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Analysis of adverse drug reactions reported to national pharmacovigilance center of Bhutan

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ABSTRACT

Introduction: Medicines prescribed for diseases often causes adverse drug reactions (ADRs) in patients ranging from mere inconvenience to permanent disability and death. This is because, most ADRs especially those serious and latent ones may not have occurred during their clinical trials and vulnerable populations like children, pregnant women, and the elderly are not all included in clinical trial studies considering the ethical and safety issues. **Methods:** A total of 222 ADR reports received at the NPC from January 2016 to May 2018 were analyzed using Epi-Data Analysis version 2.2.2.182. Descriptive statistics in frequencies and percentages were used to report the results. Categorical variables were compared using Fisher's exact or Pearson's Chi-Square depending upon the expected frequencies in the cells. *p*-value of <0.05 was considered statistically significant for the study. **Results:** Of the reports with information on sex, 143 (64.4%) concerned female and 79 (35.6%) male. Rashes (*n*=81, 36.5%) was the most common ADRs reported. Antibiotics was the most common causal drug for ADRs (*n*=108, 48.7%), particularly penicillins (*n*=35, 32.4%). ADRs were reported by pharmacy professionals (*n*=86, 38.7%), physicians (*n*=30, 13.5%). **Conclusions:** ADRs resulting from use of antibiotics, particularly penicillins, were most common. Measures to improve detection and reporting of ADRs by all categories of health care professionals (HCPs) should be undertaken, to improve reporting of ADRs. Future research may focus on exploring ADRs in female patients, particularly those on antibiotic treatments, to enhance our understanding of nature and impact of these drugs in causing ADRs.

Keywords: Adverse drug reactions; Antibiotics; Bhutan; Causal drug groups; National pharmacovigilance center.

INTRODUCTION

Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem" [1]. Pharmacovigilance plays a crucial role in patient safety owing to the increasing numbers of medicines put onto the market every single day[2] but it relies very much on the ADRs reported by the healthcare professionals (HCPs)[3]. ADRs can be defined as unwanted, harmful, and unpleasant effect of a medicinal product used for therapeutic purposes[4]. Medicines prescribed for diseases often cause ADRs in patients ranging from mere inconvenience to permanent disability and death[5]. This is because, most of the ADRs especially the serious and latent ones may not have occurred during the clinical trials[6], and vulnerable populations such as children, pregnant women, and the elderly are not all included in clinical trial studies considering the ethical and safety issues[7,8].

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Healthcare in Bhutan is provided free of cost by the government as per the Constitution[9]. However, private pharmacies are increasingly becoming a source of medicines especially for those who can afford[10]. ADR reporting in Bhutan began after the establishment of the Drug Regulatory Authority (DRA) in 2004 but a proper reporting system was instituted only after 2008[11]. The DRA is the national pharmacovigilance center (NPC) of Bhutan and is a member of the International Drug Monitoring Program since December 2014[12]. Pharmacovigilance centers located at the three referral hospitals detect, collect, assess, and report ADRs to NPC. HCPs from other hospitals report ADRs directly to NPC or through the pharmacovigilance centers to NPC.

Although ADR reporting is not mandatory in Bhutan, HCPs are encouraged to report ADRs voluntarily. HCPs can report ADRs either online or using the hard copy ADR reporting forms. There have been increasing incidences of ADRs with varying clinical manifestations as evidenced from the empirical findings of ADRs reported at NPC. However, there are no studies published to support this statement. Hence, this study was conducted to explore the demographic characteristics and types of ADRs, and common drugs causing these reactions from the ADR reports received at the NPC of Bhutan.

METHODS

Study design and sample size

A retrospective cross-sectional study design was used to analyze the ADRs reported to the NPC located at the DRA office in Thimphu. Universal sampling was used for the study, i.e. 222 ADRs reported during the study period were included in this study.

Study variables

The research instrument was used to collect study variables like demography of patients (age and sex), type of reporters (health center, health professionals), type of reactions, and suspected causative drugs for ADRs. The drug causing ADRs were grouped into different categories like antibiotics, anti-hypertensives, anti-diabetics, anti-depressants, anti-ulcers, vitamins, and others. Antibiotics were further classified as penicillins, anti-tuberculosis, quinolones, cephalosporins, macrolides, nitrofurans, and others. The gastrointestinal disorders (GI) with symptoms like diarrhea, abdominal discomfort, and vomiting were clubbed as GI disorders under the types of ADRs".

Causality assessment of ADRs using Naranjo's Scales

Naranjo Scale is a questionnaire designed for determining the likelihood of whether an ADR is actually due to the drug rather than the result of other factors[13]. Probability is assigned via a score termed as definite, probable, possible, or doubtful. The ADRs are grouped into four categories based on the scores obtained. If the score is ≥ 9 = definite ADR, 5-8 = probable ADR, 1-4 = possible ADR and 0 = doubtful ADR.

