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Research Article

A Pattern of Potential Drug-Drug Interactions in Diabetic Foot Ulcer Patients at a Tertiary Care Teaching Hospital

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Abstract

A wide number of drugs are introduced every year, and many new interactions between drugs are largely reported. Clinically potential drug interactions may occur when two or more drugs are taken concurrently. By the persistent expansion in the inventory of drugs producing drug interactions, discernment of these interactions from the medication regimens becomes more essential to provide better care for the patient. The aim of the current study is to check the pattern of drug interactions in the prescriptions of diabetic foot ulcer patients and to create awareness among prescribers of these interactions to control the incidence of clinically adverse effects. In a uniquely developed and validated data entry proforma, the data about the following basis were gathered- types of drugs given, major drug class prescribed, the pharmacological class of the drugs and commonly happening drug interactions. The possible drug interactions were recognised and assessed using standard drug interaction reference database called Micromedex. During the study period, 84 prescriptions of diabetic foot ulcer inpatients were screened. Of the 84 prescriptions, 46 (54.76%) prescriptions had not less than one possible drug-drug interaction. This study showed that out of 295 drug interactions, 116 (39.3%) of the above prescriptions had major interactions, 61 (20.67%) had moderate interactions, 22 (7.45%) had minor interactions and 6 (2.03%) were contraindicated combinations. Of these, the antibiotic Ciprofloxacin which was prescribed for diabetic foot ulcer accounted for causing 55 interactions followed by Metronidazole caused 47 interactions. Metformin given to treat diabetes caused sixteen interactions. So, screening of prescriptions by the clinical pharmacist assist to reduce the clinical occurrence of potential/severe drug interactions in diabetic foot ulcer patients.

Keywords: *Diabetic Foot Ulcer; Drug Interactions; Evaluation; Prescriptions; Clinical Pharmacist; Interventions*

Introduction

Drug interaction refers to an alteration of response to one drug by the other when they are taken concomitantly. The change is mainly quantitative i.e. the drug response is either elevated or declined in strength, but rarely it is qualitative i.e. an unusual or a varied response is exhibited. DDIs may occur either from modification of the pharmacokinetic parameters such as absorption, distribution, or elimination of one drug by the another drug or from a combination of their action. The possibility of drug interaction emerges when a patient concomitantly receives more than one drug and the possibility increase in the number of drugs taken [1]. Today, with the increasing accessibility of convoluted medicinal agents and polypharmacy, the probability of causing drug interaction is greater. Otherwise the appearance of drug interaction is expounded as when the effects of one drug are changed by the existence of another drug, food, or any chemical agents. The total result of the combination may be:

1. Synergism
2. Antagonism
3. Idiosyncratic effects

Adverse drug reactions (ADRs) are related to notable morbidity, transience, and financial loss [2,3]. ADRs are accountable for over one million deaths per annum and are regarded to be the fourth significant cause of mortality in the United States [4]. Among the various components responsible for Adverse drug reactions, drug–drug interactions (DDIs) played a pivotal position [5].

A research study performed in two hospitals in the United Kingdom observed DDIs as cause for the origin of over 15% of all the ADRs [6]. Generally, geriatrics and patients who are on polypharmacy are at a high possibility for encountering DDIs [7].

More recent reports recommend that around 6% of the world's population is suffering from diabetes [8]. Diabetics are at a great danger for undergoing severe complications such as cardiovascular diseases. Patients with complicated diseases require being treated with polypharmacy.

Polypharmacy is a presenting element of causing DDIs [7]. A research study from Nepal showed that around 53% of the patients joined in the Medicine ward undergone a minimum of one drug interaction during their stay in the hospital [9]. A research study from India performed in a community pharmacy environment observed around 26% of the prescriptions had a minimum of one DDI [10].

A study on the diabetic patients taking home-based services from the United States stated that approximately all the patients i.e. 92.5% were at chance of getting "moderate" drug interactions, and around 70.5% are at risk of getting "mild" drug interactions [11]. As the information pertaining to the prevalence and pattern of potential drug interactions in the diabetic foot ulcer patients is unavailable in India, the current research study was executed.

