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An Assessment of Azithromycin Prescribed Interactions' at the Outpatient Setting

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Authors' contributions

This work was carried out in collaboration among all authors. Authors NJA and ZSA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NJA, ZSA, AAM and MAM managed the analyses of the study. Author MAA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The present study was designed to identify and assess the severity of azithromycin interactions with other drugs in the outpatient setting in Alkharj.
Methodology: A retrospective analysis was performed of azithromycin prescriptions in the outpatient setting in a public hospital in Alkharj in order to determine the incidence of interactions between azithromycin and other medications.
Results: There were 182 prescriptions included in the study. There was a major interaction in only 1 prescription (0.55%) and moderate interactions in 15.30% of the prescriptions. So the percentage of overall interactions was about 20.88%. The most common drug interactions in the present study were between azithromycin and salbutamol.
Conclusion: It can be concluded that the interactions between azithromycin with other medications

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were common, but these interactions could lead to irregular heart rhythm and lead to muscle pain and weakness. Adoption of international standard and locally conformable guidelines of antibiotic use can help in avoiding such problems.

Keywords: Azithromycin; drug Interactions; DDIs; outpatient.

1. INTRODUCTION

When the physician identifies the patient problem and the diagnosis is made the next step is to choose the appropriate drug therapy [1]. Using numerous medications for the patient (polypharmacy) is common and is known to increase the occurrence of drug-drug interactions [2]. There are many factors noticeably contribute to one or more interactions that include patient`s age more than 60 years, polypharmacy, and patients with chronic diseases [3]. Consequently, concurrent use of two or more drugs may result in diminished response or an increased risk of adverse drug reaction [4].

Drug interactions are common and lead to increased morbidity and mortality rates globally [5]. In the United States, drug - drug interactions contribute to about 20% of all adverse drug events [6]. These interactions cause approximately 770,000 deaths, cost $30 billion to $180 billion in healthcare expenditures [7,8], and lead to four hospitalizations per 1,000 people yearly [9]. Therefore, to optimize patient safety care, it is important to recognize and avoid these interactions.

Patients in outpatient settings usually take several medications concurrently; including antibiotics this may increase the risk of drug-drug interactions [10]. Different Resources classify interactions differently. Tatro classifies drug interactions depending upon their severity into serious, significant, and minor [4,11]. Micromedex classifies the interactions into contraindicated, major, moderate, and minor [12], and the Drugs.com interaction checker classifies the interactions to major, moderate, or minor depending upon their severity [13].

Azithromycin is a macrolide-type antibiotic that is used to prevent and treat several types of infections. It interacts with several drugs especially with the drugs that affect the heart rhythm and lead to QT- prolongation such as disopyramide and amiodarone [14].

In outpatient settings, patients are subjected to use several drugs but knowledge about outpatients exposed to drug-drug interactions is poor [15]. Therefore, the present study was designed to identify and assess the severity of azithromycin interactions with other drugs in the outpatient setting in Alkharj.

2. METHODOLOGY

This is a retrospective study includes the review of electronic outpatient prescriptions in a public hospital in Alkharj, Saudi Arabia in order to determine the incidence of interactions between azithromycin and other medications in the period between 01-01-2017 until 30-06-2017.

The inclusion criteria include the prescriptions that include azithromycin and at least 1 other medication. The Exclusion criteria include the prescriptions that don't include azithromycin, the prescriptions that include only 1 medication, and the prescriptions that include azithromycin topically as a cream or drops.

The data included the number of drugs in the prescriptions, the medications prescribed with azithromycin, the percentage of major, moderate and minor interactions, azithromycin interactions with other medication and common azithromycin – drug interactions.

The data were collected after the approval of the study by the IRB committee in the Ministry of health with IRB Log No. 18-474E. After that, the data was collected and analyzed using Excel software and the descriptive data were presented as a frequencies and percentages.

