Short Reports

Drug interaction: Rifampicin and glibenclamide

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ABSTRACT

Background. Rifampicin is a potent inducer of the hepatic microsomal enzyme system. However, the drug has been shown to cause clinically important interactions with many drugs. This study was designed to test the interaction of rifampicin with the oral hypoglycaemic agent glibenclamide.

Methods. Twenty-nine well-controlled diabetic patients on a combination therapy of diet and glibenclamide, and willing to participate in the trial, received a daily dose of 450 mg (body weight <50 kg) or 600 mg (body-weight >50 kg) of rifampicin for 10 days.

Results. There was a significant ($p<0.001$) worsening of fasting and post-prandial blood sugar after administration of rifampicin. Dose modification of glibenclamide was required in 15 of the 17 patients in whom the diabetes became uncontrolled. Blood sugar normalized by day 6 after stopping rifampicin in all patients.

Conclusion. Rifampicin and glibenclamide interact. Therefore, necessary dose modifications should be made in order to achieve euglycaemia if these two drugs are given together.

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INTRODUCTION

There are few studies on drug interaction in the literature. The subject is, however, important because (i) the use of several drugs is often essential to obtain a desired therapeutic objective or to treat co-existing diseases; (ii) the concurrent use of drugs can either enhance or diminish the effect of one or both drugs or lead to a new effect not seen with either; (iii) estimates of the incidence of clinical drug interactions range from 3% to 5% in patients taking a few drugs to 20% in patients taking 10 to 20 drugs.[1]

Rifampicin is a potent inducer of the hepatic microsomal enzyme system.[2] It has been shown to cause clinically important interactions when combined with other drugs including oral anticoagulants,[3,4] oral contraceptives,[5,6] glucocorticoids,[7] digoxin,[8] nifedipine,[9] verapamil,[10] quinidine,[11] methadone,[12] barbiturates,[13] theophylline,[14,15] cyclosporine,[16] ketoconazole[17] and phenytoin.[18] Interaction between oral hypoglycaemics and rifampicin has been studied in diabetics who present with tuberculosis.[19,20] The presence of tuberculosis itself, however, could have altered glucose metabolism and may be a confounder. Zilly *et al.*[13] found evidence of an interaction between intravenous tolbutamide and rifampicin in healthy volunteers. We therefore designed this study to evaluate the interaction between glibenclamide and rifampicin in otherwise healthy diabetic volunteers.

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PATIENTS AND METHODS

Diabetics presenting to the medical outpatient clinic of our hospital were included in the study. Patients had to have adequate control of diabetes (fasting plasma sugar <140 mg/dl and 2-hour post-prandial plasma sugar <200 mg/dl) on a combination of diet and glibenclamide. Patients were excluded if they were on biguanides, if their blood sugar was poorly controlled or if they were on other drugs known to be hepatic enzyme inhibitors or inducers. Those with a past history of allergy to rifampicin or raised serum liver enzyme levels were also excluded.

Twenty-nine patients who fulfilled the inclusion criteria and gave informed consent formed the study population. The intervention was the administration of rifampicin (450 mg once daily for patients <50 kg body weight and 600 mg once daily for those >50 kg) on an empty stomach for 10 days. This duration was chosen as the interaction of rifampicin with other drugs such as oral anticoagulants is said to occur between 5 and 8 days.[1]

Patients were advised not to change their dietary habits during the study period and also to report any adverse effects.

Blood sugar measurement was repeated after 10 days of administration of rifampicin and subsequently every third day and the dose of glibenclamide was adjusted to obtain euglycaemic levels.

Statistical method

Wilcoxon sign–rank test was used to analyse the change in blood sugar between pre- and post-rifampicin administration and the change in the dose of glibenclamide.

RESULTS

There were 13 males (45%) and 16 females (55%). The mean age of the study population was 50.4 years (26–71 years). A majority of the patients (76%) were using 10 mg or less of glibenclamide per day for diabetic control.

The mean pre-intervention fasting blood sugar level was 114 mg/dl and the mean post-prandial blood sugar was 170 mg/dl. There was a significant change ($p<0.001$) in the mean fasting (129 mg/dl) and post-prandial blood sugar (209 mg/dl) on day 10 (Table I). The blood sugar increased in 17 out of 29 (59%) patients (fasting blood sugar >140 mg/dl; post-prandial sugar >200 mg/dl). Dose modification of oral hypoglycaemic agents was required in 15 out of 17 patients to achieve euglycaemia. Dose modification was not required in 2 patients whose fasting blood sugar levels were only mildly raised (145 mg/dl and 147 mg/dl). Blood sugar levels returned to normal in 11 of these patients by day 13, and in the remaining by day 16 after starting rifampicin. The mean dose changes of glibenclamide are shown in Table II.

DISCUSSION

There are few reports on drug interaction between oral hypoglycaemic agents and rifampicin.[13,19,20] These reports[19,20] were on patients who had co-existing diabetes and tuberculosis.

TABLE I. Changes in blood sugar levels after rifampicin therapy

	Mean (SD) blood sugar (mg/dl)	p value *
Baseline (n=29)		
Fasting	114 (20)	
Post-prandial	170 (28)	
Day 10 (n=29)		
Fasting	129 (31)	0.001
Post-prandial	209 (31)	0.001
Day 13 (n=15)†		
Fasting	134 (34)	ns
Post-prandial	194 (46)	ns
Day 16 (n=4)+		
Fasting	127 (10)	ns
Post-prandial	199 (20)	ns

* p values—comparison of blood sugar with baseline values ns not significant
† Blood sugar estimations on the 15 patients who required dose modification
+ Blood sugar estimations on the 4 patients who were not controlled on day 13

TABLE II. Mean dose of glibenclamide for 29 patients

	Mean (SD) glibenclamide dose (mg)
Pre-study	8.1 (5.9)
Day 10	9.7 (6.3)*
Day 13	9.9 (6.3)†
Day 16	9.9 (6.3)

* Two patients also required metformin for control
† Three patients required metformin for control

Our study was undertaken in otherwise healthy diabetic volunteers.

We found that glibenclamide and rifampicin interact as evidenced by a rise in the blood sugar levels in 17 of 29 patients (59%). To achieve euglycaemia a change in the dose schedule of oral hypoglycaemic agents was required in 15 of 17 patients. By day 16 of the study, the blood sugar values showed a decline, indicating that enzyme induction had ended. There were no adverse effects.

We conclude that blood sugar levels should be carefully monitored and the dose of oral hypoglycaemic agents adjusted in all diabetics who are put on rifampicin therapy.

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