Aim and Objectives

To get the demographic information of diabetic foot ulcer patients admitted to the inpatient department at chance of developing potential drug-drug interactions.

- To assess the pattern of possible drug interactions.
- To determine the therapeutic class of the medicines handling a greater chance for DDIs.
- To determine the more-risk drugs causing possible DDIs.
- To determine the frequent interacting couple of drugs.

Materials and Methods

Study type: Prospective cross-sectional study.

Study site: Inpatient department of General surgery in Sri Venkateswara Ramnarain Ruia Government Hospital (SVRRGGH) in Tirupati, India.

Study duration: November 2016 to April 2017 (6 months).

Inclusion criteria: All diabetic foot ulcer patients who are admitted to surgery department with or without co-morbidities.

Exclusion criteria:

- Age less than 20 years.
- Patients who are unwilling to participate in the study.
- Outpatients.

Tools

The Micromedex database (electronic) was utilised to determine and examine the pattern of possible DDIs. Micromedex has an individual section about DDIs termed as the Drug-REAX System. On recording the drugs in order, the program provides the information of possible DDIs and classifies drug interactions based on their onset, severity and documentation status.

DDI severity was classified as contraindicated, major, moderate and minor.

- Contraindicated, Major drug interactions are fatal, and medical intercession is necessary to minimize or prevent serious adverse effects.
- Moderate drug interactions results in an intensification of the patient's situation and require an modification in therapy.
- Minor drug interactions have finite clinical consequences.

Operational Modality: Patients were registered in this research study after taking written consent from them and this consent was prepared in the regional language. The drugs given in the prescription were written in a specially designed patient profile form. The procured data was then recorded into a Microsoft Excel sheet.

Potential drug interactions were obtained through the Micromedex database which exhibited the existing drug-drug interaction combinations, their severity, mechanism of interaction, and outcomes in the formulated regimens. Microsoft office Excel was used to perform the data analysis.

Then we were able to detect the following factors:

- The incidence of potential DDIs.
- The division of potential DDIs based on the patient's age, gender, and disease.
- The standard number of drugs per each patient who were at a chance of getting drug interactions.
- The categorization of drug interactions based on severity.

We identified the most frequently interacting drugs and also the drug pairs that caused drug interactions.

Results

A total of 84 patients, prescribed 884 drugs (average of 10.52 drugs per prescription), were enrolled. Among these patients, 46 (54.76%) were at a risk of encountering 205 DDIs.

The age wise distribution of patients is provided in table 1.

Sl. No	Age group (Years)	Number of Patients	Percentage (%)
1.	< 40	2	4.34
2.	41 - 50	12	26.08
3.	51 - 60	12	26.08
4.	61 - 70	15	32.60
5.	71 - 80	3	6.52
6.	> 80	2	4.34

Table 1: *Age distribution of patients with Drug interactions (n = 46).*

Gender wise distribution (n = 84): Total, 32 (69.56%) males and 14 (30.43%) females studied were at a chance of getting a minimum of one drug interaction. The gender wise distribution of patients is provided in table 2.

S. No	Gender	No.	Percentage (%)
1.	Male	32	69.56
2.	Female	14	30.43

Table 2: *Gender distribution of patients with Drug interactions (n = 46).*

The Average number of drugs per prescription: The standard number of drugs per each prescription was "6.41".

The Severity of the DDIs (n = 84) of the total 295 drug interactions 6 (2.03%) was contraindicated combinations, 116 (39.3%) of the potential DDIs were major, 61 (20.67%) were moderate and 22 (7.45%) were minor.

Therapeutic class of high-risk drugs: Altogether, 295 potential DDIs were observed and involved 363 drugs.

