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Original Article

Potential Drug Interactions between Antibiotics and Risk of Antimicrobial Resistance: A Database Research Study

Pradeep Battula[1,*], Bhupalam Pradeep Kumar[2]
[1]Department of Pharmaceutical Sciences, Jawaharlal Nehru Technological University Anantapur (JNTUA), Ananthapuramu, Andhra Pradesh, INDIA.
[2]Department of Pharmacy Practice, Raghavendra Institute of Pharmaceutical Sciences (RIPER) Autonomous, Anantapur, Andhra Pradesh, INDIA.

ABSTRACT

Background: When two antibiotics are used at the simultaneously, they interact. The interaction could be either synergistic or antagonistic. However, an antagonistic combination may halt the action of another antibiotic, resulting in the treatment failure and risk for the development of antimicrobial resistance. **Materials and Methods:** The Micromedex drug database was used to find potential antibiotic interactions among the antibiotics. The Micromedex drug database is a trustworthy database that can be used to examine various details such as drug information, interactions, disease information, and dose calculations. **Results:** As a result, 1923 antibiotic interactions were identified, which were divided into three categories: major, moderate, and minor. The interaction values were 1260 (65.52 %), 68 (3.53 %), and 595 (30.94 %) respectively. Among the 1923 interactions, 715 (37.18%) interactions were identified as risk for developing the AMR. The 715 interactions (37.18 %) were again grouped into three categories: major, moderate, and minor. The values are 354 (49.51%), 12 (1.67%), and 349 (48.81%), respectively. **Conclusion:** Antimicrobial resistance is a major public health concern around the world and it must be aware by everyone. All healthcare professionals look for potential drug interactions in the prescription and need to eliminate the risk of antimicrobial resistance that helps in improvement in the patient outcomes in terms of antimicrobial resistance.

Keywords: Antimicrobial resistance, Antagonistic interaction, Drug interactions, Antibiotics, Clinical pharmacist.

Correspondence

Dr. Pradeep Battula
Research Scholar, Department of Pharmaceutical Sciences, Jawaharlal Nehru Technological University Anantapur, Ananthapuramu-515002, Andhra Pradesh, INDIA.

Email id: doctorbattulapradeep@gmail.com

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INTRODUCTION

Antibiotics, also known as antimicrobial medications, are secondary metabolites produced by bacteria, and synthetic or semi-synthesized chemicals can inhibit bacterial growth and survival, providing the immune system the upper hand. Thus, these medications can be used to treat infectious diseases.[1,2] Antibiotics are no longer prescribed alone; instead, clinicians are prescribing antimicrobials in combinations to achieve the optimal effectiveness in killing the bacteria. When antibiotics are administered in combination, it may result in improved efficacy and resistance reduction some times. But when antibiotics are given in the combinations causes to interactions between the prescribed antibiotics. The interaction may be synergistic or antagonistic interactions. The synergistic and additive combinations are prescribed to achieve maximum therapeutic effect. But an antagonistic combination may reduce the effect of another antibiotic causes to failure of the treatment provided to the patient.[3,4]

However, due to the interactions (Synergistic and Antagonistic) between antibiotics could lead to development of antimicrobial resistance (AMR). AMR is a serious global health problem and challenge to the whole world. It is predicted that by 2050, AMR will have caused more than 10,000 million fatalities per year.[3,5] Recently, there has been a lot of attention paid to the development of AMR through interactions. Several studies mentioned about AMR with synergistic and antagonistic interactions. And also some studies stated that antagonistic interaction could slow down the evolution or development of AMR. Its indicating that occurring of AMR is compulsory because of the interactions.[2,4] The objective of this database study is to predict the antimicrobial resistance among antibiotics based on antagonistic interactions.

MATERIALS AND METHODS

The Micromedex 20.0 version, 2022 was used in the study to get the information concerning the antibiotics. The current Micromedex database is managed by IBM Corporation Health Care, United States. Micromedex is a drug information database that provides evidence-based data on medications, drug interactions, patient care notes, IV compatibility, dose calculations, drug comparisons, and disease information.