Statistical analysis

The data were coded into Epi-data entry (version Epidata 3.1) and Epi-Data Analysis version 2.2.2.182 was used for statistical analysis. Descriptive statistics in frequencies and percentages were used to present the demographic characteristics of ADRs, types of reporters, and drugs suspected to have caused ADRs. Categorical variables were compared using Fisher's exact or Pearson's Chi-Square depending upon the expected frequencies in the cells. If the expected frequencies in the cells containing less than 5 are more than 20%, then Fisher's exact test was used, otherwise Pearson's Chi-Square was used to find the association between variables. *p*-value <0.05 was considered statistically significant for the study.

Ethical considerations

The study was approved by the Research Ethics Board of Bhutan, Ministry of Health. (Ref. No. REBH/Approval/2018/039 dated 28th June, 2018)

RESULTS

Demographic characteristics

A total of 222 ADRs were reported to the NPC during the study period. The median age of the patients was 40 years, ranging from two months to 91 years. 73% (*n*=162) of ADRs occurred in adult groups while 13.5% (*n*=30) were observed in children and elderly. Our study showed that more than 64% (*n*=143) of the ADRs occurred in female patients. Statistically, no significant difference was found in the distribution of gender in the age groups (*p*-value = 0.08) as shown in Table 1.

Table 1. Demographic characteristics of patients whose ADRs were reported to the NPC of Bhutan from January 2016 to May 2018

Parameters	Frequency (n)	Percentage (%)
Age		
Median (IQR): 38(55-25)		
Mini-Max: 2 months-91 years		
Children	**30**	**13.5**
<2 years	5	2.3
2-11 years	7	3.2
12-18 years	18	8.1
Adults (19-64 years)	162	73.0
Elderly	**30**	**13.5**
65-74 years	18	8.1
75-84 years	11	5.0
>=85 years	1	0.5
Gender		
Female	143	64.4
Male	79	35.6

Type of reporters

Health facilities from the western region of the country contributed to 39.6% of total ADRs reported, followed by central region (31.1%) and eastern region (29.3%). Highest (*n*=73, 32.8%) number of ADRs reported were from Jigme Dorji Wangchuck National Referral hospital in Thimphu. Pharmacy professionals reported the highest number of ADRs (*n*=86, 38.7%), followed by Physicians (*n*=30, 13.5%). Other healthcare professional's (Nurses, Clinical Officers, Assistant Clinical Officers, and Health Assistants) altogether accounted for 47.8% of the total ADRs reported.

Types of ADRs

The most common ADRs reported was rashes (*n*=81, 36.5%) followed by GI system disorder (*n*=33, 14.9%) with symptoms like diarrhea, abdominal discomfort, and vomiting. The least reported ADRs were clinical manifestations related to peripheral edema (*n*=8, 3.6%), pyrexia (*n*=8, 3.6%), and electrolyte imbalance (*n*=3, 1.4%). No ADRs were significantly associated with age groups of the patients as shown in Table 2. Moreover, antihypertensive drugs were associated with all patterns of ADRs. Antibiotics were also associated with all patterns of ADRs except for electrolyte impairment as shown in Figure 1.

Table 2. Types of ADRs reported to the NPC of Bhutan from January 2016 to May 2018

ADRs	Total *n* (%)	Children *n* (%)	Adult *n* (%)	Elderly *n* (%)	*p*-value
Rash	81 (36.5)	16 (53.3)	56 (34.6)	9 (30.0)	0.107
Respiratory disorder	11 (5.0)	0 (0.0)	9 (5.6)	2 (6.8)	0.505
Anaphylactic reaction	8 (3.6)	0 (0.0)	7 (4.3)	1 (3.3)	0.840
GI system disorder	33 (14.9)	6 (20.0)	23 (14.2)	4 (13.3)	0.692
Peripheral edema	8 (3.6)	0 (0.0)	5 (3.1)	3 (10.0)	0.092
Headache/dizziness	28 (12.6)	0 (0.0)	25 (15.4)	3 (10.0)	0.058
Electrolyte imbalance	3 (1.3)	1 (3.3)	1 (0.6)	1 (3.3)	0.298
Lethargy/drowsiness	16 (7.2)	2 (6.8)	14 (8.6)	0 (0.0)	0.241
Pyrexia	8 (3.6)	1 (3.3)	6 (3.7)	1(3.3)	0.991
Others	26 (11.7)	4 (13.3)	16 (9.9)	6 (20.0)	0.273

Table 3. Classification of causal drugs for ADRs reported to the NPC of Bhutan from January 2016 to May 2018

Drugs	Frequency (n)	Percentage (%)
Antibiotics	108	48.6
Anti-hypertensives	33	14.8
Anti-depressant & anti-convulsant	18	8.0
NSAIDS**	14	6.3
Anti-ulcer	11	5.0
Anti-protozoal	8	3.6
Anti-diabetic	5	2.3
Vitamins	3	1.4
Others	22	10.0

***Non-steroidal anti-inflammatory drugs*

Causal drug groups

The most common drug group causing ADRs was antibiotics (*n*=108, 48.7%) followed by anti-hypertensive drugs (*n*=33, 14.9%) as shown in the Table 3. Among antibiotics, penicillins (*n*=35, 32.4%), followed by Quinolones and Cephalosporins (*n*=20, 18.5%) and Nitrofurans (*n*=14, 13%) were the most common causal drug groups.

