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Adverse Drug Reactions among Patients Admitted to Eritrean Hospitals: Prevalence Causes and Risk Factors a prospective analysis of 5848 patients

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Abstract

Background: Eritrea is one of the developing countries which has shortage of physicians at all levels. As a result, lower health cadres are authorized to prescribe medicines. In addition, due to shortages of laboratory setups, lab-based therapeutic monitoring is a challenge. The Eritrean society is also highly involved in self-medication; all these could have contributions to ADRs. Thus, the objective of the study is to investigate and analyze the prevalence, causes, and risk factors of Adverse Drug Reactions (ADRs) among patients admitted to Eritrean hospitals.

Methods: A prospective study was carried out for a period of five-month in all Eritrean hospitals. All patients admitted to the Eritrean hospitals from March 20 – August 20, 2014, were screened for ADR related hospital admissions.

Results: A total of 5,848 patients admitted to Eritrean hospitals were screened for ADRs and 922 (15.8%) patients were identified with at least one suspected ADR before or after admission. The prevalence of ADR as a cause of admission was found to be 7%. ADR related death was found to be 0.82% (48/5848) and 75% of them were preventable. 40.8% of the suspected ADRs were found to be preventable.

Conclusions: ADR is becoming one of the major public health problems, causing significant morbidity and mortality among patients admitted to Eritrean hospitals. Around 41% of the ADRs could have been prevented through appropriate clinical and laboratory monitoring, appropriate drug history taking, proper management of ADRs, good dispensing and prescribing practices as well as refraining from self-medication.

Keywords: Adverse Drug Reactions; Occurrence; Risk Factors; Hospital Admissions; Hospitals; Eritrea

Introduction

Adverse Drug Reaction (ADR) is one of the major public health problems in many countries. Studies conducted in developed countries show that the burden of ADR is significant. A study on 18,820 patients admitted to two National Health Service hospitals in the UK show that 6.5% of patient admissions were related to ADRs [1]. This finding is broadly compatible with pooled data from older studies, and with other similar studies [2-5]. A recent review on the epidemiology of ADRs in Europe found that 3.5% of hospital admissions were due to ADRs [6]. An observational study aimed at measuring the burden of ADRs in medical wards of four hospitals conducted in South Africa also found 8.4% ADR related hospital admissions [7].

The African healthcare delivery system is immature and highly stretched which have inadequacy of well-trained healthcare professionals [8,9]. The high prevalence of public health diseases like HIV, multi-drug resistant TB and malaria urged the emergence of new medicines to tackle the diseases burden without proper therapeutic monitoring in many parts of the continent [8,9]. Despite the high probability of occurrence of ADRs in African countries, to-date, no nationwide ADR studies have been conducted. Studies so far conducted in Africa focus either to certain provinces or hospitals in specific age groups.

Eritrea has also shortage of physicians (1:18,041) at all levels of healthcare delivery points [10]. As a result, several lower categories of health workers are authorized to prescribe medicines. In addition, as there are shortages of laboratory setups, lab-based therapeutic monitoring is a challenge, even for patients taking drugs with serious ADR profiles or drugs with

narrow therapeutic margins. Prescriptions, therefore, heavily depend on empiric treatment in many of the hospitals. Though comprehensive research data are lacking, the Eritrean society is also highly involved in self-medication; all these could have potential contributions to ADR related harms. However, no ADR related studies have been conducted to-date. The objective of the study is therefore, to investigate and analyze the prevalence, causes, and risk factors of ADR related hospital admissions among patients admitted to Eritrean hospitals.

Methods

Study Design, Setting and population

The study was a prospective one carried out for five-month period in all Eritrean hospitals which include: seven national referral hospitals, five regional referral hospitals, eight community hospitals and one private hospital. Both Adi-keih hospital and Berhan Eye National Referral hospital disqualified from the study during the third month as the researchers couldn't comply with pre-set standards. The study was conducted by the Eritrean Pharmacovigilance Center in collaboration with the WHO Country Office and Asmara College of Health Sciences.

All patients admitted between March 20 and August 20, 2014 were included in the study. The study population consisted of all age groups except neonates. For the purpose of this study, the WHO definition of an ADR was used. WHO defines ADR as "a reaction which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function [11].

