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Detect Drug Interactions with Metronidazole

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Metronidazole has been prescribed to treat infections for over a century and continues to be helpful in the therapy of amoebiasis, trichomoniasis, and giardiasis. Metronidazole is a cost-effective medication because of its low price, few adverse effects, and favorable pharmacokinetic and pharmacodynamic properties; nevertheless, it interacts with a wide variety of other medications. Some interactions with other medicines diminish its effectiveness, while others increase it.

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Aims: The study aims to detect and evaluate metronidazole interactions with other medicines at King Abdulaziz Specialist Hospital.
Methodology: This retrospective study encompasses the review of 360 computerized prescriptions inside the outpatient clinic at King Abdulaziz Specialist Hospital in Saudi Arabia between March and September 2020 to detect and evaluate interactions among metronidazole and different medications.
Results: Metronidazole interactions are mostly major or moderate. Metronidazole had the most common interactions with domperidone (15.83 %), famotidine (13.89 %), and ciprofloxacin (11.67 %). Metronidazole contains a nitroimidazole ring, which suppresses the metabolism in the liver of numerous medications, including those that may be metabolized by the CYP3A4 and/or CYP450 2C9 isoenzymes. The combination of metronidazole with phenytoin or phenobarbital can cause metronidazole elimination to be accelerated and phenytoin clearance to be reduced. Metronidazole may improve warfarin's anticoagulant effects, leading to a longer prothrombin time and a higher risk of bleeding. Concurrent use of metronidazole with alfuzosin, escitalopram, and ondansetron may raise the risks of QT-interval prolongation and arrhythmias.
Conclusion: Most metronidazole drug interactions can be avoided by following excellent clinical care and clinical pharmacology concepts, such as avoiding complex treatment regimens, educating patients. and identifying patient risk factors. Furthermore, before prescribing and dispensing medicines, physicians and pharmacists should utilize drug-drug interactions checkers such as Micromedex and Lexicomp or a book such as Stockley's Drug Interactions.

Keywords: Metronidazole; drug interaction; antibiotic; domperidone.

1. INTRODUCTION

Metronidazole (2-(2-methyl-5-nitro-1H-imidazole-1-yl) ethanol) is a mainstay medication for the treatment of anaerobic infections and the treatment of choice for the majority of patients with Clostridium difficile-related diarrhea [1,2]. Metronidazole is available in 375 mg capsules, 250 mg and 500 mg tablets, oral suspension, vaginal gel, and skin cream.

Metronidazole's mode of action against obligate anaerobes is a four-step process that includes entrance into the organism, reductive activation through intracellular transport proteins, interactions with intracellular targets, and breakdown of cytotoxic-intermediate metabolites. Metronidazole is toxic to facultatively anaerobic bacteria such as Gardnerella vaginalis and Helicobacter pylori. However, the mode of action against these bacteria is unknown. Metronidazole has two distinguishing features: it reaches high blood concentrations after oral administration and has good tissue penetration [3,4].

Metronidazole side effects involve stomach discomfort, appetite loss, headache, and an unpleasant mouth taste. Metronidazole also may cause drowsiness, dizziness, and confusion. Convulsions, hallucinations, and leukopenia are uncommon metronidazole adverse effects [5,6].

Metronidazole is not recommended during the first three months of pregnancy or in individuals who have a history of metronidazole hypersensitivity. Metronidazole is a cost-effective medication because of its low price, few adverse effects, and favorable pharmacokinetic and pharmacodynamic properties; nevertheless, it interacts with a wide variety of other medications. Some interactions with other medicines diminish its effectiveness, while others increase it [7–9].

A drug interaction occurs when food, dietary supplements, formulation excipients, other medicines, or illness alter a patient's response to a drug. Drug interactions (drug-drug interactions) may be beneficial or detrimental. Unfortunately, drug-drug interactions are a common cause of adverse drug reactions and higher hospitalization rates in patients [10,11].

Metronidazole has a major interaction with alfuzosin, amitriptyline, clarithromycin, escitalopram, famotidine, levofloxacin, mirtazapine, ondansetron, and warfarin. In addition, it interacts with carbamazepine, cimetidine, cyclosporine, lithium, lixisenatide, phenindione, and phenytoin at a moderate level. Furthermore, there is a mild interaction with saxagliptin, celecoxib, and phenobarbital [12,13].

It is possible to prevent most metronidazole medication interactions by providing good clinical care, educating patients, and avoiding complicated treatment regimens. However, to our

knowledge, no study has been done to detect and evaluate metronidazole interactions with other medicines at King Abdulaziz Specialist Hospital. Metronidazole is the most used drug daily in outpatient clinics and one of the drugs that have interactions with other drugs. Therefore, our study aims to identify and evaluate these drug interactions.

