RESEARCH ARTICLE

Adverse Drug Reactions at Primary Health Centres in Malaysia

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ABSTRACT

Background: Adverse drug reactions can lead to a substantial economic burden on patients and the country. This study aims to analyze the pattern of adverse drug reactions and assess the causality of the adverse events and severity of adverse drug reactions in primary health centers in Malaysia.

Methodology: This retrospective study used case series analysis and data from six Malaysian primary health centers. The patients were analyzed for gender, age, class of drugs involved, organ system involved in the adverse reaction, severity using Hartwig's severity assessment scale and causality using the Naranjo ADR probability scale. Data were analyzed using descriptive statistics.

Results: In 113 adverse drug reactions were reported. Cardiovascular drugs commonly caused adverse drug reaction (38%), followed by anti-infective agents (20%), skin and subcutaneous disorders were the common adverse drug reactions encountered (23%). The severity of the adverse reaction was level 2 in most patients (69. 9%). Adverse drug reaction was mostly found to be probable (48.7%), and 64% of the patients recovered from the adverse drug reaction.

Conclusion: Cardiovascular drugs commonly cause adverse drug reactions. Level 2 and mild reactions were widely observed. The causality assessment was probable in most of the patients.

Keywords: Adverse drug reactions, Primary Health center, Malaysia.

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INTRODUCTION

Adverse drug reaction (ADR) is defined as a harmful, unintended effect of a drug which occurs at standard doses in humans for the prevention, diagnosis, or therapy of the disease or the modification of its physiological function.[1] They are associated with significant morbidity, mortality and permanent disability and are a substantial economic burden on the patients and the country due to prolonged hospitalization.[2] Adverse drug reactions can also harm the prescriber-patient relationship.[3] The estimated incidence of ADRs is 5 to 6% of all hospital admissions caused by drug-induced problems throughout the world.[4] Many issues can be associated with introducing drugs into the human body, and adverse drug reactions represent one of eight identified categories of drug-related problems.[5] Each time a drug is administered, we can never be guaranteed what might happen. The worse example of this is the thalidomide tragedy which occurred in the late 1950s. This drug was prescribed as a safe hypnotic to a pregnant woman, and it eventually caused phocomelia in babies born to these mothers.[6] Pharmacovigilance, or ADR monitoring, was established by world health organization (WHO) in the 1960s in the aftermath of the thalidomide tragedy and is now a collaborative effort involving more than 70 countries worldwide. Following this catastrophe, many counties implemented drug monitoring programmes in order to discover and prevent any drug-related morbidity and mortality as early as possible.[7] Research has shown enormous human and economic costs of adverse drug reactions. Most studies in the united kingdom (UK) revealed that ADRs account for up to 6.5% of admissions, with three-quarters of these being preventable. In 2.3% of patients admitted with an ADR died.[8] According to a systematic review, ADRs were responsible for 7% of hospital admissions and one out of every ten hospital bed days in the UK.[9]

In 1987, Malaysia launched its pharmacovigilance system, and in 1990, it joined the WHO's international drug monitoring programme.[10] The national centre regulates pharmacovigilance activities for adverse drug monitoring, a division within the national pharmaceutical regulatory agency (NPRA) established under Malaysia's drug control authority (DCA). Malaysian adverse drug reactions advisory committee (MADRAC) provides DCA with important information about drug safety issues.[11] Because the form used to report ADR to MADRAC is blue, the adverse drug reaction reporting system

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is referred to as the blue card reporting scheme. To encourage ADR reporting, MADRAC has made online reporting of ADR available.[12] The MADRAC newsletter 2018 reported adverse drug reactions of 15,936 in 2017. Over the past few years, there is a steady increase in the adverse drug reactions reported in the country.[13]

The Malaysian healthcare system is divided into two distinct sectors: public and private. The Ministry of Health is in charge of formulating and funding all policies and programmes. Patients seeking medical care at government health institutions will only have to pay a little charge because other medical costs, including the cost of the pharmaceuticals themselves, are covered by the government. On the other hand, the private sector is self-funded, and patients must pay for all their medical bills, either through private health insurance or out of pocket.[14] Because they pay directly for their healthcare, patients seeking medical treatment at private health institutions have higher expectations and are more demanding. As a result, private health facilities must maintain their reputation to keep current patients and attract new ones.[15] Hence, they need to decrease the hospital stay and reduce the incidence of adverse drug reactions may be one of the ways to do it.

