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Original Article

Antibiotics related adverse drug reactions in Ethiopia

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Abstract

Antibiotics are one of the most common drugs that can induce adverse drug reaction (ADR). A retrospective analysis was conducted using suspected antibiotic-related ADR data collected from the Ethiopian Pharmacovigilance Center over a 5-year period (2014-2019). There were a relatively large number of antibiotic-related ADRs (57.9%) containing 462 suspected drugs reported, with adults aged 18-64 (65.5%) and females (61.5%) predominating in the reported cases. Monotherapy and oral route administration were responsible for 85% and 83% of ADRs, respectively. Co-trimoxazole and amoxicillin were responsible for more than half of the reported ADRs and skin disorder was half of the affected system organ (SOC). Serious ADRs constituted 26% of all reported ADRs. The outcome of the patient showed that (44.7%) of patients were completely recovered after discontinuing the offending drug and additional intervention. The finding in this study suggests that antibiotic related ADRs are a significant health problem for patients in Ethiopia and further health facility based research is suggested.

Keywords: antibiotics, adverse reactions, Ethiopia, retrospective study, spontaneous report

1. Introduction

Adverse drug reaction (ADR) is a harm that is directly caused by the drug at normal doses, during normal use (Ritter, Lewis, Mant, & Ferro, 2008). Studies confirmed that no drugs, including antibiotics, are free from adverse reactions (Rieder, 2018). Globally, the high prevalence of ADRs has increased morbidity and mortality in both hospital and community settings (WHO, 2015). In the general population, fatal ADR can be the seventh cause of death (Wester, Jonsson, Spigset, Druid, & Hagg, 2008). The incidence of adverse drug reactions in different clinical settings is reported to be 10–25 % (Tripathi, 2013).

Several studies indicate that antibiotics are one of the most important drugs widely known as ADR-inducing. A systematic review of 25 ADR studies in India shows that antibiotics are more prone to ADRs (35.33%) (Akshaya, Kalyani, & Srihitha, 2017), whereas, antibiotics (cephalosporins and penicillin) were the most frequently reported drug associated with ADRs (22%) in Portugal over a 10 year-period (Marques, Ribeiro-Vaz, Pereira, & Polonia, 2014). In a study conducted in a tertiary care hospital in South Korea, antibiotics (penicillin and quinolones) were responsible for 62.8% of ADR, with skin manifestations being the most frequently reported symptom (Jung *et al*., 2014), similarly, in an Indian tertiary care hospital, beta-lactam were responsible for 42.2% ADRs, with skin rashes and urticara accounting for 57.2% (Kumar, 2019).

Antibiotic use is common in the inpatient setting in Uganda; antibiotics contributed to 41% of all suspected ADRs in hospitalized patients (Kiguba, Karamagi, & Bird, 2017) and 11% of emergency department visits in India (Sekhar, Mary, Anju, & Hamsa, 2011); and are also responsible for a significant proportion of hospital acquired ADRs in the US (10%) (Weiss, Elixhauser, Bae, & Encinosa, 2011). A retrospective study conducted in Malaysia revealed that vancomycin and co-trimoxazole were the major contributors to ADR. However, penicillin was responsible for the majority of the severe ADRs, and the skin was the most affected organ by ADRs, followed by gastrointestinal system (Arulappen, Danial, & Sulaiman, 2018).

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In Ethiopia, there is a lack of evidence for antibiotics-related ADRs. However, inappropriate antibiotic use is a major concern (Muhie, 2019), with 56% of prescriptions containing one or more antibiotics (Worku & Tewahido, 2018). This inappropriate and over use of antibiotics has been linked to an increased risk of ADRs. Therefore, the main objective of this study was therefore to characterize the recent spontaneously reported antibiotics-related ADR.

2. Materials and Methods

This was a retrospective and descriptive analysis using antibiotic related ADR data collected from the Ethiopian National Pharmacovigilance (PV) Center that was submitted by health facilities over a 5-year period (2014-19). The data extracted from the suspected ADR reports which contained; patient-related variables, suspected drug, ADRs description, reaction necessitated and outcome.

2.1 Data analysis and interpretation

The data collected from spontaneous ADR reports were entered into MS Excel 2013 and transferred to SPSS V22 for analysis. Data on ADRs according to patient characteristics, ADRs, drugs profiles, seriousness of the reaction, outcome and time of occurrence were described as frequencies and percentages and were presented in tables and graphs. The reported ADRs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) (Thiessard *et al*., 2005) and seriousness of reactions was classified according to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2A criteria (ICH Guideline, 1994). An individual ADR reported with over one drug in a single case were considered one time (Cliff-Eribo, Choonara, Dodoo, Darko, & Sammons, 2015). Two or more ADRs reported in one patient and two or more medications involved in one event were counted as different (WHO, 2013). If, within the same report, there was over one adverse reaction belonging to the same SOC, that SOC was counted just once. No causal assessment was realized thus all the collected ADRs are going to be considered suspected ADRs (Potchoo *et al*., 2018).