Drug Interactions Checker (https://www.drugs.com/drug_interactions.html) was used to check for the drug - drug interactions in the prescriptions [13]. The interactions were classified into major, moderate, and minor interactions. For example, increase the risk of a dangerous side effect on muscles is moderate interaction and the interactions that lead to increase the risk of an irregular heart rhythm with some drugs it is major and with other drugs it is moderate. Minor interactions do not usually cause harm or require a change in therapy.

3. RESULTS

From 01-01-2017 until 30-06-2017, there were 182 prescriptions contain at least 2 medications and contain azithromycin. The majority of the prescriptions contain only 2 medications, azithromycin, and other medication (84.61%). Table 1 shows the number of drugs prescribed.

About 47.80% of the prescriptions contain Paracetamol and 7.14% contain salbutamol. Table 2 shows the medications prescribed with azithromycin.

There was a major interaction in only 1 prescription (0.55%) and moderate interactions in 15.30% of the prescriptions. So the percentage of overall interactions was about 20.88%. The percentage of major, moderate, and minor interactions is shown in Table 3.

About 39.47% of the azithromycin interactions were with albuterol (salbutamol), this interaction with albuterol is classified as moderate. Table 4 shows the interaction between azithromycin interactions with other medications.

In the present study, there are many interactions between azithromycin other medications. For example, the interaction with formoterol increases the risk of irregular heart rhythm, and the interaction with simvastatin increases the risk of a dangerous side effect on muscles. Table 5 shows the common azithromycin – drug interactions.

4. DISCUSSION

There are several interactions between Azithromycin and other medications. Micromedex divides the interactions to contraindicated, major, moderate, and minor. Micromedex mentions contraindicated interactions between azithromycin and 16 medications such as with ergotamine and sparfloxacin and major interactions with more than 150 medications such as with moxifloxacin, metronidazole, and erythromycin and moderate interaction with 13 medications such as with atorvastatin and minor interaction with 12 medications such as with antacids [12].

Table 1. Number of drugs in the prescriptions

Number of drugs in the prescriptions	Frequency	Percentage
2 drugs	154	84.61 %
3 drugs	20	10.99 %
4 drugs	6	3.30 %
5 drugs	2	1.10 %

Table 2. The medications prescribed with Azithromycin

Medications	Number *N*=	Percentage
Paracetamol	87	47.80 %
Omeprazole	12	6.59 %
Guaifenesin	15	8.24 %
Salbutamol	15	8.24 %
Cefuroxime	7	3.85 %
Amoxicillin/Clavulanic Acid	5	2.75 %
Prednisolone	5	2.75 %
Chlorpheniramine	9	4.94 %
Oral Rehydration Salt	9	4.94 %
Other medications*	58	31.87 %

**Other medications such as formoterol, tramadol, salmetrol, metronidazole, amoxicillin, moxifloxacin, olanzapine, simvastatin, erythromycin and atorvastatin*

Table 3. The percentage of major, moderate and minor interactions

Interaction	Frequency	Percentage
Major	1	0.55 %
Moderate	28	15.38 %
Minor	9	4.95 %
No Interaction	144	79.12 %

Table 4. Azithromycin interactions with other medications

Medications	Number of interactions *N*=	Percentage	Severity
Salbutamol	15	39.47 %	Moderate
Amoxicillin / clavulanate	5	13.16 %	Minor
Formoterol	4	10.53 %	Moderate
Tramadol	3	7.89 %	Moderate
Salmeterol	2	5.26 %	Moderate
Metronidazole	2	5.26 %	Minor
Amoxicillin	2	5.26 %	Minor
Moxifloxacin	1	2.63 %	Major
Olanzapine	1	2.63 %	Moderate
Simvastatin	1	2.63 %	Moderate
Erythromycin	1	2.63 %	Moderate
Atorvastatin	1	2.63 %	Moderate

