



Research Article

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NECESSITY OF DOSAGE ADJUSTMENT IN CONCURRENT DRUG THERAPY IN DIABETES: EVIDENCES FROM A CROSS -SECTIONAL STUDY

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ABSTRACT

Diabetes treatment when gets associated with other age-related disorders, lead to various side effects that are often moderate when this is not evaluated holistically the problem does not just persist but leads to severe clinical conditions requiring emergency interventions. It was long noticed by the physicians of unrelated complications in patients on antidiabetic therapy, which prompted us to investigate the cases. Therefore the cross-sectional study was carried out in the hospitals of Gwalior on outpatients to identify potential drug-drug interactions due to concurrent uses of drugs with antidiabetic therapy which may lead to severe complications. The commonest complication was muscular pain associated with acidity. The major cause of interaction can be attributed to the nondisclosure to physicians of concurrent drug administration, most often as self-medication of drugs freely available “over the counter” of Pharmacies, which are often not attended by a competently qualified personals. Herbal medications that are considered to be safe that maynot be taken by patients with known interactions. This concept of a safe drug also prevents patients from disclosing this information to the physician. It is ultimately the ability of the physicians to dig into the patient’s therapeutic regimen, besides their tendency for self-medication. On the other hand the pharmacies which practice prescription-less sales of drugs and inability to counsel every customer who is a patient, is the major cause of such drug interactions. Conclusively it is the absence of qualified and updated pharmacists that leads to problems.

Keywords: Concurrent medication, Clinical case, Diabetes, Metformin, Self-medication

INTRODUCTION

The disease of diabetes had been recognized by ancient Indian Physicians and described in Hindu Mythology since to 1500 B.C. They name this disease as ‘Madhumeha’ meaning ‘honey urine’ as the urine of the infected persons attracted ants.¹ Later the ancient Indian physician, Sushruta and the surgeon Charaka (400–500 A.D.) worked upon this and identified the two types, later to be named, Type I and Type II diabetes. Diabetes mellitus may be defined as a disorder of metabolism of carbohydrates which is characterized by the impaired ability of the body to produce or respond to insulin and thereby not being able to maintain proper levels of sugar (glucose) in blood.² These days, due to improper food habits and lifestyle, more and more people are getting affected by diabetes; hence it is becoming a major cause of morbidity and mortality not only because of Diabetes Mellitus but also due to the development of other related disorders as a result of chronic diabetes mellitus. For the treatment of diabetes Type II, Metformin is the most commonly prescribed drug by physicians in developing countries but this antidiabetic drug has complex drug-drug interactions and brings about severe problems if the patient is not informed before taking along with the drugs like β -blockers, Nonsteroidal Anti-inflammatory drugs (NSAIDs), Cimetidine, Cephalexin. Drug interactions result from the inhibitory activity of these drugs on different types of organic cation transporters (OCTs) and multi drug and toxin extrusion protein MATEs which are responsible for the pharmacokinetic movements of Metformin and other antidiabetic drugs. Cephalexin is a zwitterionic substrate of MATE1 and it reduces the elimination of Metformin resulting in its accumulation. Being a potent inhibitor of MATE1 Cimetidine reduces the excretion of Metformin thereby increases the risk of

Metformin-associated Lactic Acidosis (MALA).^{3,4} The recent study suggests that systemic metformin sulfonylurea combinations are able to block Diclofenac-induced antinociception in rats.⁵ Another anti diabetic drug, Repaglinide, which is also significantly used by patients worldwide also have some drug-drug interactions with Gemfibrozil, Mangiferin and other ayurvedic formulations. In the present study, a survey was conducted on diabetic patients of different age groups (20-60 years) who were on long term antidiabetic medications for 2-8 years and data were collected pertaining to clinical symptoms on concurrent medications for different ailments simultaneously. Nine clinical cases were identified that suggest interactions demanding immediate dose prescription modification. From the current study it is concluded that patients must be discussed by the pharmacists while dispensing the medications about their adverse effects so that drug interactions incidents might be minimized. Also, pharmacists must regularly keep themselves updated related to new clinical studies about drugs.

MATERIAL AND METHODS

Questionnaire preparation

Questionnaires were prepared as per the complications developed in different body parts as a result of diabetes. The complications of each organ related to diabetes were included in the Questionnaire. The Questionnaires were given to patients individually, to read it carefully and reply if they were affected by any diabetic disorders. Patients were also advised to discuss the concurrent uses of other drugs with antidiabetic therapy.

Choice of study centers

Hospitals within the vicinity of Gwalior city were visited before choosing the centers for the study. Prominent multispecialty hospitals were finalized in order to achieve different age groups patients to be included in the study by taking their consents. Necessary permissions from hospital management and physicians who were involved in the examination of diabetic patients were obtained along with the consent of the participating patients.

Interacting with local Pharmacies in the vicinity

Local pharmacies were also consulted about the antidiabetic drugs consumptions during this study. They were requested to discuss how they deal with the prescriptions given by physicians. Whether they involve in the distribution of cheaper quality of drugs or they discuss the adverse effects or drug interactions to the patient or precautions they should take while undergoing anti diabetic therapy concomitantly. Finally, obtained data from the questionnaires were compiled as a score card in the Excel Format for further interpretation.