S. No	Category of prescription screened	Number of prescriptions	Percentage (%)
1.	Prescription with drug interactions	46	54.76
2.	Prescription without drug interactions	38	45.23

Table 3: *Total number of prescriptions screened in Diabetic foot ulcer patients (n = 84).*

S.no	No. of drugs per prescription	No. of Patients (n = 84)	Percentage (%)
1.	< 5	2	2.38
2.	6 to 10	35	41.66
3.	11 to 15	30	35.71
4.	16 to 20	13	15.47
5.	21 to 25	3	3.57
6.	> 25	1	1.19

Table 4: *Number of drugs prescribed in diabetic foot ulcer prescriptions.*

Number of Interaction(s)	Number of Prescription	Percentage (%)
1	7	15.21
2	11	23.91
3	3	6.52
4	10	21.73
5	2	4.34
6 and above	13	28.26

Table 5: *Number of Drug Interactions per Prescription in Diabetic foot ulcer Prescriptions (N = 46).*

Sl. No	Category of Drug interaction	No. of times	Percentage (%)
1.	Contraindicated	6	2.03
2.	Major	116	13.3
3.	Moderate	61	20.67
4.	Minor	22	7.45

Table 6: *Classification of drug interactions based on Severity.*

S.no	Drug category	No. of Drugs (n = 884)	Percentage (%)
1.	Antibiotics	285	32.23
2.	Antidiabetics	94	10.63
3.	Analgesics	144	16.29
4.	Antihypertensives	29	3.28
5.	Antiplatelets	14	1.58
6.	Antiasthmatics and Antitussives	8	0.91
7.	Antiulcerants	77	8.71
8.	Antiemetics	33	3.73
9.	Vitamin Supplements	184	20.81
10.	Other Drugs	16	1.81

Table 7: *Major Classes of Drugs Prescribed in Diabetic foot ulcer Prescriptions.*

The top 10 drugs with a great chance for causing drug interactions: The drugs with great risk accountable for causing drug-drug interactions were listed in table 8. Ciprofloxacin was involved in a majority number of potential DDIs.

Ranking	Drug	No.
1	Ciprofloxacin	55
2	Metronidazole	47
3	Ondansetron	40
4	Iron	25
5	Amikacin	22
6	Diclofenac	22
7	Tramadol	20
8	Pantop	19
9	Levofloxacin	18
10	Metformin	16

Table 8: *Top ten drugs with a high probability of causing Drug–Drug Interactions.*

Common interacting drug pairs: The first ten drug combinations with the possibility of interacting are given in table 9. The most common DDI observed was between Pantoprazole and Iron, Ciprofloxacin and Metronidazole.

Ranking	Drug combination	No. of Encounters
1	Pantop + Iron	17
2	Ciprofloxacin + Metronidazole	17
3	Metronidazole + Ondansetron	14
4	Piperacillin + Amikacin	13
5	Ondansetron + Tramadol	12
6	Ciprofloxacin + Diclofenac	8
7	Ciprofloxacin + Tramadol	6
8	Ciprofloxacin + Ondansetron	5
9	Amoxicillin + Amikacin	5
10	Ciprofloxacin + Metformin	4

Table 9: *Top ten drug pairs with the potential to cause Drug–Drug Interactions.*

The total number of prescriptions screened: In the study duration, a total of 84 prescriptions of diabetic foot ulcer inpatients were screened. Of them, we identified that 46 prescriptions contain at least one drug interaction.

Discussion

This study determined the prevalence and pattern of possible drug interactions in diabetic foot ulcer patients admitted to the inpatient General Surgery department at SVRRGGH, Tirupati, India. Patients undergoing the most DDIs were administering a larger number of the prescribed drug. Most of the potential drug interactions observed were "major" category. Ciprofloxacin was accountable for the utmost number of potential DDIs. The highest number of potential DDIs was found between metronidazole+ ciprofloxacin and pantoprazole+iron.

Diabetes is a persistent condition affecting carbohydrate, protein and lipid metabolisms. If unsuppressed, diabetes causes many serious consequences. Moreover in, type-2 diabetes, the incidence of hypertension may be more than 50% [12]. To control these DDIs, all the healthcare providers should get sufficient data about DDIs. In SVRR government general hospital, our Drug Information Center has been delivering evidence-based effective drug information to healthcare professionals and patients since 2012. In a research study, a primary assessment of the queries asked to the centre showed that around 7.1% of the total queries were related to drug interactions [13].