Despite studies on Malaysia's adverse reactions, we do not have enough research on the pattern of adverse drug reactions in primary health centers. This study was planned to give us insight into reporting adverse drug reactions in the Petaling district's health centers. The study aims to assess the pattern of adverse drug reactions in the Petaling district's health centers and assess their causality and severity.

MATERIALS AND METHODS

Study Design

This was a retrospective study based on a case series analysis conducted in six primary health centers in the Petaling district, Malaysia. Petaling district is in the state of Selangor and has a population of 1,812,633 people. All reported cases of adverse drug reactions from 01-01-2014 to 31-12-2014 in six health centers following the grant of permission were analyzed.

Procedure

The National Institute of Health and Medical Research and the Ministry of Health Malaysia Research Ethics Committee (MREC) approved the study. Ethical clearance was also obtained from the Institutional Ethical Committee. Data regarding adverse drug reactions in the above said period was obtained from the six health centers' pharmacies in the Petaling district. The data was collected in an excel sheet and was analyzed for age, gender, race, drugs involved, type of adverse drug reaction and organ system involved in the reaction, causality assessment, severity assessment and outcome.

The medications causing adverse drug reactions were classified as per the anatomical therapeutic classification (ATC level 1). WHO recommends this classification and has five levels. We used level 1 classification to classify the active substances into 14 main groups depending on the organ or system they act upon.[16] The organs involved in the adverse drug reactions were classified as per the Medical Dictionary for Regulatory Activities (MedDRA)system order class. MedDRA is a globally recognized clinically validated medical terminology regulatory authorities use, divided into 26 system order classes (SOC).[17]

The causality assessment was done using the Naranjo probability assessment scale.[18] This scale consists of 10 objective questions for which the answers include yes, no, and don't know for each item, and the scores are given +1, 0 and 0, respectively. The scores were collated, and the drug reactions were classified as definite (9), probable (5–8), possible (1–4), and doubtful (0) as per the total scores.

The severity assessment was done using Hartwig's severity assessment scale.[19] The scale has seven levels depending on the extent of damage to the patient due to adverse drug reactions. Levels 1 and two are considered mild reactions, levels 3 and four as moderate and 5, 6, and 7 as severe.

Statistical Analysis

IBM SPSS version 25 was used to analyze the data. The results were expressed as %ages.

RESULTS

A total of 113 adverse drug reactions were reported from all six primary health centers. The mean age of these patients was 49.4 ± 18.4 years, and most of the patients were from the adult age group. The demographic details of these patients are shown

Table 1: Demographic details of the patients

Variable	*Percentage*
Age distribution	
≤ 18 years (Paediatric)	9
19–64 years (Adult)	72
≥ 65 years (Geriatrics)	19
Gender	
Male	33
Female	67
Ethnicity	
Malay	60
Chinese	17
Indian	23

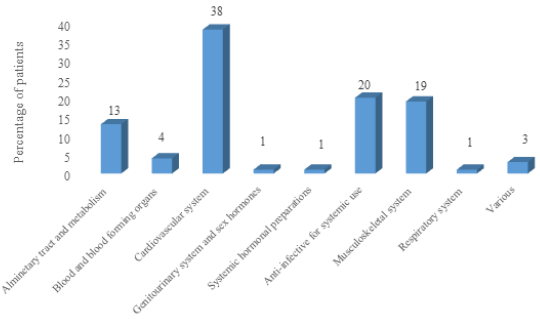

Figure 1: ADRs for drugs distributed by therapeutic group (ATC level 1)

in Table 1. Most of the patients were females (67%), and the common ethnic group was Malay (60%).

As shown in Figure 1, the most common group of drugs causing adverse drug reactions is cardiovascular drugs (38%), followed by anti-infectives for systemic use (20%).

The common adverse reactions seen is skin and subcutaneous disorders (23%) followed by immune system disorders (21%) (Figure 2).

The adverse drug reaction's causality was probable in most of the patients (48.70%) (Figure 3).

Most of the patients had level 2 (69.9%) severity of adverse drug reactions (Figure 4), followed by level 3 (21.20%).

As shown in Table 2, most of the patients had mild reactions (78%) and most recovered from the adverse drug reactions (64%).

