SURVEY OF PATTERN OF DRUG INTERACTIONS IN PATIENTS BEING PRESCRIBED ANTI-DIABETIC MEDICATIONS IN A TERTIARY CARE HOSPITAL: PROSPECTIVE CROSS SECTIONAL STUDY

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Abstract

Background: Potential importance of drug–drug interactions (DDIs) is increasing as polypharmacy becomes more prevalent. Because additional data on the incidence and pattern of potential DDIs among diabetic patients are lacking in India, and supplemental pharmacodynamic or clinical outcome information is needed to address importance of a drug- drug interaction.

Aim and objectives: To identify and analyze the pattern of DDIs in patients being prescribed anti-diabetic drugs in a tertiary care hospital.

Material and Methods: This prospective cross-sectional study was carried out for a period of three months in 200 Type 2 diabetes mellitus (Type 2 DM) patients who were taking at least one antidiabetic agent during the period of past six months, of any age and either sex admitted in medicine ward of a tertiary care teaching hospital. Only one prescription was included for each patient on his/her 3rd day of hospitalization in the ward.

Results: A total of 1217 drugs were prescribed in 200 prescriptions, resulting in an average of 6.1 drugs per prescription. A total of 637 potential DDIs were noted. The majority were seen in middle aged and elderly people. No overall difference was detected in the patients on insulin or metformin therapy taking or not taking additional drugs with the potential to interact. Worse control was found in the group of patients on sulphonylurea therapy taking interacting drugs ($P < 0.05$). This difference was most marked in the group of patients over 60 years of age, who also had the highest intake of potentially interacting drugs (57%; <35 years-37%).

Conclusion: Antidiabetic drugs have numerous interactions. A good practice is to use a drug–drug interaction checker if any questions arise, several are available online. Quality care starts with the clinician obtaining a complete medication list for each patient at the start of each visit.

Keywords: diabetes mellitus, drug interactions, hypoglycemic agents, drug therapy, co-morbidity, polypharmacy

Introduction

Diabetes mellitus refers to a group of chronic metabolic diseases which are generally characterized by hyperglycemia, which eventually leads to damage of multiple body systems. The prevalence of diabetes has been increasing globally. In 2015, an estimated 415 million adults were living with diabetes, and this number is projected to increase to 642 million by 2040. Over 70% of those with T2DM live in developing countries, and this proportion is increasing annually ^[1]. Most adults with diabetes have at least one co-morbidity, such as high blood pressure, heart disease or neurological complications ^[2]. Patients may take an average of 4 to 5 medications daily for their diabetes and comorbidities, excluding OTC medications, vitamins, and minerals ^[3]. Patients with T2DM are usually treated with multiple drugs, and are therefore at an increased risk of harmful drug–drug interactions (DDIs).

Polypharmacy is a contributing factor for DDIs ^[4]. A study from India conducted in a community setting identified 26% of the prescriptions had at least one DDI ^[5].

Drug interactions can occur in 4 ways ^[6]:

1. Inhibition of metabolism. A CYP450 enzyme can be inhibited by a number of drugs. Drug elimination slows down due to enzymatic inhibition of metabolism and drug levels increase.
2. Induction of metabolism. Similarly, CYP450 enzyme can be induced by drugs administered concomitantly which in turn increases metabolism, and drug levels decrease.
3. Inhibition of excretion. The inhibition of certain excretion pathways in the kidney can increase drug levels.
4. Synergism/Antagonism. When 2 medications are taken together and the effect of one, or both, is either increased or decreased, causing enhanced therapeutic or adverse effects or therapeutic failure.

The clinical importance of drug interactions involving anticoagulant, antihypertensive and antidepressant drugs is well known. Numerous theoretical interactions between antidiabetic agents and other drugs have been reported,

but the importance of these interactions in clinical practice has not been assessed ^[7]. Potential importance of drug – drug interactions is increasing as polypharmacy becomes more and more prevalent. In vitro data cannot reliably predict clinical drug - drug interactions but may provide a rationale for initiation of human studies to confirm or exclude possible interactions.