The linchpin of controlling and preventing severe complications is pharmacotherapy. As these patients may be suffering from numerous diseases, polypharmacy normally becomes inevitable.

In this study, men were at a greater risk when compared to women encountering potential drug interactions. Possibly this was because more men were registered in the study. Usually, cardiovascular diseases are more in men, which may increase their defenselessness to polypharmacy and may create a greater incidence of DDIs [14]. This particular association was not scrutinized in the current study.

We observed that patients between 61-70 years of age group were at great risk of experiencing drug interactions. Generally, geriatrics are at greater risk for DDIs [15]. It may be due to they are probably to suffer from numerous diseases that generally occur with a more time span of diabetes. As they are suffering from many other comorbidities, polypharmacy is normal in these patients.

In the current study, the average number of drugs per each prescription was 14. Thus, it was obvious that polypharmacy is an influencing factor for the occurrence of drug interactions.

One study has determined an adverse drug reaction rate of 7% in patients who are administering 6-10 drugs; this rate inclined to 40% in patients taking 16 to 20 drugs. This increase was partly a consequence of the occurrence of drug interactions [16].

In a study conducted in the United States, diabetic patients taking home-based care services, the average number of drugs administered was observed to be 8.9 per day. That study provided a conclusion that polypharmacy was a factor among home care patients suffering from diabetes [11].

In this study, most of the potential drug interactions were major. These potential drug interactions indicate that there is a requirement for dosage alteration of drugs in the patients.

A study conducted in the United States provided a conclusion that 92.8% of diabetes patients are at great risk for moderate DDIs [12].

The documentation status of majority of the potential drug interactions was good, indicating that these interactions may be prevented by an evidence-based therapy. One of the ideal ways is to get the information regarding drugs from a drug information center during prescribing, thus ideally controlling drug interactions in these patients.

In our study, antibiotic drugs exhibited the greater risk for potential DDIs, followed by antidiabetic drugs. It is recorded in the literature that the prevalence of DDIs is greater in patients with comorbid conditions [7,17,18]. Among the various drugs incriminated for potential drug interactions, ciprofloxacin stood in primary place. The most common potential interaction was observed between ciprofloxacin and metronidazole.

In this study, metformin exhibited a potential interaction with Insulin. The concomitant use of Insulin with metformin may cause hypoglycemia.

We also identified a potential interaction between Amikacin and Furosemide. This combination can lead to increased Amikacin plasma concentrations and ototoxicity and nephrotoxicity. This study observed a great number of potential interactions between clopidogrel and aspirin. The concomitant administration of these medications may lead to increased risk of bleeding. The same effect can be observed for the combinations amlodipine and clopidogrel, clopidogrel and diclofenac, diclofenac and aspirin. If this combination cannot be circumvented, patients should be checked for PT-INR.

We also identified a potential interaction between atorvastatin and erythromycin. This combination may cause an increased risk of myopathy or rhabdomyolysis. Increased risk of serotonin syndrome was observed for the combination ondansetron and tramadol. Increased risk of respiratory depression was observed with the combination of ciprofloxacin and tramadol. The same effect was observed for erythromycin and tramadol combination also.

Increased risk for QT interval prolongation is higher if ondansetron is given along with fluconazole and this is a contraindicated combination [19-21].

Limitations of the Study

We concede that the current study had some limitations. It was built predominantly on the evidence gathered from the Micromedex database.

We did not observe the patients for the incidence of DDIs clinically. Furthermore, the diabetic patients visiting the hospital as outpatients were ostracized from the enrolment.