Causality assessment

According to the assessment based on Naranjo's scale[13], more than 95% of ADRs reported were categorized as possible while less than 5% of ADRs belonged to other classes.

DISCUSSION

This retrospective study was an attempt to analyze the ADR reports reported to the NPC from January 2016 to May 2018. In our study, pharmacy professionals reported the highest numbers of ADRs (*n*=86, 38.7%) followed by physicians (*n*=30, 13.5%) which may be explained by the fact that most pharmacy professionals in Bhutan are working in pharmcovigilance centers. Probably,

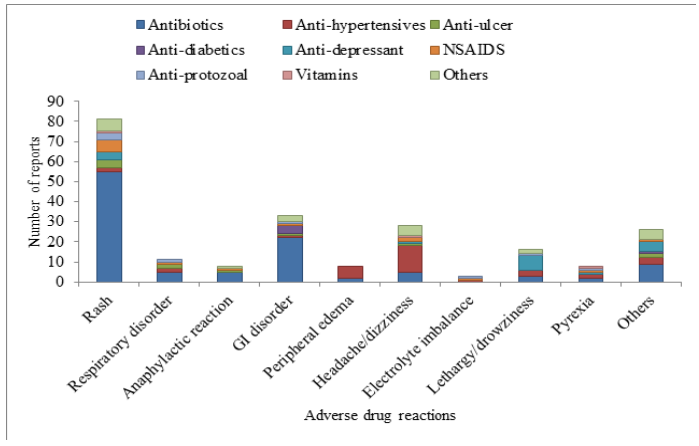

Figure 1. Number of ADRs classified based on specific group of drugs causing the ADR, from January 2016 to May 2018

pharmacy professionals may be more aware of reporting ADRs than other HCPs. Limited knowledge on pharmacovigilance and awareness on ADR reporting were attributed to underreporting [14–16]. Further, we speculate that more patients could have opted to consult pharmacy professionals over others on reporting ADRs.

In our study period, most (*n*=143, 64.4%) ADRs occurred in females than in males (*n*=79, 35.6%). This is in consistent with other studies[17–22]. There may be different factors contributing to higher ADRs in females such as the incidence of ADRs may be higher in female patients and females would have visited hospitals and consulted physicians more frequently than the males. A recent study by Zucker and Prendergast (2020) posited that females are likely to experience ADRs nearly two times that of males due to differences in their pharmacokinetic profiles[23]. On the other hand, some studies also showed that ADRs were implicated more in males as compared to females[6,24-26]. Therefore, further investigations are needed to explain this finding.

Many studies have reported skin as the most affected organ system by ADRs[17,27–30]. Our study showed that rashes (*n*=81, 36.5%) was the most commonly reported ADRs followed by GI system disorder (*n*=33, 14.9%) which is in congruent with the findings of another study[29]. This may be because dermatological reactions are easy to be identified and most of the suspected drugs were administered orally in our study. Also, the most common drug groups were antibiotics which are known to cause skin reactions.

The most common causal drug groups were antibiotics (*n*=108, 48.7%) followed by anti-hypertensive drugs (*n*=33, 14.9%) and this was supported by other studies conducted in Nepal and Iran [27,28,31]. The higher number of ADRs from these therapeutic groups may be due to higher consumption of these drugs which mostly cause immediate and easily observable reactions for which causality between the drug and the reaction can easily be made. This is also explained by the fact that the percentage of serious ADRs reported with these drugs was relatively low[17].

The common causality association with the suspected drug was "possible" (*n*=212, 95.5%) which was similar to the results of other studies[24,29,32]. Causality assessment has been a challenge due to a lack of information about de-challenge and re-challenge, concurrent use of multiple drugs, and the existence of comorbidities with similar symptoms. However, this does not undermine the importance of causality assessment.

Limitations of the study

This was a retrospective study and relied fully on spontaneous reports. Underreporting, inability to find incidence rate, lack of follow up data till recovery, and lack of information about substitute drugs used for the treatment of ADRs are the major limitations.

CONCLUSIONS AND RECOMMENDATIONS

This study analyzed the ADRs reports received at the NPC of Bhutan from January 2016 to May 2018. Most ADRs occurred in adults and rashes were the commonly reported ADRs. ADRs resulting from use of antibiotics (particularly penicillins, quinolones, and cephalosporings) were most common. The existing system of voluntary reporting of ADRs by HCPs may have resulted in underreporting. Training of HCPs on detection and reporting of ADRs must be prioritized to improve reporting by all categories of HCPs. Future research may focus on exploring ADRs in female patients, particularly those on antibiotic treatments, to enhance our understanding of nature and impact of these drugs in causing ADRs.

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AUTHORS CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

PC: Concept, design, data collection and analysis, manuscript writing and review.

JT: Design, data collection and analysis, manuscript writing and review

T: Design, data collection and analysis, manuscript writing and review

JD: Design, data collection and analysis, manuscript writing and review

KJ: Design, data collection and analysis, manuscript writing and review

Author agree to be accountable for all respects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

None

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