RESULTS AND DISCUSSION

Data were obtained from eighty nine patients of different age groups and gender overall in this cross-sectional study. It was observed that Type 2 diabetes have several co-morbidities leading to additional pharmacological interventions mostly hypertension, high blood lipids, CNS disorders and depression. Diabetic patients concurrently, are most often predisposed to cardiac conditions, necessitating the use of related therapy for dyslipidemia, hypertension, antiplatelet, glycemic control for blood lipids. It, also being age and lifestyle-related disease; a patient may come for relief from many other symptoms. It is to the common knowledge of the healthcare professionals that the effects of the impaired absorptive and excretory mechanism of drugs based on OCT, MATE and Cytochrome P450. Metformin a Biguanide, most common and safest choice for Type 2 diabetes. This is a cation at physiological pH, is not metabolized but excreted as such by the kidney. Any concurrently used drug that hinder with OCTs, MATEs can increase the plasma concentration due to decreased elimination leading to MALA. Biguanides and Sulphonylurea together or separate can block Diclofenac induced anti-nociception (DIA) thus negating effects of Diclofenac, leading to increasing the dosage of Diclofenac which in turn leads to gastric discomfort and ulceration MALA may compel prescription or self-medication of Diclofenac Sodium with altered therapy instigating higher dose and use of antacids.⁵ The phenomenon of hyperglycemia-induced angina pectoris and ischemia has been reported as early as 1994. Hence any drug that hinders renal elimination of metformin can besides causing MALA also reduce blood sugar to a state that can cause ischemia and angina.

Case I

This one patient was concurrently administered metformin with cephalixin for UTI that caused of decrease MATE1 leading to decrease metformin elimination causing MALA syndrome. Patient complained of severe muscular pain and cramps.⁴

Case II

In a similar case as above, this patient was administered Diclofenac sodium for pain and Cimetidine to reduce acidity. While MATE1 got further depressed by Cimetidine led to aggravated MALA syndrome.⁴

Case III

A cardiac patient on Propranolol had a compromised OCT 1, 2 and 3 that caused lowering in the absorption of metformin. Patient experienced fatigue and lower stamina until dose adjustment in the next visit.⁴

Case IV

A hypertensive patient was prescribed Gemfibrozil to alter his lipid profile. Gemfibrozil inhibits CYP2c8 and OATP1b1, causing an increase concentration of Repaglinide and Hypoglycemia causing the patient to complain of severe muscular pain.⁶

Case V

A patient was concurrently taking Mangiferin an Ayurvedic medicine for diabetes along with Repaglinide. Metaglinide binds to ATP dependent K⁺ channel on pancreatic cells thus releasing insulin. This is metabolized in the liver by CYP34 and CYP268. Many herbal preparations are known to inhibit this enzyme leading to increasing plasma level of Metaglinides and their hepatotoxicity.

Mangiferin is known to inhibit CYP3a4 and modulates CYP450 necessary for metabolizing Repaglinide thus increasing plasma level and Hypoglycemia that caused ischemia and anginal pain in this patient.⁷

Case VI

This patient was being administered metformin along with Glibenclamide. At one point of time he was also administered Diclofenac sodium SOS along with Omeprazole. With reduced anti-nociception of Diclofenac, caused by metformin and Glibenclamide, made the patient increase the frequency and uptake of Diclofenac. Also that NSAIDS and metformin interact by charge transfer complex associated with inter and intra-molecular arrangement, therefore reducing the bioavailability of both the drugs.⁸ Now Diclofenac potentiated Glibenclamide while Omeprazole and Diclofenac Sodium caused lower uptake and reduced bioavailability of metformin. The net result with this patient was erratic blood sugar, continuous gastric pain caused by excessive Diclofenac that did not seem to significantly reduced pain.

Case VII

Herbal supplements are seemingly assumed to be safe. A diabetic patient on Repaglinide was also on *Aloe vera* which is known to inhibit CYP3a4 and CYP2d6 that potentiated the effect of Repaglinide causing the patient to visit the ICU for ischemia.⁹

Case VIII

In a similar case this patient was on Ayurvedic formulation with *Andrographis paniculata* which similarly depressed CYP3a4 and CYP2c9 potentiating Repaglinide causing angina pain though not severed as in the earlier case.¹⁰

Case IX

This patient was being administered metformin along with Glibenclamide, visited another doctor for UTI, and was prescribed Cephalixin that caused MATE 1 inhibition.⁴ With increased AUC of the metformin caused severe muscular pain in this patient.

CONCLUSION

A patient afflicted with diabetes has much comorbidities especially when it is related to advancing age. Common BEING cardiac and arthritis that originate as a small interaction when this is not viewed holistically, considering the medications for comorbidities, patients metabolic predisposition and habitual self-medication of some, this interaction aggravates exponentially. Problem gets compounded by two factors

1. Hesitation in discussing complications by patients with the physicians.
2. The inability of a pharmacist to educate and warn the patient of impending complications.

It becomes all the more essential to have qualified pharmacists who are updated regularly on the latest clinical studies to be in a position to educate and advise patients about the right course of therapy. A knowledgeable pharmacist will also be beneficial to the physician who can be consulted for latest verified information.

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