ORIGINAL ARTICLE

Pattern of Potential Drug-Drug Interactions in Diabetic Out-patients in a Tertiary Care Teaching Hospital in Nepal

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SUMMARY

A prospective study was conducted at Manipal Teaching Hospital, Pokhara, Nepal to identify and analyze the pattern of the potential DDIs (drug-drug interaction) in diabetes patients. A total of 182 patients who were prescribed 685 drugs (average, 3.76 drugs per prescription) were enrolled. Patients 51 to 60 years of age had a higher risk [43 patients, or (23.6%)] of developing DDIs. It was found that 174 (92.1%) of the potential DDIs were of "moderate" severity. Cardiovascular drugs carried a risk of DDIs (187 drugs, or 49.5%). The most common potential DDI observed was between metformin and enalapril (n = 64).

KEY WORDS:
Diabetes mellitus, Drug interactions, Nepal

INTRODUCTION

Adverse drug reactions (ADRs) are associated with significant morbidity, mortality, and economic loss[1,2]. ADRs were responsible for more than one million deaths annually and were considered to be the fourth major cause of death in the U.S[3]. A multicentre study from Nepal, conducted in five major hospitals, revealed that 0.63% of hospitalizations were attributable to drug therapy[4]. Among the various factors responsible for ADRs, drug–drug interactions (DDIs) played an important role. A DDI occurs when the effects of one drug are modified by the prior or the concurrent administration of another agent or of the same drug[5]. DDIs may arise either from alteration of absorption, distribution, biotransformation, or excretion of one drug by another or from a combination of their action or effects[5].

A landmark study conducted in two hospitals in the United Kingdom identified DDIs as being the source of more than 15% of the total number of ADRs[6]. In general, elderly patients and patients who are taking multiple drugs are at a high risk for experiencing DDIs[7].

More recent estimates suggest that nearly 6% of the world's population has diabetes[8]. Diabetic patients are at a high risk for experiencing chronic complications such as cardiovascular disease. Patients with chronic diseases often require multiple drugs, and thus these patients are more vulnerable to polypharmacy.

Polypharmacy is a contributing factor for DDIs[7]. A study from Nepal indicated that 53% of the patients admitted in the Department of Internal Medicine experienced at least one DDI during their hospital stay[9]. A study from India conducted in a community setting identified 26% of the prescriptions had at least one DDI[10].

A study of diabetic patients receiving home care services from the U.S. noted that nearly all the patients (92.5%) were at risk of developing "moderate" DDIs, and 70.5% could have been at risk of developing "mild" DDIs[11]. Because additional data on the incidence and pattern of potential DDIs among diabetic patients are lacking in Nepal, the present study was performed.

Our study was conducted with the following goals:

- to evaluate the demographics of diabetic patients attending the outpatient department at risk of potential drug–drug interactions
- to assess the pattern of potential drug–drug interactions
- to identify the therapeutic category of the drugs carrying a higher risk for DDIs
- to identify the high-risk drugs responsible for potential DDIs
- to identify the common interacting pairs of agents

MATERIALS AND METHODS

Study type, site, and duration

This prospective cross-sectional study was conducted at the outpatient pharmacy of Manipal Teaching Hospital in Pokhara, Nepal. The study was carried out from August 22 to December 7, 2006.

Inclusion and exclusion criteria

All diabetic patients who visited the outpatient pharmacy during the study period were enrolled in the study. Patients who were not taking medications from our pharmacy were excluded.

Tools

The MicroMedex electronic database was used to identify and analyse the pattern of potential DDIs. Micromedex contains a separate section on DDIs known as the Drug-REAX System. On entering the drugs one by one, the program lists the possible DDIs and categorizes DDIs according to their severity, onset, and documentation status.

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DDI severity was classified as major, moderate, or minor.
- Major DDIs may be life-threatening, and medical intervention may be necessary to minimize or prevent serious adverse effects.
- Moderate DDIs may result in an exacerbation of the patient's condition and may require an alteration in therapy.
- Minor DDIs have limited clinical effects.

The onset of potential DDIs was classified as rapid, delayed, or not specified.
- Rapid-onset DDIs lead to the clinical "conflict" or adverse effects within 24 hours of drug administration.
- Delayed-onset DDIs did not lead to the onset of clinical conflict or adverse effects within the first 24 hours following drug administration.

The documentation status of the potential DDI was classified as excellent, good, fair, poor, or unlikely.
- Excellent: Controlled studies have clearly established the existence of the drug interaction.
- Good: The documentation strongly suggests that a drug interaction exists, but well-controlled studies are lacking.
- Fair: Available documentation is poor, but pharmacological considerations may lead clinicians to suspect the existence of a drug interaction; or documentation may be good for a pharmacologically similar drug.
- Poor: Documentation is scant, such as in limited case reports; however, the possibility of a clinical conflict exists.
- Unlikely: Documentation is poor, and a sound pharmacological basis is lacking.

Operational Modality
Patients were enrolled in the study after giving verbal consent. The drugs written in the prescriptions were entered in a structured patient profile form. The collected data were then entered into an Excel spreadsheet.