2.2 Ethical approval

In order to comply with accepted ethical standards, no reference to the actual names of patients or health facilities has been recorded. Thus, no individual or health facilities were linked to a particular finding, thereby ensuring anonymity. Ethical approval was obtained from the City Government of Addis Ababa Health Bureau Research Ethics Committee (registration number 39279/227) and official permission was obtained from the Ethiopian Food and Drug Administration (EFDA).

3. Results and Discussion

3.1 General description of reported ADR cases

There were 409 ADRs related to antibiotic drugs reported to the National Pharmaco-vigilance (PV) center of Ethiopia during the 5-year period. This indicate that antibiotics-related ADRs were found to be relatively high (57.9%) as compared to the total reported 707 ADR cases. This is illustrated in other Japanese and Portuguese studies (Morimoto *et al*., 2011; Scripcaru, Mateus, & Nunes, 2017). This study found that more ADRs were reported in adult patients aged 18-64 years, 268 (65.5%), than in children aged 0-17 years, 132 (32.2%) (Table 1). A similar finding was reported in studies conducted in German and Indian studies (Dhar *et al*., 2015; Dubrall *et al*., 2018). A South Korea study also found that suspected ADRs were reported more frequently in adult patients (Jung *et al*., 2017)

ADRs were reported at a higher rate in females (61.5%) than in males (37.4%). This result was consistent with other studies (Naidu & Tharun, 2016; Dubrall *et al*., 2018). According to one study conducted in the Netherlands, females are more likely to develop ADRs in all drug classes, including antibiotics, due to differences in pharmacokinetics (PKs), pharmacodynamics (bioavailability, distribution, metabolism, excretion) and drug use (Rodenburg, Stricker, & Visser, 2011). Women have a lower body weight and organ size, as well as a higher percentage of body fat, which affects drug absorption and distribution. The greater the volume of distribution, the more likely the drug will be found in body tissues. Women had higher blood concentrations and longer elimination times for the majority of the FDA-approved drugs studied, and these pharmacokinetics (PKs) were strongly linked to sex differences in ADRs (Zucker & Prendergast, 2020)

The other factor could be sex differences in reporting rates. A global analysis of spontaneously reported ADR reveals that female reports outnumber male reports across the world (Watson, Caster, Rochon, & Den Ruijter, 2019). Additionally, the distribution of reported ADRs by age and sex can also be clarified by the fact that healthcare professionals do not report all ADRs they detect to the Pharmacovigilance Center. In Ethiopia, the ADR reporting rate was found to be 1 and 1.28 per million populations in 2009 and 2015, respectively (Aagaard, Strandell, Melskens, Petersen, & Hansen, 2012; Ampadu *et al*., 2016). This under-reporting may have an impact on the sex distribution of reported ADR cases, as it is possible that ADRs experienced in one sex or age group are reported to a lesser extent than in the other, which would affect our data. Another reason for the predominance of adult and female patients may be that these groups are working class and more exposed to communicable diseases; thus, antibiotics are more likely to be prescribed which may increase their risk of ADRs (Tandon, Sharma, Khajuria, Mahajan, & Gillani, 2015). Sex and age distribution of the patient is shown in Table 1.

3.2 The causative drugs

A total of 462 suspected drugs were reported as causing ADRs 348 (85 %) were attributed to monotherapy, while 44 (10.8%) were attributed to combination therapy. The most troublesome class of antibiotics reported was beta-lactam, which accounted for 172 (37.2%), followed by sulfonamide (co-trimoxazole), which accounted for 128 (27.7 %) (Table 2). Importantly, these two antibiotics accounted for more than 60% of the reported ADRs, possibly indicating the

Table 1. Gender by patient age

Gender	≤17 (%)	18-64(%)	65+ (%)	Total (%)
Male	57 (13.9)	92 (22.4)	4(1)	153(37.4)
Female	73 (17.9)	174(42.4)	5 (1.2)	252 (61.5)
Others	2 (0.5)	2(0.4)	0(0)	4(1)
Total	132 (32.2)	268 (65.4)	9 (2.2)	409 (100)

Table 2. Most common antibiotics causing ADRs (n=462)

Class	Antibiotics	Frequency	%
Sulfonamide	Co-trimoxazole	128	27.7
Beta-lactam	Amoxicillin	103	22.3
	Ampicillin	8	1.7
	Cloxacillin	23	5
	Ceftriaxone	38	8.2
Fluoroquinolone	Ciprofloxacin	49	10.4
	Norfloxacin	31	6.7
Tetracycline	Doxycycline	13	2.8
Macrolide	Azitromycin	12	2.6
	Others	57	10.2
	Total	462	100

area of intervention and prevention of ADRs. Several studies have found that beta-lactam predominated over other antibiotics classes in ADR (Erin & Jamuna, 2020; Palappallil, Ramnath, & Gangadhar, 2017; Vijaishri & Andhuvan, 2017).