Exclusion Criteria

The study only measures the magnitude of the problem at the three hospital levels (tertiary, secondary and primary). Other lower health facilities and outpatient departments were not part of the study. Mothers admitted for delivery reasons were excluded from the study as they were not part of our prevalence (indicative of patients admitted due to ADRs). Moreover, Neonates, less than one month old, were also excluded from the study due to the difficulty to diagnose ADRs in those patients.

Study instruments and data collection approach

The study protocol, data collection tools and field guide were developed by a group of expert's different disciplines and institutions. 'Good Case Management Practice: a Field Guide' was prepared to help the research team in clinical assessment of ADRs like determination of causality, seriousness, expectedness, preventability, diagnosis, case follow-up approaches and good case narrative writing. In each hospital, a Physician and a Pharmacist were recruited to assess ADR related admissions on daily basis for five months. All eligible patients were screened for ADR related hospital admissions. During screening, the investigators were taking detailed drug and medical history. Demographic information of all the eligible patients admitted in the five-month period was also documented using a 'Patient Listing Form'.

Causality and Preventability assessments were performed for all suspected ADR cases using Naranjo probability scale and P-method respectively [12,13]. The preventability criteria are those that are considered by the reviewer as crucial (determinant) for the occurrence of ADRs. These risk factors constitute 20 criteria that are used to assess the avoidability of ADRs. It explores risk factors in relation to healthcare professionals' practices, patient factors and medicines quality. The case is considered as 'preventable' when one or more critical criteria (factors contributed to the likelihood of an ADR) are identified. The ADR is deemed 'non preventable' if none of the critical criteria are identified. The case is categorized as 'not assessable' if there are no data or insufficient data for assessment (e.g. an anaphylactic reaction due to penicillin is deemed 'not assessable' if the patient's previous history of drug allergy is not documented) or if the situation is controversial [13,14].

All cases initially categorized as having an ADR were assessed again in the Eritrean Pharmacovigilance Center by panel of experts, to reach an agreed decision on causality and exclude doubtful cases. Expectedness of ADRs was assessed by referring updated summary of product characteristics and reliable medical references and publications.

To ensure that patients with ADRs had not been missed, the field supervisors were assessing 10 - 15 random patients categorized as 'not having ADR' at every supervision visit in each hospital.

Outcome measures

In this study, adverse drug reaction related hospital admissions, patients developed ADRs while admitted for other reasons, ADR related hospital stay, ADR related deaths, patients with preventable ADRs and economic burden of ADR related management costs were the primary outcomes measured.

Data Processing and Statistical Analysis

Data was captured into computer using an entry program developed with CSPro version 5.0 software package. All questionnaires were entered twice; that is 100% verification was done to eliminate keying errors during entry. Data was edited during and after data entry using CSPro and Statistical Package for Social Science version 20 (SPSS-20). Both descriptive and analytical analysis was carried out on the data using SPSS. These include both univariate and bivariate analysis. The results are presented either as medians and interquartile ranges or percentage frequencies and 95% confidence intervals, as appropriate. A P-value <0.05 was regarded as being statistically significant.

Ethical considerations

The Research Ethics and Protocol Review Committee

of the Ministry of Health, Eritrea has approved the study to be carried out throughout the country. In addition, consent was obtained from each patient prior to his/her participation in the study.

Results

In this study, a total of 5,848 patients admitted to Eritrean hospitals were screened for ADRs and of these, 52.8% (3088) were male. Of the whole cohort screened for ADRs, 2,433 (41.6%) were pediatrics (aged between 1 month and 15 years) and 15% were geriatrics (> 61 years). A total of 922 (15.8%) patients were identified with at least one suspected ADR before or after admission. It was also found that 7.0% (409/5,848) of all screened patients were admitted due to suspected ADRs (Table 1). ADR was a cause of admission in 6.2% (190/3,088) of males and 7.9% (219/2,760) of females. Similarly, the overall occurrence rate of ADRs was for males and females was 15.1% and 16.5% respectively (Table 1). The variation in the occurrence rate of ADRs between males and females was statistically not significant

Table 1: Incidence and Prevalence of ADR by age and sex

Characteristics	ADR as a cause of hospital admission (prevalence)	Overall occurrence rate of ADRs	Number of Patients
	%	%	
Sex			
Male	6.2	15.1	3088
Female	7.9	16.5	2760
Age			
Under 1 year	1.9	7.5	729
1-5	3.2	10.0	1178
6-15	11.8	20.2	526
16-60	9.1	19.6	2540
61 and above	7.3	16.5	875
Total	7.0	15.8	5848

The highest ADR related hospital admissions (11.8%) and the highest occurrence rate of ADRs (20.2%) was seen in pediatric patients aged 6 – 15 years. The variation in the incidence of ADRs by age was statistically significant.