Potential DDIs were noted via the MicroMedex database, which displayed the existing DDI combinations, their severity, onset, documentation status, mechanism of interaction, and outcomes in the prescribed regimens.
Microsoft Excel was used to perform the data analysis. We were then able to discern the following:
- the incidence of potential DDIs
- the distribution of potential DDIs according to the patent's age, sex, and disease
- the average number of drugs per patient who were at a risk of developing DDIs
- the classification of DDI severity
- the onset
- documentation status
- mechanism of action

We studied the most commonly interacting drugs and the drug combinations that resulted in DDIs.

RESULTS

A total of 182 patients, prescribed 685 drugs (average of 3.76 drugs per prescription), were enrolled. Among these patients, 95 (52.2%) were at a risk of encountering 189 DDIs. The age distribution of the patients is listed in Table I.

Sex distribution (n = 182)
Altogether, 52 (28.6%) males and 43 (23.6%) females studied were at a risk for at least one DDI.

Average number of drugs per prescription
The average number of drugs per prescription was 3.76. Among the patients who were at risk for experiencing DDIs, the number was 4.54. Among patients not at risk, the number was 2.17.

Severity of the DDIs (n = 189)
Ten (5.3%) of the potential DDIs were major, five (2.7%) were minor, and 174 (92.1%) were moderate.

Onset (n = 189)
Among the potential DDIs, 134 (70.9%) were of delayed onset; the remaining [55 (29.1%)] were of rapid onset.

Documentation status
Among the potential DDIs, 19 (10.1%) were of excellent documentation status, 149 (78.8%) had good status, and 21 (11.1%) were of fair status.

Mechanism of action
Of the 189 potential DDIs, 65 (34.5%) were pharmacodynamic and 58 (30.7%) were pharmacokinetic. The mechanism of action for these DDIs was not known (66 [34.9%]).

Therapeutic class of high-risk drugs
Altogether, 189 potential DDIs were observed and involved 378 drugs. The therapeutic classification of drugs with a potential risk for producing DDIs is listed in Table II.

Top 10 drugs with a high risk for drug–drug interactions
The high-risk drugs responsible for DDIs are listed in Table III. Metformin was the antidiabetic agent with the greatest risk; among the nondiabetic drugs, enalapril was associated with a high number of potential DDIs.

Common interacting drug pairs
The top ten drug pairs with the potential for interacting are listed in Table IV. The most common DDI observed was between metformin and enalapril.

Therapeutic index status (n = 378)
Of the total 378 drugs at risk for causing potential DDIs, 363 (96.0%) had a broader therapeutic index. The remaining 15 agents (3.4%) had a "narrow" therapeutic index.

DISCUSSION

This study identified the incidence and pattern of potential DDIs in diabetic patients attending the outpatient pharmacy department at Manipal Teaching Hospital. Patients experiencing the most DDIs were taking a greater number of prescribed drug. Most potential DDIs were "moderate" and had "good' documentation status. Metformin was responsible for the maximum number of potential DDIs. The highest

Table I: Age Distribution of patients enrolled in a study of Drug–Drug Interactions (DDIs) (n = 182)

	Risk of Experiencing DDIs (n = 95)		No Risk of Experiencing DDIs (n = 87)	
Age Group (Years)	No.	Percent (%)	No.	Percent (%)
Younger than 10	0	0.0	1	0.6
11-20	0	0.0	0	0.0
21-30	0	0.0	3	1.7
31-40	3	1.7	10	5.5
41-50	15	8.2	16	8.8
51-60	43	23.6	25	13.7
61-70	20	11.0	19	10.4
> 70	14	7.7	13	7.1

Table II: Classification of drugs associated with a high risk of Drug–Drug interactions (n = 378)

Therapeutic Category	No.	Percent (%)
Cardiovascular drugs	187	49.5
Antidiabetic drugs	118	31.2
Nonsteroidal anti-inflammatory agents (NSAIDs)	35	9.3
Diuretics	18	4.8
Anticoagulants	9	2.4
Antihistaminics	3	0.8
Calcium supplements	3	0.8
Antidepressants	2	0.5
Proton pump inhibitors	1	0.3
Iron supplements	1	0.3
Antimicrobials	1	0.3

Table III: Top ten drugs with a high probability of causing Drug–Drug Interactions

Ranking	Drug	No.
1	Metformin	91
2	Enalapril	90
3	Atenolol	52
4	Aspirin	34
5	Amlodipine	19
6	Glibenclamide (glyburide, U.S.)	10
7	Gliclazide (U.K.)	9
8	Digoxin	8
	Insulin	8
9	Ramipril	6
	Frusemide	6
	Warfarin	6
10	Amiloride	5
	Amiodarone	5

Table IV: Top ten drug pairs with the potential to cause Drug–Drug Interactions

Ranking	Drug Combination	No. of Encounters
1	Metformin + enalapril	64
2	Amlodipine + atenolol	18
3	Atenolol + metformin	17
5	Aspirin + enalapril	16
6	Atenolol + gliclazide	6
7	Aspirin + glibenclamide	6
8	Aspirin + insulin	4
9	Atenolol + glibenclamide	4
10	Metformin + ranitidine	3

number of potential DDIs was found between metformin and enalapril.