Because additional data on the incidence and pattern of potential DDIs among diabetic patients and supplemental pharmacodynamic or clinical outcome information mainly control of diabetic state, is needed to address importance of a drug- drug interaction. Therefore, we planned this study to assess the impact of drug interactions on diabetic control of the patients. We aimed this study to monitor the potential DDIs in diabetic patients admitted in medicine ward at a tertiary care hospital.

Materials and methods:

This prospective cross-sectional study was carried out for a period of three months in 200 Type 2 diabetes mellitus (Type 2 DM) patients who were taking at least one antidiabetic agent during the period of past six months, of any age and either sex admitted for (i) treatment of the same disease condition (uncontrolled blood sugar levels), and / or ii) associated co-morbidities (diabetic complications including hypertension) and / or (iii) any other ailments including infections.

Only one prescription was included for each patient on his/her 3rd day of hospitalization in the ward. Demographic information (age and sex), length of hospital stay, main diagnosis (ICD-10) and details of comorbidities were obtained from the clinical records. Their prescriptions were analyzed for any possible drug – drug interactions (DDI) using a computerized DDI database system (DrugReax-Micromedex, 2008). This was also cross checked from Pubmed and Pharmacology textbooks and reference books.

The data was analyzed for the following descriptive parameters:

1. Average number of drugs per prescription.
2. Most commonly prescribed anti-diabetic drugs.
3. Related co-morbidities and most commonly prescribed drugs for co-morbidities.
4. Average number of potentially interacting drug pairs per prescription.

Results

Two hundred Type 2 DM patients were included in the study. Out of 200, 110 were females (55%) and 90 were male patients (45%). (Figure1)

Figure 1: Gender distribution of patients

Table 1: Age distribution of patients

Age group (years)	Number of Patients
21-30	35
31-40	41
41-50	46
51-60	41
61-70	31
>70	6

A total of 1217 drugs were prescribed in 200 prescriptions, resulting in an average of 6.1 drugs per prescription. A total of 637 potential DDIs were noted. The majority were seen in middle aged and elderly people (Figure 2).

Figure 2: Age distribution vs Number of DDIs

Insulin was the treatment in 52 patients (26%), sulphonylureas in 39 patients and metformin in 27 patients. 81 patients were taking sulphonylurea and metformin therapy and one patient was on insulin and metformin (Figure 3).

Figure 3: Anti-diabetic drugs distribution among patients

Figure 4: Drugs other than antidiabetic medications for various co-morbidities or co-infections

Using the arbitrary criteria (Table 2) the control of the diabetic state was compared in the groups of patients taking or not taking additional interacting drugs (Table 3).

Table 2: Arbitrary criteria for control of diabetes based on information from current and three previous readings.

Number of unsatisfactory tests*	
Category of control	Blood sugar
Excellent	0
Good	Not >2
Fair	Not >3
Poor	>4

*Unsatisfactory blood sugar level >200 mg % (11.1 mmol/l) or <60 mg % (3.3 mmol/l).

Table 3: Arbitrary criteria of control and percentage of patients in each category who had taken, or not taken drugs with the potential to interact with the antidiabetic drugs.

Category of control	All patients (200)	Concurrent interacting drugs	
		Taken (103 patients)	Not taken (97 patients)
	%	%	%
Excellent	37.6	37.6	37.7
Good	23.7	24.4	22.9
Fair	21.7	20.9	22.6
Poor	16.9	17.0	16.8

The group of patients not taking additional interacting drugs was well matched by numbers, age and sex with the group taking medicines with the potential to interact. No significant overall differences in control were evident (Figure 5).