On average, every ADR patient in this study was taking 2.5 drugs per prescription. In the Central region, where the highest occurrence rate of ADRs was documented, 29% of the patients with ADRs were taking more than or equal to five drugs per prescription.

During the study period, a total of 1,126 ADRs were documented among the 922 patients admitted due to ADRs, out of which 811 (72%) were serious. Adverse drug reactions were described as serious those caused either death or life-threatening, hospitalization, prolonged hospitalization, permanent/persistent disability, congenital anomalies, or require intervention to prevent permanent injury [15]. 4.4% of the documented ADRs were fatal and the variation in fatality rate of ADRs between males and females was not statistically significant.

About 92% of the ADRs encountered were previously documented or labeled in universally accepted medical literatures. 15% (139/922) of the patients with ADRs had a similar reaction to the same or similar drugs in previous exposures. Of all admitted patients, 0.82% (48/5,848) were died of suspected ADRs. Of the total ADR related deaths, 85.4% were suspected to be directly caused by ADRs and the rest were contributory. It was also found that, 39.6% (19/48) of the total deaths were children. With respect to drug–reaction relationship (causality assessment), 63.8% of the ADRs were found to be probable (Table 2). The causal relationship in majority of the suspected death cases was found to be possible (58.3%) (Table 3).

Table 2: Causality and preventability assessments of all ADRs

Assessment	Category	Frequency of ADRs (n; %)*
Causality	Certain	64 (5.7%)
	Probable	718 (63.8%)
	Possible	344 (30.5%)
Preventability	Preventable	459 (40.8%)
	Non preventable	628 (55.8%)
	Non assessable	39 (3.4%)

*Denominator, total number of ADRs, n=1126

Table 3: Causality and Preventability assessments of the ADR related deaths

Assessment	Category	Frequency of ADRs (n; %)*
Causality	Certain	1 (2.1%)
	Probable	19 (39.6%)
	Possible	28 (58.3%)
Preventability	Preventable	36 (75%)
	Non preventable	9 (18.8%)
	Non assessable	3 (6.2%)

*Denominator, the total number ADR related deaths, n=48

Using the P-Method, 40.8% of all the suspected ADRs was preventable. Of the total preventable cases, 82.7% were related to professional practice, of which 26% were attributed to inappropriate laboratory or clinical monitoring of medicines, while 17.3% of the preventable cases were patient related factors

(non-compliance and self-medication with non OTC drugs). 75% (36/48) of the ADR related deaths were preventable (Table 3).

43.5% (490/1126) of the ADRs led to discontinuation of a medication as part of case management and 77.2% of the ADRs were given specific or symptomatic treatment. Following treatment and/or management, 76.8% of the reactions were recovered.

The overall mean duration of hospital stay of patients admitted with ADRs during the study period was 9.2 days. With regard to the economic burden, the average management cost for the encountered ADRs was used 318 per patient.

Discussion

This study showed that ADR related hospital admissions accounted for 7.0% of all hospitalizations. This 7% prevalence of ADR as cause of admission in Eritrea is more or less similar to the findings of a study conducted in Mumbai, India (6.9%), South Africa (8.4%) and much higher than that of European countries (3.5%) [16,7,6]. However, it good note that the age distribution of our study population is dramatically different which includes all segments of our population except neonates.

ADR related death in our study (0.82%) was also similar to the findings from India (0.83%) and South Africa (2.9%) but much higher than the findings of studies conducted in developed countries like US (0.32%), UK (0.15%) and EU (0.25%) countries[17,1,2,6]. Though the occurrence rate of ADRs in our study (15.8%) was found to be similar with the findings from UK (14.7%), US (15.1%) and EU (17.0%), ADR related death was much higher in our case and also in other developing countries like India and South Africa which may reflect the differences in the level of development of the healthcare delivery systems between developing and developed countries. The differences in fatality rates could be due to drug utilization and monitoring systems, level of awareness on management of ADRs, self-medication habits, prescribing and dispensing practices and inter-country differences in susceptibility.