Table 2: Seriousness and outcome of the adverse drug reactions

Variable	*Percentage*
Seriousness	
Mild	78
Moderate	21
Severe	1
Outcome	
Unknown	36
Recovered	64

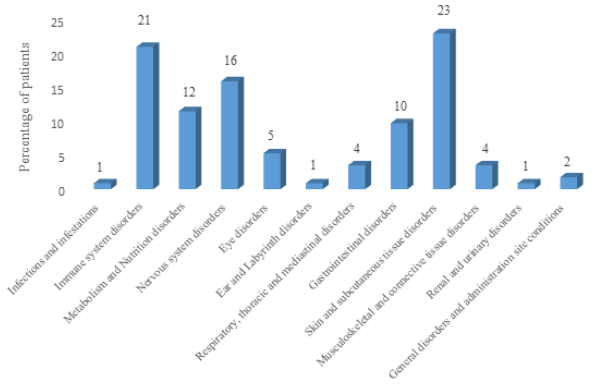

Figure 2: ADRs as per MedDRA system order class (SOC)

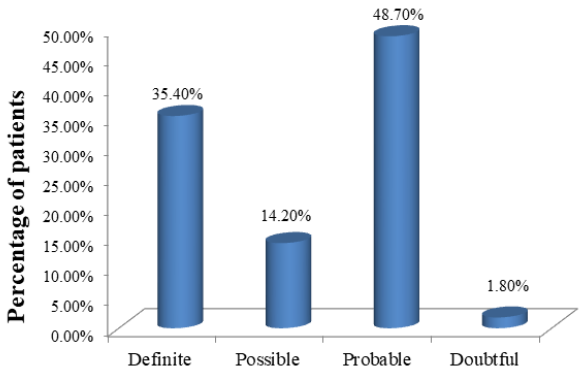

Figure 3: Naranjo's causality assessment of the adverse drug events

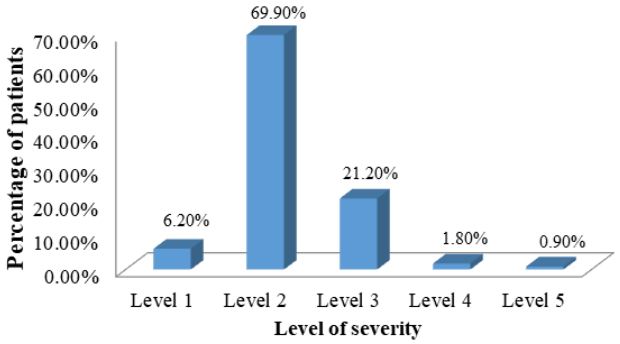

Figure 4: Hartwig's severity assessment of the adverse drug events

DISCUSSION

The occurrence of adverse drug reactions after previous exposure to the same drug is a significant risk factor. Reintroduction of the offending drug due to insufficient documentation can amount to medical negligence. Hence, documentation of the adverse drug reactions with the relevant dechallenge and rechallenge information and keeping the patient aware of potential ADR in the future is essential. Our study emphasizes the importance of studies that give an overview of the common offending agents causing adverse drug reactions. The study would help the regulatory authorities and healthcare professionals take the necessary steps to reduce the incidence of adverse drug reactions.

Our patients' mean age was closer to the elderly age group, as most of the patients were in the adult age group. This finding was in consensus with India's study, which reported that the mean age of the patients who experienced adverse effects was 49.26 years.[20] In research conducted in Penang, Malaysia on cutaneous adverse drug reactions, the mean age was 45 years.[21] Age is considered a risk factor for adverse drug reactions, and studies have found a higher incidence of adverse reactions in elderly and pediatric age groups. However, in our research, we found more adverse drug reactions in the adult age group. This finding could be because most of the patients attending the health centers included in our study were from this age group. The presence of comorbid conductions and polypharmacy could also be a reason for adverse drug reactions in our patients as our patients' mean age was high.

We found a female predominance in our study. A study conducted on adverse drug reactions on antibiotics in Malaysia found male predominance in patients with adverse drug reactions.[11] A study conducted in Brazil also showed a male predominance, unlike ours.[22] However, a study conducted in India showed a female with a higher prevalence.[23] The difference in adverse drug reactions between men and women could be attributed to differences in body mass index (BMI) and fat content or hormonal influences on drug metabolism. We also found that adverse drug reactions were more among Malays in our study population. This was in concurrence with the study conducted on cutaneous adverse drug reactions and the study conducted on adverse drug reactions to antibiotics

conducted in Malaysia.[11,21] Malaysia has three ethnic groups: Malay, Chinese and Indians, of which Malay is the predominant ethnic group. This reason for Malay predominance could be because the patients attending these primary health centers mostly belong to the Malay ethnic group.