2. METHODOLOGY

This retrospective study encompasses the review of 360 computerized prescriptions inside the outpatient clinic at King Abdulaziz Specialist Hospital in Saudi Arabia between March and September 2020 to detect and evaluate interactions among metronidazole and different medications.

The inclusion criteria are prescriptions that have a metronidazole drug interaction. Prescriptions without metronidazole drug interaction, without oral metronidazole dosage forms, and prescriptions were written before March 2020 and after September 2020 are excluded.

The Excel software was used to collect and analyze the data. The descriptive data were expressed using percentages and frequencies. According to Micromedex, the interactions' severity was classified as mild, moderate, major, and contraindicated [14].

3. RESULTS

This study includes the revision of 360 electronic prescriptions between March and September 2020 to define and evaluate the interactions of metronidazole with different medications. Approximately 58% of the prescriptions were for females, while 42% were for males with metronidazole drug interactions (Fig. 1).

Most metronidazole interactions are major or moderate. The common interactions were metronidazole with domperidone (15.83%), famotidine (13.89%), and ciprofloxacin (11.67%). Table 1 displays the medications that were attracting metronidazole and the number of prescriptions with a percentage.

Approximately 86% of interactions were caused by metronidazole interactions with medical medications, considered major interactions. Metronidazole has a major interaction with alfuzosin, amitriptyline, azithromycin, ciprofloxacin, clarithromycin, domperidone, escitalopram, famotidine, fluconazole, levofloxacin, mirtazapine, ondansetron, and sulpiride.

Approximately 10% of the interactions were moderate interactions. Metronidazole interacts moderate with carbamazepine, cimetidine, cyclosporine, ergotamine, lithium, lixisenatide, phenindione, and phenytoin.

Approximately 4% of the metronidazole interactions were minor interactions. Metronidazole interacts minor with saxagliptin, celecoxib, and phenobarbital (Fig. 2).

4. DISCUSSION

In this study, Metronidazole is given to females to treat vaginal infections caused by bacterial vaginosis; therefore, female prescriptions (58%) exceed male prescriptions (42%) [15,16].

Around 86% of metronidazole interactions with drugs are major. On the other hand, about 10% of interactions are moderate, indicating that the patient has a significant risk of experiencing an adverse drug reaction, which raises the risk of hospitalization [17].

Adverse drug reactions that may occur as a result of concurrent use of metronidazole and other drugs include prolonged QT interval and increased risk of arrhythmia, rhabdomyolysis, myalgia, and decreased renal function, increased risk of bleeding, increased risk of toxicity of certain drugs, and increased or decreased effectiveness of certain drugs (Table 2).

The use of metronidazole in conjunction with alfuzosin, levofloxacin, mirtazapine, ondansetron, and sulpiride may cause a longer QT interval and a greater risk of arrhythmia. Therefore, high-risk patients may need electrocardiogram monitoring and avoid medications that induce QT interval prolongation [18,19].

Concurrent usage of warfarin and metronidazole raises the risk of bleeding due to warfarin's anticoagulant action being enhanced and prothrombin time being prolonged. Therefore, patients at increased risk of bleeding may need monitoring of their prothrombin time, INR, and signs or symptoms of bleeding [20,21].

Table 1. Displays the medications that were attracting metronidazole and the number of prescriptions with a percentage

Drug Name	Number Of Prescriptions	Percentage
Domperidone	57	15.83%
Famotidine	50	13.89%
Ciprofluxacin	42	11.67%
Azithromycin	41	11.39%
Warfarin	37	10.28%
Fluconazole	28	7.78%
Carbamazepine	22	6.11%
Escitalopram	13	3.61%
Levofloxacine	12	3.33%
Clarithromycin	11	3.06%
Cyclosporine	9	2.5%
Phenytoin	7	1.94%
Mirtazepine	6	1.67%
Amitriptyline	5	1.39%
Phenobarbital	3	0.83%
Sulpiride	2	0.56%
Ondansetron	2	0.56%
Alfuzosin	2	0.56%
Others	11	3.05%