Antibiotics Search Strategy

The total antibiotics availability in databases was found through a Micromedex databases keyword search. Giving name of antibiotics in keyword search, it was given about 200 antibiotics as a result. In the mentioned list some antibiotics that were not available in Micromedex database. Which includes Sulfadoxine, Sulfamethopyrazine, Sulfasalazine, Mafenide, Cotrimoxazole, Pefloxacin, Prulifloxacin, Cefazolin, Ceftamet Pivoxil, Cefpirome, Ceftobiprole, Faropenem, Sisomicin, Framycetin, Tedizolid, Fusidic acid, Colistin, Methenamine, Phenazopyridine, and Isoniazid.

Procedure for Drug Interactions

Figure 1 shows the procedure for obtaining drug interactions for the available antibiotics in the database, as well as the results of interactions. After logging into the database, select the drug interaction option, then enter the 200 antibiotic drugs one by one using the database's options. Select the necessary antibiotic in the matching antibiotic drugs by giving the name of the antibiotic and transferring it into the drug to check. Once entry of all antibiotics was completed click the submit option. It

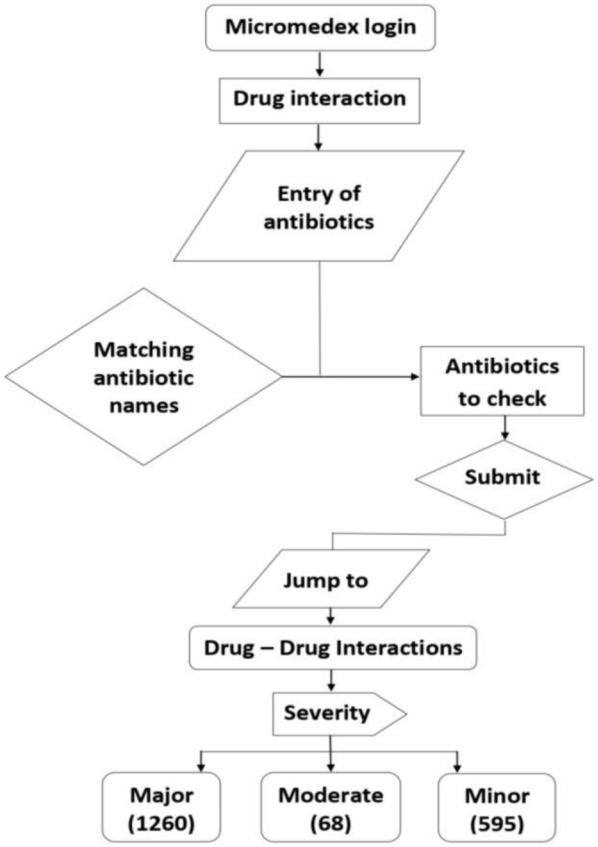

Figure 1: Process of drug interaction search and results.

provides all the interactions to the selected antibiotics and allows the user to move to other interactions options as desired (Drug, Food, Ethanol, Lab, Pregnancy, and Lactation).

Drug Interaction Analysis

After getting the all-antibiotic drug interactions, the information was double-checked to know the information regarding the missed entry of antibiotics. Analysis revealed that no antibiotics were missed during the entry into the drug to check.