Conclusion

This study was triumphant in detecting the prevalence and pattern of potential drug-drug interactions in diabetic foot ulcer patients at a tertiary care teaching hospital. The patients who were administering a greater number of drugs had a higher chance of experiencing drug interactions. Ciprofloxacin and Metronidazole were the great-risk drugs for drug interactions. The hospital Drug Information Centre can play a significant role in declining drug interactions in diabetic foot ulcer patients by providing drug-drug interaction -related information to health care practitioners.

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Conflict of Interest

None.

Bibliography

1. Tripathi KD. "Essentials of Medical Pharmacology, 6th edition". Jaypee Brothers, Medical Publishers (P) Ltd (2013): 889-896.
2. Classen DC., *et al*. "Adverse drug events in hospitalized patients". *Journal of the American Medical Association* 277.4 (1997): 301-306.
3. Johnson JA and Bootman JL. "Drug-related morbidity and mortality". *Archives of Internal Medicine* 155.18 (1995): 1949-1956.
4. Lazarou J., *et al*. "Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies". *Journal of the American Medical Association* 279.15 (1998): 1200-1205.
5. Hartshorn EA. "Drug interactions, general considerations". *Annals of Pharmacotherapy* 40.1 (2006): 166-186.
6. Pirmohamed M., *et al*. "Adverse drug reaction as cause of admission to hospital: prospective analysis of 18,820 patients". *British Medical Journal* 329 (2004): 15-19.
7. Hussar DA. "Drug interactions". In: Gennaro AR, Mardirosian AHD, Hanson GR (eds). Remington: The Science and Practice of Pharmacy, 20th edition. Baltimore: Williams & Wilkins (2000): 1746-1761.
8. Mayor S. "Diabetes affecting nearly 250 million adults in the world". *British Medical Journal* 333 (2006): 1191.
9. Bista D., *et al*. "Pattern of drug interactions in internal medicine wards of Manipal Teaching Hospital, Pokhara, Nepal". Sixth annual conference of the Society of Pharmacovigilance (India). Kurupanidhi College of Pharmacy, Bangalore, India (2006).
10. Nagavi BG and Singhal R. "Drug interactions in prescription from selected Indian community pharmacies". *Journal of Pharmacy Practice and Research* 35 (2005): 332.
11. Ibrahim IA., *et al*. "Polypharmacy and possible drug–drug interactions among diabetic patients receiving home health care services". *Home Health Care Services Quarterly* 24.1-2 (2005): 87-99.
12. Cantrill JA and Wood J. "Diabetes mellitus". In: Walker R, Edwards C (eds). Clinical Pharmacology and Therapeutics, 3rd edition. New York: Churchill Livingstone (2003): 657-677.
13. Palaian S., *et al*. "Contribution of the regional drug information center towards drug safety: An experience from Western Nepal". *Journal of Nepal Medical Association* 45.161 (2006): 216-218.
14. Scott D. "Coronary heart disease". In: Walker R, Edwards C (eds). Clinical Pharmacology and Therapeutics, 3rd edition. New York: Churchill Livingstone (2003): 279-297.

15. Juurlink DN., *et al*. "Drug–drug interactions among elderly patients hospitalized for drug toxicity". *Journal of the American Medical Association* 289.13 (2003): 1652-1658.

16. Smith JW., *et al*. "Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility". *Annals of Internal Medicine* 65.4 (1966): 629-640.

17. Girardin F and Pechere-Bertschi A. "Antihypertensive therapy and drug–drug interactions". *Revue Médicale Suisse* 1.32 (2005): 2099-2100, 2102-2104.

18. Lindblad CI., *et al*. "Potential drug–disease interactions in frail, hospitalized elderly veterans". *Annals of Pharmacotherapy* 39.3 (2005): 412-417.

19. Franzetti I., *et al*. "Possible synergistic effect of metformin and enalapril on the development of hyperkalemic lactic acidosis". *Diabetes Research and Clinical Practice* 38.3 (1997): 173-176.

20. Klasco RK. "DRUG-REAX System". Thomson Micromedex, Greenwood Village, CO (2006).

21. Avandamet (rosiglitazone maleate and metformin HCl), product information. Research Triangle Park, NC: GlaxoSmithKline (2003).

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