen.²¹ The difference is obviously

produced by sample. In those studies, most cases are from Internal Medicine where AMAs are frequently used whose main ADR is dermatological. However, in our case most ADRs are from Psychiatry patients taking anti-depression. The most frequent longterm ADRs of SSRI, the most commonly prescribed antidepressants, are Weight gain, fatigue and sexual dysfunction.³⁸

We found underreporting of ADR like most literature says. There is still lack of proactive ADR detection and reporting.

CONCLUSION

Most reported ADRs were from young (18-40) female presented to the department of Psychiatry. Awareness and training both to health care professionals and patients regarding ADR detection and reporting, may improve ADR monitoring.

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