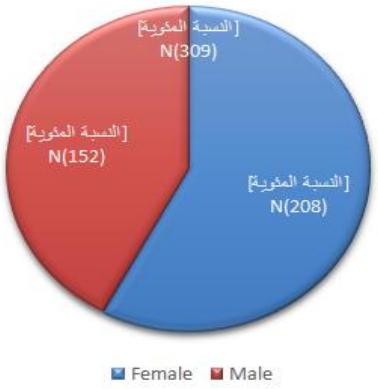

Fig. 1. Show the number of prescriptions and percentage for females and males

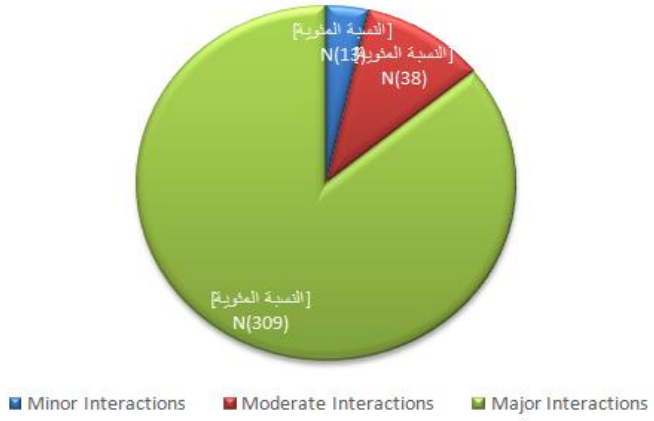

Fig. 2. Show the severity of metronidazole drug interactions

Table 2. Explain the possible outcomes of drug interactions.

Drug interactions	**Severity**	**Possible outcomes**
Phenobarbital with metronidazole	Minor	May result in decrease metronidazole effectiveness.
Carbamazepine with metronidazole	Moderate	May result in increased carbamazepine serum concentrations and potential carbamazepine toxicity. Such as dizziness and diplopia.
Cyclosporine with metronidazole	Moderate	May result in an increased risk of cyclosporine toxicity. Such as nephrotoxicity, cholestasis, and paresthesias.
Lithium with metronidazole	Moderate	May result in elevated lithium plasma levels and possible lithium toxicity. Such as weakness, tremor, and confusion.
Phenytoin with metronidazole	Moderate	May result in an increased risk of phenytoin toxicity. Such as nystagmus, ataxia, and drowsiness.
Alfuzosin with metronidazole	Major	May raise the risk of QT prolongation and arrhythmias.
Ciprofloxacin with metronidazole	Major	May raise the risk of QT prolongation and arrhythmias.
Domperidone with metronidazole	Major	May raise the risk of QT prolongation and arrhythmias.
Escitalopram with metronidazole	Major	May raise the risk of QT prolongation and arrhythmias.
Famotidine with metronidazole	Major	May raise the risk of QT prolongation and arrhythmias.
Ondansetron with metronidazole	Major	May raise the risk of QT prolongation and arrhythmias.
Amiodarone with metronidazole	Major	May raise the risk of QT prolongation and arrhythmias.
Mycophenolate with metronidazole	Major	May result in decreased mycophenolate plasma exposure and possible reduced efficacy.
Capecitabine with metronidazole	Major	May result in an increased risk of capecitabine toxicity. Such as granulocytopenia, thrombocytopenia, and stomatitis.
Warfarin with metronidazole	Major	May result in a prothrombin time prolong and a higher risk of bleeding.

Metronidazole combined with 5-fluorouracil prodrugs such as fluorouracil, capecitabine, doxifluridine, and tegafur may increase 5-fluorouracil exposure; therefore, fluorouracil toxicity such as thrombocytopenia, granulocytopenia, anemia, and stomatitis must be monitored [22,23].

Disulfiram and metronidazole in combination may cause CNS toxicities, including confusion and psychotic symptoms. Consequently, metronidazole should not be administered to a patient who has recently taken disulfiram [24, 25].

The most frequently encountered interactions between metronidazole and domperidone (15.83 %), famotidine (13.89 %), and ciprofloxacin (11.67 %) because these medications are frequently prescribed in combination with metronidazole in the outpatient department at King Abdulaziz Specialist Hospital.

Most metronidazole drug interactions may be prevented by following excellent clinical care and clinical pharmacology concepts. For example, avoid complex treatment regimens, promote antimicrobial stewardship, and identify the patient's risk factors. Furthermore, before prescribing and dispensing medications, physicians and pharmacists should use drug-drug interaction checkers such as Micromedex and Lexicomp, as well as a book such as Stockley's Drug Interactions.

5. CONCLUSION

Metronidazole has long been the medication of choice for treating parasite infections, anaerobic infections, and bacterial infections. However, it exhibits a pleiotropic mode of action when compared to most other antibacterial drugs. As a result, it interacts with a broad range of drugs. Many drugs interact, leading to a longer QT interval and a higher risk of arrhythmia, rhabdomyolysis, myalgia, and impaired renal function; it also increases the risk of bleeding and enhances or lowers the efficacy of some drugs.

By applying good clinical care and clinical pharmacology principles, drug interactions can be avoided. For example, avoid complicated therapeutic regimens, educate patients and identify risk factors for patients. In addition, the use of antimicrobial stewardship. Physicians and Pharmacists should use drug-drug interactions programs such as Micromedex, Uptodate, and Lexicomp or use books such as Stockley's Drug Interactions and Handbook of Drug Interactions before prescribing and dispensing the medications.

CONSENT

It is not applicable.

ETHICAL APPROVAL

We conducted our research after obtaining proper iec approval.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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