The two most commonly reported antibiotics in this study were penicillin 134 (78%) among beta-lactam and co-trimoxazole 128 (27.7%) among sulfonamide. This finding was reported in an Indian study (Sharma, Jayakumar, & Palappallil, 2019). According to the findings of this study, penicillins and cephalosporins were the most commonly reported drugs among beta-lactam agents. This could be explained by the fact that these two drugs were chosen to treat a wide range of pathogens that cause common diseases. Furthermore, the most commonly ADR-related drugs in the antibiotic drug class were co-trimoxazole 128 (27.7%) and amoxicillin 103 (22.3%). Both antibiotics (co-trimoxazole and amoxicillin) were suspected of causing 50% of ADRs.

The findings are consistent with another study that found amoxicillin and co-trimoxazole to be the most commonly suspected drugs for a wide range of skin reactions (Salvo *et al*., 2007). Co-trimoxazole is the standard of care for HIV/AIDS patients in Africa to prevent opportunistic infections. Thus, the high prevalence of HIV/AIDS in Ethiopia implies an increased risk of co-trimoxazole-associated ADRs (Mouton *et al*., 2015). Furthermore, the high prevalence of reported skin reaction can be explained by the fact that all four types of immunologically mediated hypersensitivity reactions have been linked to beta-lactam (Vardakas, Kalimeris, Triarides, & Falagas, 2018). Co-trimoxazole, on the other hand, has a high rate of fatal ADRs. (Baddour, Dayer, & Thornhill, 2019). The most common antibiotics causing ADRs are given in Table 2.

3.3 Route of drug administration

According to the findings of this study, 340 (83%) of the patients had taken oral drugs, while 76 (18.6%) had taken parenteral drugs (Table 3). In contrast to this finding, it has been stated that parenteral administration, followed by oral administration, is responsible for the majority of adverse reactions (Lu *et al*., 2013; Tandon, Sharma, Khajuria, Mahajan, & Gillani, 2015). This clearly shows that adverse drug reactions, whether expected or not, occur with almost all drugs and have been observed regardless of route or mode of administration (Huang, Lertora, Markey, & Atkinson, 2012). This is supported by a study that found that both oral and parenteral administration of beta-lactam is associated with gastro-intestinal disorders. Their frequency is higher with oral formulations and varies between the different classes (Vardakas, Kalimeris, Triarides, & Falagas, 2018). The route of administration by the number of prescribed drugs is shown in Table 3.

Table 3. Route of administration by number of prescribed drugs

Route	1(%)	2(%)	3(%)	>3(%)	Total (%)
Orally	286 (69.9)	40 (9.8)	11(2.7)	3 (0.6)	340 (83)
Parenteral	66 (16)	6 (1.5)	4 (1)	0 (0)	76(18.6)
Topical	2 (0.5)	0(0)	3(0.7)	2 (0.4)	7(1.7)
Total	348(85)	44(10.8)	14(3.4)	3(0.6)	409(100)

3.4 Affected body systems

A total of 612 affected body systems (SOCs) have been reported in 409 patients. ADRs have thus affected an average of 1.5 body systems. Skin and subcutaneous tissue disorders 334 (54.6%) were the most affected organ system due to antibiotics, which is consistent with other studies (Ibrahim, Ramlee, Lah, & Rosemi, 2013; Shin *et al*., 2009), followed by the general disorders 79 (12.9%) (Marques, Ribeiro-Vaz, Pereira, & Polonia, 2014) and gastrointestinal disorders 39 (6.4%) (Table 4). In the case of SOC 'general disorders', we found a discrepancy in the reports, as other studies indicated that skin was the most affected organ by ADRs, followed by the gastrointestinal system (Arulappen, Danial, & Sulaiman, 2018; Jayanthi, Chaithra, & Reddy, 2017).

In this study, the most common skin disorders caused by co-trimoxazole, amoxicillin, and ciprofloxacin were severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, as well as less severe forms such as rash all over the body, maculopapular rash, erythema multiforme, erthematous rash, and pruritus. Several studies have confirmed that antibiotics are the most common cause of adverse skin reactions (Neupane & Basnet, 2017; Sharma, Jayakumar, & Palappallil, 2019). On the other hand, studies have revealed that a significant number of skin reactions have been reported for sulfonamide and beta-lactam antibiotics (Trubiano *et al*., 2016). Table 4 provided the distribution of affected body system (SOCs).