Table 5. Common azithromycin – drug interactions

Interactions	Severity	Effect
Azithromycin - formoterol	Moderate	Increase the risk of an irregular heart rhythm
Azithromycin - olanzapine	Moderate	Increase the risk of an irregular heart rhythm
Azithromycin - salmeterol	Moderate	Increase the risk of an irregular heart rhythm
Azithromycin - tramadol	Moderate	Increase the risk of an irregular heart rhythm
Azithromycin - erythromycin	Moderate	Increase the risk of an irregular heart rhythm
Azithromycin - albuterol	Moderate	Increase the risk of an irregular heart rhythm
Azithromycin - moxifloxacin	Major	Increase the risk of an irregular heart rhythm
Azithromycin - simvastatin	Moderate	Increase the risk of a dangerous side effect on muscles
Azithromycin - atorvastatin	Moderate	Increase the risk of a dangerous side effect on muscles

Azithromycin with atorvastatin or simvastatin results in an increased risk of rhabdomyolysis. Moxifloxacin or metronidazole or erythromycin or ciprofloxacin or levofloxacin with azithromycin may result in an increased risk of QT-interval prolongation.

In the present study, there are many interactions between azithromycin other medications that include the interaction with formoterol, olanzapine, salmeterol, tramadol, erythromycin, moxifloxacin, and albuterol that increase the risk of irregular heart rhythm. As a result, the patient should tell the prescriber if he develops sudden dizziness, fainting, lightheadedness, heart palpitations, or shortness of breath during treatment with these drugs.

Additionally, using azithromycin together with simvastatin or atorvastatin may increase the risk of a dangerous side effect on muscles [16]. The patient should tell his prescriber if he has muscle symptoms such as muscle weakness, pain, or tenderness.

In the present study, Drug Interactions Checker (https://www.drugs.com/drug_interactions.html) was used to check for the drug - drug interactions. These interactions in the present study that increase the risk of side effects on muscle or that increase the risk of irregular heart rhythm are categorized as moderate according to "drugs.com classification" except the interaction of azithromycin with moxifloxacin is a major interaction. Minor interactions were seen between azithromycin and some antibiotics such as amoxicillin [13].

In the present study, paracetamol is the most prescribed drug with azithromycin followed by guaifenesin, albuterol, and omeprazole. But there are no interactions between azithromycin with paracetamol, omeprazole, or guaifenesin. So the most common drug - drug interactions in the present study was between azithromycin and albuterol (salbutamol).

Sharma et al. reported that among hospitalized cardiac patients in a teaching hospital in Western Nepal, atorvastatin/azithromycin (10.4%) was one of the most common interacting pairs. But in the present study, only 1 patient received atorvastatin so this interaction is lesser than other interactions [17].

Azithromycin causes fewer drugs - drug interaction than other Macrolides. Previous studies stated that because of its structural differences, azithromycin does not interact with SLCO1B1, CYP3A4, or SLCO1B3, and therefore causes fewer drug interactions and has a longer half-life than other macrolides [18,19].

Felstead reported that azithromycin is likely to be associated with fewer significant drug interactions than other modern macrolides [20]. Moreover, Pai et al stated that azithromycin has not been demonstrated to cause an inhibition in the cytochrome P450 system in studies using a human liver microsome model and that to date hasn't produced the classic drug - drug interactions characteristic of the macrolides [21]. Amsden stated that the pharmacokinetic drug interactions for erythromycin and clarithromycin with theophylline, terfenadine, and carbamazepine are not found with azithromycin [22]. Additionally, Alvarez-Elcoro and Enzler reported that for mycobacterium avium complex prophylaxis in patients with late-stage acquired immunodeficiency syndrome, both azithromycin and clarithromycin are active but azithromycin may be the preferred agent due to its fewer drug-drug interactions [23].

5. CONCLUSION

It can be concluded that the interactions between azithromycin with other medications were common, but these interactions could lead to irregular heart rhythm and lead to muscle pain and weakness. These interactions affect the quality of life and could lead to an increased morbidity or mortality rate. Adoption of an international standard and locally conformable guidelines of antibiotic use can help avoid such problems.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s). The data were collected after the approval of the study by the IRB committee in the Ministry of health with IRB Log No. 18-474E.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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