When we analyzed the drugs causing adverse drug reactions, we found cardiovascular drugs frequently encountered drugs causing these reactions. Amlodipine and perindopril were the common cardiovascular drugs involved. The next common was anti-infective, of which amoxicillin was the common offender. A retrospective study conducted in Bulgaria showed a constant ADR occurrence due to cardiovascular and neurological drugs from 2013-2016.[24] In a study conducted in India, the researchers found antimicrobials to be the common group causing adverse drug reactions, which was second most common in our study population.[25] Kanjanarat *et al.* reported that quantitative analysis showed cardiovascular drugs were most frequently associated with adverse drug reactions,[26] which is in concurrence to our study. Most commonly, we encounter patients with cardiovascular conditions, especially hypertension, in primary health centers. This finding could be the reason for reactions due to cardiovascular drugs being prevalent in our patients. In research on hospital admissions owing to iatrogenic illness, Lakshmanan *et al.* discovered that antihypertensive medicines were responsible for the majority of iatrogenic admissions.[27] Our patient population's mean age was 49.4 ± 18.4, where cardiovascular conditions are common due to age-related pharmacodynamics and pharmacokinetic alterations with comorbid conditions and polypharmacy. This could be why there is a frequent occurrence of adverse drug reactions due to cardiovascular drugs in our study.

The common symptoms reported in our study were skin and subcutaneous tissue disorders. Unlike our observation, two South India studies reported central nervous system (CNS) and gastrointestinal adverse effects as a common occurrence.[7,25] However, our research findings concur with another study that said skin reaction was common in their population.[23] A study conducted in Malaysia on adverse reactions due to antimicrobials had skin reactions as a common occurrence.[11] Our skin and subcutaneous reactions were common because we commonly encountered mild reactions and very less severe reactions.

The assessment of causality of adverse events is an important part of pharmacovigilance since it helps to better understand the risk-benefit profile of medications. It's a way of determining the extent of the association between a drug and a suspected reaction.[6] Assessment based on clinical judgments may be subjective and imprecise.[28,29] In our study, most of the adverse drug reactions were probable, followed by definite. This finding was contradictory to the studies conducted in Malaysia and India, which showed possible as the common reaction.[30] However, other studies conducted in Malaysia and India on adverse drug reactions showed probable as the common causality, which was in consensus with our research.[20,11] To improve the quality of causality assessment, the health professionals must be familiarised with the ADR reporting forms and ensure that it is duly filled, with all the necessary details for the causal analysis.

Hartwig's severity scale shows that our patients mostly had level 2 severity and mild adverse drug reactions. This finding did not agree with the studies conducted in India and Malaysia, were moderate reactions was commonly encountered.[7,11] However, another study's results were in consensus with ours, where the adverse reactions they found were primarily mild.[25] Mild reactions do not require any changes in treatment or additional treatment needed for these reactions. Discontinuing the drug can be the only intervention necessary for mild reactions. In our study, the common reactions we observed were skin and subcutaneous tissue reactions. The severity of such reactions is mild, and they do not require interventions, and just withdrawing the drug will suffice. There was only one severe adverse reaction in our study, and it was for metformin, where the patient had blurred vision. We did not encounter any fatal, life-threatening, disabling adverse drug reaction, nor any ADR requiring or prolonging hospitalization. Most of our patients recovered as we commonly experienced mild reactions in most of our patients.

We observed that there might be an underreporting of the adverse drug reactions by the patients or the health professionals. The number of adverse reactions reported is very few compared to the vast population of patients and the country's incidence rate. Underreporting can be a crucial hindrance to the improvement of health care. The uncertainty of reaction types to report, ADR being regarded as too insignificant or well-known to be notified, and lack of information about the presence, function, and purpose of national ADR reporting were all significant factors that kept physicians from reporting ADR in Malaysia. Improvement in reporting of adverse drug reactions is essential, as it is the only post-marketing surveillance system in Malaysia.[31]

CONCLUSION

In our study, cardiovascular drugs were the common cause of adverse drug reactions and skin and subcutaneous reactions are the typical reactions seen. Most reactions were probable as per the Naranjo causality assessment. The adverse drug reactions were primarily level 2 and mild as per Hartwig's severity scale, and most of the patients recovered from the adverse reactions. Adverse drug reactions are an inevitable risk in patients taking medications. However, this can be limited by rational drug prescribing practices. Dissemination of information regarding ADRs to healthcare professionals and patients can go a long way in curtailing this problem.

Limitation of the study

The study's limitations were that the study was conducted only in a single district and just six health centers. More health centers from different districts could give a more holistic picture of the whole country's situation. The study provides baseline data for more extensive studies, and further studies with larger population size are required to substantiate our findings.

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