RESULTS

As a result, 1923 antibiotic interactions were identified, which were divided into three categories: major, moderate, and minor. The major, moderate, and minor interaction values were 1260 (65.52 %), 68 (3.53 %), and 595 (30.94 %) respectively. Antibiotic interactions were found as having an AMR risk development among these interactions. Among the 1923 interactions, 715 (37.18%) interactions were identified as risk for developing the AMR. The 715 interactions (37.18 %) were again grouped into three categories: major, moderate, and minor. The values are 354 (49.51%), 12 (1.67%), and 349 (48.81%), respectively. The most common antibiotic interactions were between the penicillin (penicillin's, penicillin combinations) and tetracycline (tetracycline's and tetracycline combinations) classes, which occurred 298 times (41.67%), and the results showed that concurrent use of penicillin's and tetracyclines may reduce antibacterial effectiveness. Other major interactions were less frequent, with a frequency of 56 (7.83%), and the data showed that using clindamycin and erythromycin at the same time taken could result in antagonistic antimicrobial effects. The only moderate antibiotic interaction was found between ceftazidime and chlorampenicol, with the results indicating that concomitant use of ceftazidime and chlorampenicol may result in decreased ceftazidime effectiveness, With a frequency of 12 (1.67%). The three minor interactions were also seen, the first between was aminoglycosides and penicillins with a frequency of 307 (42.93 %), with the results indicating that concurrent use of aminoglycosides and penicillins may result in loss of aminoglycoside efficacy. The second minor interaction was between penicillin G and chlorampenicol, which occurs 36 (5.03%) of the time. This interaction indicates that using penicillin G and chlorampenicol at the same time may reduce antibacterial efficiency. With a frequency of 6 (0.83%), the third minor interaction was found between penicillin v and chlorampenicol. This interaction suggests that taking penicillin v and chlorampenicol at the same time may reduce antibacterial effectiveness. Table 1 contained information on all antibiotic interactions. Table 2 shows the risk of developing antimicrobial resistance. Which were provides the detailed information on antibiotic interactions, their severity and frequency of occurrence, as well as the possibility of AMR.

DISCUSSION

Antibiotics proved to be effective in treating bacterial illnesses. Unfortunately, antibiotics have been overused for the past 50 years, and experts have recommended combination therapy to improve patient outcomes. Combination therapy aids in achieving optimum therapeutic efficacy while also increasing the chances of microorganism resistance. It will be achieved by the interactions of antibiotics. When two medications are taken at the same time, synergistic, additive, and antagonistic effects may occur.[4-7]

AMR risk was predicted in this database study based on interactions. The risk of AMR development was focused primarily on antagonistic effects in this study. The data was already shown in the Table 1. All of the interactions observed may have the potential to develop AMR. Antimicrobial resistance development is delayed by antagonistic drug combinations, according to Bollenbach T *et al*., and antimicrobial resistance development is slowed by antagonistic drug combinations, according to Yeh PJ *et al*. The same information about AMR has also been mentioned in recent studies.[3,4]

The Table 1 contained all interactions, might pose a threat to the development of AMR. The risk was determined using the antibiotic spectrum, and information on the risk of AMR to antibiotics was provided in a Table 2. Antibiotics work on those microorganisms, killing or inhibiting their growth. However, due to antibiotic interactions, antibacterial efficiency is reduced or antagonistic antimicrobial effects occur. As a result, AMR will progress slowly. However, even if the process is slower, AMR development is unavoidable.[8-10]

As a reason, consumer education and awareness are essential in the fight against AMR. Health professionals must play a vital role in addressing this important global health issue. The pharmacist must educate and counsel patients on the use of antibiotics, and the patient would be free of such outcomes and other consequences that follow. So, clinical pharmacy is a professional service that is widely available in all nations and will be beneficial in this regard. To ensure the rational use of medicines, clinical pharmacists must attend to ward rounds and verify every prescription for drug, dose, duration, frequency, and dosage forms. The clinical pharmacist would serve as a bridge between the patient and the physician, resulting in better pharmacological treatment for the patient.[5,11] The AMR occurring not only in the developing countries, but it is occurring throughout the world. So, all health care professionals and every citizen must take action to fight against slow destruction phenomenon i.e., AMR.

Table 1: Antibiotics interactions showing risk of AMR.