3.5 Time to onset of ADRs and its seriousness

There were 303 (74%) non-serious and 106 (26%) serious ADRs reported. The reported time to onset for 23 (5.6%) patients was less than one day, and 188 (46%) occurred within a week of the drug's administration (Table 5). According to a parallel study, ADRs occurred within an hour (26.78%), followed by within a week (48%) (Tandon, Sharma,

Table 4. Body systems affected (SOCs)

Affected body system	N	%
Skin disorders	334	54.6
General disorders	79	12.9
Gastro-intestinal disorders	39	6.4
Nervous system disorders	27	4.4
Immune system disorders	23	3.8
Respiratory system disorders	13	2.1
Pregnancy and contraceptive	11	1.8
Vascular disorders	9	1.5
Cardiac disorders	8	1.3
Others	69	11.3
Total	612	100.0

Table 5. ADRs according to seriousness and onset

Serious	<1 day	1-7 day	8-30 day	Unspecified	Total
Yes	12 (2.9)	39 (9.5)	45 (11)	4 (1)	106 (25.9)
No	11 (2.7)	149 (36.4)	134 (32.8)	3 (0.7)	303 (74)
Total	23 (5.6)	188 (46)	179 (43.8)	7 (1.7)	409 (100)

Khajuria, Mahajan, &, Gillani, 2015). Most ADRs, on the other hand, occurred within 1 to 24 hours of administration (Palappallil, Ramnath, & Gangadhar, 2017). However, the reason for the delay in the occurrence of ADRs in this study is that the majority of ADRs were caused by oral antibiotics. On the other hand, a study on oral antibiotic use in the primary care settings found an unusually high reported rate of severe and fatal ADRs (Baddour, Dayer, & Thornhill, 2019).

The total reported ADRs in this study were classified as serious 26% and fatal 2.2%. In contrast, other studies found that 3.2% (Vora, Trivedi, Shah, & Tripathi, 2011), 3.4% (Jung *et al*., 2017) and 7.14% (Tandon, Sharma, Khajuria, Mahajan, & Gillani, 2015) of all spontaneous reports are classified as serious. Similarly, the reported death rate was 1.21% (Baddour, Dayer, & Thornhill, 2019), 4.5% (Jung *et al*., 2017) and 5.5% (Dubrall *et al*., 2018). The time of the onset and seriousness of ADRs is shown in Table 5.

3.6 Management and outcome

Adverse drug reactions are typically managed by monitoring specific parameters and then taking corrective action. A common course of action is to modify or remove a drug suspected of causing an ADR. However, the course of action taken to treat the ADR is likely to differ from clinician to clinician (Coleman & Pontefract, 2016). In this study, the majority of ADRs were managed by treating ADRs 129 (31.5%), followed by discontinuing/changing the offending drug 108 (26.4%) (Table 6). The results, on the other hand, show that 14.4% of the reaction was recovered when the drug was stopped and 14.2% when a specific treatment was given, resulting in a complete recovery of 183 (44.7%) patients.

This finding is lower than the 3-year experience; 235 (59.94%) ADR recovered from an Indian tertiary care teaching hospital (Tandon, Sharma, Khajuria, Mahajan, & Gillani, 2015). Furthermore, a study found that the majority of the adverse reactions caused by beta-lactam subsided after the offending drug was removed (Vardakas, Kalimeris, Triarides, & Falagas, 2018). Table 6 presents the outcome and management of the adverse reactions.

4. Conclusions

There were limited data available and no studies have been conducted on spontaneously reported antibiotic related ADRs in Ethiopia. Antibiotic-related adverse reactions were found to be significantly more common in female and adults. The most common antibiotics that cause ADRs are penicillin and co-trimoxazole, and skin manifestations are the most frequently experienced adverse reactions. The majority of ADRs was non-serious, occurred within a week of drug administration and was managed by treatment of ADRs. As evidenced by this relatively large number of reported ADRs, antibiotic-related adverse reactions are a significant public health issue in Ethiopia.

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Table 6. Most common management and outcome of patients

Management	Recovered N (%)	Recovered with sequelae N (%)	Recovering N (%)	Fatal N (%)	Unknown N (%)	Total N (%)
Discontinued	59 (14.4)	16(3.9)	3 (0.7)	0 (0)	30 (7.3)	108 (26.4)
Treated	58 (14.2)	16 (3.9)	8 (1.96)	1 (0.2)	46 (11.2)	129 (31.5)
Both	42 (10.3)	12 (2.9)	8 (1.96)	2 (0.5)	26 (6.4)	90 (22)
Unspecified	24 (5.9)	11 (2.7)	5 (1.2)	6 (1.5)	35 (8.6)	81 (19.8)
None	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.2)
Total	183 (44.7)	56 (13.7)	24 (5.9)	9 (2.2)	137 (33.5)	409 (100)

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