Nearly three-fourths of the reported ADRs in this study were serious, with a fatality rate of 4.4%. Fatality rate indicates the percentage of fatal ADRs out of all the reactions encountered. The fatality rate and occurrence of ADRs were significantly higher in children compared to the other age groups (Table 4).

This is possibly because children are more susceptible to ADRs as their capacity to metabolize drugs is not fully developed and have difficulties in reporting suspected ADRs as early as possible which could lead to poor management [18,19]. This urges policy makers and programmers need to provide utmost attention on pediatric segment of the population which include extensive therapeutic monitoring and training on proper diagnosis and management of ADRs.

Table 4: Distribution of ADR related deaths by age

Age group	Number of deaths	%	Fatality rate
< 1	4	8.3	7.3
1 – 5	9	18.8	7.6
6 – 15	6	12.5	5.7
16– 60	22	45.8	4.4
> 61	7	14.6	4.9
Total	48	100.0	

Source: Computed based on data gathered

In the Central region, where the highest occurrence rate of ADRs was documented, 29% (113/388) of the patients with ADRs were taking five to eight drugs per prescription. This finding is in line with medical literatures which state the likelihood of ADR occurrence increases with simultaneous use of several drugs [20-23]. The high number of drugs per prescription in the Central Region is linked to the availability of tertiary referral hospitals which provide healthcare services for patients with complicated health problems. This shows that taking multiple drugs or Polypharmacy was another risk factor for occurrence of ADRs.

40.8% of the ADRs and 75% of the ADR related deaths were preventable. This was found to be similar to the findings from Dormann, et al. (44.3%); whereas Pirmohamed, et al. revealed a larger number (72%). Results of a meta-analysis found the rate of preventable ADRs to be 59% [24,1,25]. The preventability rate of ADRs differs from study to study which is perhaps because different studies use different tools for assessment of preventability. Regardless of the consistency of the findings, the findings above indicate that a significant portion of the mishaps can be prevented with certain interventions.

Of the preventable ADRs in our study, 82.7% (448/459) were related to professional practice. Inappropriate therapeutic monitoring, inappropriate prescription for patient's clinical condition, inadequate medication history taking and wrong indication were found to be among the major causes of the preventable ADRs in Eritrea. Patient related factors such as self-medication of prescription drugs and non-compliance were also identified as causes and/or risk factors of preventable ADRs. This shows that most of the preventable ADRs were caused by healthcare professionals and 26% of these ADRs could have been prevented if only appropriate laboratory or clinical monitoring of treatment was in place. For instance, drug related fatal anemia accounted for 20.8% of the ADR-related deaths and these could have been prevented with appropriate laboratory monitoring. It was also noticed that, self-medication of prescription drugs was the main patient related attributing factor which can be minimized by scheduling of medicines, training and controlling

of medicines retail outlets. 15% of the patients with ADRs had a similar reaction(s) to the same or similar drug(s) in previous exposures. Meaning: more than 15% of the identified ADRs could be prevented by taking appropriate medication history. Hence, it is also important to note that inaccurate medication histories taken in hospitals and inappropriate treatment monitoring are causing serious preventable ADRs.

Zidovudine/Lamuvidine, Tenofovir/Emitrictabine), first-line anti-TB medicines and phenobarbitone were the top three medicines implicated in causing ADR related deaths (Table 5). Co-trimoxazole, Insulin, Ampicillin, Quinine sulphate injection and Zidovudine/Lamuvidine were also found to be the top five medicines that most frequently reported in causing ADRs. Furthermore, anti-TB, anti-retroviral drugs and other anti-infectives were the most commonly offending class of drugs in causing ADRs. In this regard, it is high time for the Public Health Programs to integrate Pharmacovigilance into their systems.

ADR is found to be an important cause of hospital admission and prolonged hospitalization in Eritrea. The mean length of hospital stay of patients admitted with suspected ADRs was 9.2 days as compared to the overall hospital stay (4.5 days) of the country in 2013. This is consistent with the previous findings that suggested patients with ADRs stay longer in hospitals compared to those admitted with other disease conditions [26-28]. The economic burden part of this study will be published separately in the subsequent publication.