Drug involved in drug-drug interaction	Severity	Summary	Frequency (%)	Documentation
Penicillins + Tetracyclines	Major	Concurrent use of Pencillins and Tetracyclines may results in decreased antibacterial effectiveness.	298 (41.67)	Good
Clindamycin + Erythromycin		Concurrent use of Clindamycin and Erythromycin may result in antagonistic antimicrobial effects	56 (7.83)	Fair
Ceftazidime + Chlorampenicol	Moderate	Concurrent use of Ceftazidime and Chlorampenicol may results in decreased Ceftazidime effectiveness	12 (1.67)	Good
Aminoglycosides + Penicillins	Minor	Concurrent use of Aminoglycosides and Penicillin's may results in loss of Aminoglycoside efficacy.	307 (42.93)	Good
Penicillin G + Chlorampenicol		Concurrent use of Penicillin G and Chlorampenicol may results in decreased antibacterial effectiveness.	36 (5.03)	Fair
Penicillin V + Chlorampenicol		Concurrent use of Penicillin V and Chlorampenicol may results in decreased antibacterial effectiveness.	6 (0.83)	Fair

Major: The interaction may be life-threatening and require medical intervention to minimize or prevent serious adverse effects.

Moderate: The interaction may result in exacerbation of the patient's condition and require an alteration in therapy.

Minor: The interaction would have limited clinical effects and major alteration in therapy not required.

Good: Documentation strongly suggests the interaction exists, but well controlled studies are lacking.

Fair: Available documentation is poor, but pharmacologically considerations lead clinicians to suspect the interaction exists; or documentation is good for a pharmacologically similar drug.

Table 2: Risk of AMR in microorganisms.

Family/Antibiotic	Risk of Resistant Microorganism	
	Gram Positive	Gram Negative
Penicillins e.g: Amoxicillin Ampicillin Piperacillin Oxacillin	*Listeria monocytogenes*	Escherichia Coli Proteus Species Salmonella Typhi Shigella Haemophilus Influenzae Helicobacter Pylori Pseudomonas Aeruginosa Klebsiella
Tetracyclines e.g: Demeclocycline Minocycline Oxytetracycline Tetracycline	*Bacillus anthracis*	Rickettsiae Species Chlamydiae Species Brucella Abortus Mycoplasma Leptospira
Clindamycin	Penicillin Resistant Staphylococci *Streptococcus pyogenes* *Streptococcus pneumonia* *Clostridium perfringens*	Bacteroides Fragilis
Erythromycin	*Corynebacterium diphtheriae* *Listeria monocytogenes*	Neisseria Gonorrhoeae Mycoplasma Legionella Pneumophila Chlamydia Trachomatis Bordetella Pertusis
Ceftazidime	-	Pseudomonas Aeruginosa Bacteroides Fragilis
Aminoglycosides e.g: Amikacin Neomycin Gentamycin Tobramycin	*Streptococci* Viridans *Enterococcus* *Mycobacterium tuberculosis*	Pseudomonas Aeruginosa Klebsiella Escherichia Coli Proteus Species Brucella Abortus Yersinia Pestis
Penicillin G	*Streptococcus* Species, *Bacillus Anthracis* *Corynebacterium diphtheriae*	Neisseria Gonorrhoeae Neisseria Meningitidis Treponema Species Leptospira
Penicillin V	Similar to Penicillin G	
Chlorampenicol	*Staphylococcus aureus*	Haemophilus Influenzae Salmonella Typhi

Predicting AMR using antibiotic interactions is one of the benefits of this database research. The databases provided documentations are also evidence for interactions occurring, however the risk must be analyzed further using AMR databases, which confirms AMR by microbes against antibiotics; this is the study limitation. This research suggests that if the AMR database is used in this research, it will be possible to confirm statements concerning the Antimicrobial resistance.

CONCLUSION

Antimicrobial resistance is a major public health concern around the world and it must be understood by everyone. The pharmacist and other healthcare professionals look for potential drug interactions in the prescription and eliminate them to improve patient outcomes in terms of antimicrobial resistance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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