Figure 5: Diabetic state control with and without concurrent interacting drugs

Also, we analyzed the groups after subdivision into insulin, sulphonylurea and metformin treatment (Table 4). No overall difference was detected in the patients on insulin or metformin therapy taking or not taking additional drugs with the potential to interact. Worse control was found in the group of patients on sulphonylurea therapy taking interacting drugs ($P < 0.05$). This difference was most marked in the group of patients over 60 years of age, who also had the highest intake of potentially interacting drugs (57%; <35 years-37%).

Table 4: Arbitrary criteria of diabetic control with various antidiabetic drugs in patients taking and not taking interacting drugs.

	Insulin		Metformin		Sulphonylurea	
	Yes	No	Yes	No	Yes	No
Concurrent interacting drugs						
Number of patients	25	27	16	11	19	20
Category of control						
Excellent	8.1	3.0	59.2	63.2	49.2*	69.3*
Good %	16.3	26.6	30.8	20.7	38.3	21
Fair %	40.0	36.7	10	16.1	12.5	9.7
Poor %	35.6	33.7	9.7	14.2	11.6	8.2

* χ^2 9.73, $P < 0.05$

The control of the diabetic state was also examined in each of the antidiabetic drug groups for the principal interacting drugs shown in figure 4. In the sulphonylurea-treated group of patients taking diuretics, a lower number had 'excellent' control ($P < 0.05$) (Table 5). Half the patients on diuretics were taking furosemide and one-third thiazides. No significant differences were seen for the other drugs in the sulphonylurea group or for any of the drugs in the insulin or metformin groups.

Table 5: Degree of control by specific drugs: percentage of patients with 'excellent' control.

Drug	Insulin	Metformin	Sulphonylurea
Aspirin	6.5	89	70
Diuretics	0	78	46*
Patients not on interacting drugs	3.0	63	69

* χ^2 6.11, $P < 0.05$

Discussion

Half the patients on antidiabetic therapy had received drugs with the potential to interact at day three of hospitalization. The majority drug interactions were seen in middle aged and elderly people. The results were similar to earlier studies by Kirkman S. et al^[8]. The control of the diabetic state, as judged by arbitrary criteria, was adversely affected in sulphonylurea-treated patients taking drugs with the potential to interact, particularly diuretics. In the group of patients on insulin or metformin therapy the

concurrent administration of an interacting drug did not cause an overall significant deterioration in the control of the diabetic state. The finding that half the patients were taking drugs with the theoretical potential to interact suggests that doctors have not been deterred from prescribing such drugs because of lack of clinical experience of severe hypoglycaemia or hyperglycaemia. Theoretically, interacting drugs might fail to affect diabetic control in an individual patient if the effect of one drug were counteracted by concurrent administration of another drug with an opposite effect. Such a cancelling-out action could also apply in negating any overall effect in a group analysis. However, analysis by individual interacting drugs within each group did not suggest that this was a major factor in the present study. Nevertheless, despite this the analysis of the patients in the sulphonylurea group shows that control was adversely affected, particularly in older patients who are most at risk of polypharmacy.

In this study, only one group of drugs have been shown to cause an overall significant interference with the control of the diabetic state. The effect of diuretics on glucose metabolism is well known.

Angiotensin converting enzyme (ACE) inhibitors can increase the tissue sensitivity for insulin and thus cause slight vasodilation which may increase the risk of hypoglycemia but we do not come across such interaction. This interaction is also of questionable clinical relevance^[9].

The failure to demonstrate interference with control by some other drugs involved in significant interactions, for example phenytoin, valproate or ranitidine, may be due to the small number of diabetic patients exposed to them.

The criteria which we used to assess the control of the diabetic state may be criticized as unsatisfactory or too strict, or too lax. That may be the limitation of our study and so we suggest a further large scale study with more conclusive criteria for diabetic state assessment.

Conclusion

Antidiabetic drugs have numerous interactions. A good practice is to use a drug–drug interaction checker if any questions arise. Several are available online, and clinicians, nursing staff and pharmacists can scan medication profiles quickly for interactions. Quality care starts with the clinician obtaining a complete medication list for each patient at the start of each visit.

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