Diabetes is a chronic disease affecting carbohydrate, lipid, and protein metabolism. If uncontrolled, diabetes leads to several complications. Furthermore in, type-2 diabetes, the prevalence of hypertension may be as high as 50%[12]. The mainstay of controlling chronic complications is pharmacotherapy. Because these patients may have multiple diseases, polypharmacy often becomes unavoidable.

In our study, men were at a higher risk than women of experiencing potential DDIs. Perhaps this was because more men were enrolled in the study. In general, cardiovascular diseases were more numerous in men, which may increase their vulnerability to polypharmacy and may bring about a higher incidence of DDIs[13]. This relationship was not investigated in the present study.

We found that patients older than 50 years of age were at high risk of experiencing DDIs. In general, elderly patients are at higher risk for DDIs[14]. It is because they are likely to have multiple diseases that usually occur with an increased duration of diabetes. Because they have comorbidities, polypharmacy is common in these patients.

In this study, the average number of drugs per prescription was 3.76. In high-risk patients, the number was higher (4.54 drugs per prescription). Thus, it was evident that polypharmacy is a predisposing factor for DDIs.

One study had identified an ADR rate of 7% in patients taking six to ten drugs; this rate rose to 40% in patients taking 16 to 20 drugs. This increase was partly a result of the occurrence of DDIs[15].

In a U.S. study of diabetic patients receiving home care services, the average number of drugs taken was found to be 8.9 per day (standard deviation, 3.4). The authors of that study concluded that polypharmacy was a concern among home care patients with diabetes[11].

In our study, most potential DDIs were moderate. These potential DDIs suggest that there is a need for dosage adjustment.

A study from the U.S. reported that 92.8% of diabetes patients were at risk for moderate DDIs[12]. In order to prevent these DDIs, healthcare providers should have adequate information about DDIs. At our hospital, a Drug Information Centre has been providing evidence-based information to health care professionals since November 2003. A preliminary evaluation of the queries submitted to the center indicated that 7.1% of the total queries were related to DDIs[16].

We found that almost 71% of the potential DDIs were of the delayed type. For example, the DDIs between furosemide and enalapril is known to have a delayed effect[17]. Similarly, enalapril and metformin are known to interact with each other and can lead to lactic acidosis[18], an interaction of the delayed type. This suggests the need for counselling patients who are at a risk for experiencing these DDIs.

The documentation status of most of the potential DDIs was good, suggesting that these DDIs. May be prevented by an evidence-based approach. One of the better approaches is to obtain data on drugs from a drug information centre during the process of prescribing, thus ideally avoiding DDIs in these patients.

In this study, cardiovascular drugs posed the maximum risk for potential DDIs, followed by antidiabetic drugs. It is well documented in the literature that the incidence of DDIs is higher in patients with multiple diseases[7,19,20]. Among the various drugs implicated for potential DDIs, metformin ranked first. The most common potential interaction was between metformin and enalapril.

The mechanism of action for this DDI is unknown[21]. In the present study, metformin also showed a potential interaction with atenolol. The concurrent use of beta blockers with metformin can be associated with hypoglycemia, hyperglycemia, or hypertension[17].

There was also a potential interaction between metformin and ranitidine. This combination can lead to an increased plasma concentration of metformin[22]. Our study identified a high number of potential interactions between amlodipine and atenolol. The concomitant use of these medications can lead to hypotension as well as bradycardia[23–25]. If this combination cannot be avoided, patients should be monitored for cardiac function.

We also observed a potential interaction between aspirin and enalapril, glibenclamide and insulin. Aspirin can interact with enalapril, leading to a reduced efficacy of enalapril[26]. Similarly, with glibenclamide[27] and insulin,[28] the risk of hypoglycemia is high. Hence, one should be aware of the possible hypoglycemic effects associated with aspirin when prescribing for patients with diabetes.

In this study, most of the drugs posing a higher risk of DDIs (96.03%) had a broader therapeutic index. However, certain drugs having a narrow therapeutic index, such as digoxin, were also encountered. There was a potential interaction between digoxin and amiodarone. The concurrent use of these drugs can result in digoxin toxicity[29]. This DDI can even be fatal. Moreover, this DDI is of delayed type. It is known that amiodarone can increase the serum concentration of digoxin by 70% after one day[30]. This potential DDI thus suggests the need for close patient monitoring.

Limitations of the study

We acknowledge that this study had a few limitations. It was based mainly on the information obtained from the Micromedex database.

We did not monitor the patients for the occurrence of DDIs clinically. Moreover, the diabetic patients admitted in the hospital were excluded from enrollment, as were diabetic patients who did not buy their medicines from our outpatient pharmacy.

CONCLUSION

This study was successful in identifying the incidence and pattern of potential drug-drug interactions in diabetic outpatients in a Nepalese hospital. The patients who were taking a higher number of drugs had a greater risk experiencing DDIs. Metformin and enalapril were the high-risk drugs for DDIs. The hospital Drug Information Center can play an important role in minimizing DDIs in diabetic patients by providing DDI-related information to prescribers.

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