One of the major limitations of this study was under-reporting that could not be avoided at all. The supervisory team screened around 360 patients classified as 'not having ADR' and found six false negative cases, indicating that there was under reporting. Even though demographic information was collected for all patients admitted to hospitals, other potential risk factors like co-morbidities and patients' social factors (use of alcohol, tobacco…) were not documented. Besides, we did not collect information on number of drugs taken, hospital stay and so on from those patients admitted to the hospitals with other disease conditions other than ADRs. Hence, we could not compare some important variables among the study subjects to test significance levels.

Table 5: Overview of fatal ADRs with suspected drugs

	Fatal ADRs (number)	**Suspected medicine (s) (frequency)**
1.	Anemia (10)	Zidovudine/Lamuvidine (4), Tenofovir/Emitrictabine(2), Phenobarbitone (1), Abacavir/Lamuvidine(1), Glibenclamide (1) and Fluconazole (1)
2.	Severe Hepatotoxicity (9)	First line Anti-TB drugs (3), Phenobarbitone (2), Ceftriaxone (1), Cloxacillin (1), Paracetamol (1), Co-trimoxazole (1)
3.	Perfused Diarrhea (5)	F-75/100, Ampicillin, Atripla, Metronidazole, Quinine Sulphate
4.	GI Bleeding/ (2)	Rifampicin(1), Metformine Hcl (1)
5.	Hemorrhage (2)	Warfarin, Rifampicin
6.	Hypoglycemia (2)	Insulin lente
7.	Renal Failure (2)	Artesunate Injection (1), Gentamycin Sulphate(1)
8.	Acute Psychosis/Suicide (2)	Efavirenz
9.	Arrhythmia	Digoxin
10.	Electrolyte imbalance	Gentamycine Sulphate
11.	Birth Asphyxia	Co-trimoxazole
12.	Anaphylactic Reaction	Crystalline Penicillin
13.	Cushing syndrome/ Uncontrolled DM and Hypertension	Prednisolone
14.	Neurotoxicity	Artesunate/Amodiaquine tablet
15.	Pancytopenia	Gentamycine Injection
16.	Pneumonia	Prednisolone - prolonged used
17.	Diarrhea with Shock	F-75 (Therapeutic feeding)
18.	Hypotension	Enalapril and Hydrochlorothiazide interaction
19.	Thrombophlebitis	Cloxacillin Injection
20.	Respiratory Distress	Ceftriaxone and F-75
21.	Peptic ulcer disease followed by Adinocarcinoma	NASIDS (Ibuprofen and Aspirin taken daily for about 10 years)

Conclusion

This study confirmed that the ADR related morbidity and mortality in Eritrea is highly significant with substantial economic burden for the government of Eritrea and patients that need immediate intervention. The main causes and/or risk factors of ADRs in Eritrea are inappropriate therapeutic monitoring, inappropriate prescription for patient's clinical condition, inadequate medication history taking, polypharmacy, wrong indication, self-medication and non-compliance. Younger age was also identified to be one of the risk factors for the occurrence of ADRs. Hence, policy makers and relevant programs need to provide utmost attention on pediatric segment of the population.

Based on the findings, the recommended interventions for minimizing ADR related public health problems are strengthening therapeutic monitoring , equipping health facilities with required laboratory setups, involving pharmacists during word rounds, enhancement of prescribing and dispensing practices, educating the public to refrain from self-medication, introducing 'alert cards' for drug allergic patients and involvement of patients in ADR monitoring and reporting [29-33].

Authors' contribution

The idea is conceived by MR, IB and ME. MR, DT, ME, MT, IB, HA, MT, UA and SG developed the data collection and analysis tools. MR, DT, HA and EB played a key role in assessing the cases. MR and DT wrote the article and edited by the rest of the authors.

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Competing interests

The authors Mulugeta Russom, Dawit Tesfai, Medhanie Elias, Merhawi Teklai, Iyassu Bahta, Hagos Ahmed, Melake Tewolde, Usman Abdulmumini, Semere Gebregiorgis and Eyob Beyene declare that they have no competing interests. and no sources of funding were used to carry out the study.

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