ORIGINAL ARTICLE

IN VITRO AVAILABILITY OF METFORMIN IN PRESENCE OF H_2 RECEPTOR ANTAGONISTS

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ABSTRACT

Metformin is a guanidine derivative used for the treatment of NIDDM. As it is used for a long-term therapy, it may be coadministered with other drugs. Present paper deals with the *in vitro* availability studies of metformin in presence of commonly used H_2 receptor antagonists. The later drugs compete with histamine for H_2 receptors and block gastric acid secretion and some cardiovascular effects of histamine. These studies were carried out in simulated gastric juices, simulating empty and full stomach, simulated intestinal juice and buffers of pH 7.4 simulating blood pH at 37°C on a B.P. 2003 dissolution test apparatus. Commonly prescribed H_2 receptor antagonists like cimetidine, ranitidine and famotidine were used in these studies.

The present study clearly indicated that availability of metformin can be altered in presence of most of the H_2 receptor antagonists studied except in presence of famotidine at pH 4 where the drug concentration remains unaltered. The availability of metformin was increased in simulated gastric juice, pH 7.4 and pH 9 (except ranitidine at pH 9) whereas the decrease in availability was observed in presence of cimetidine and ranitidine at pH 4 and ranitidine at pH 9. On the basis of these results, it is can be suggested that metformin should be coadministered with care along with H_2 receptor antagonists especially in case of ranitidine; although chances of adverse reactions are rare but decrease availability of metformin may result in delayed effect. On the other hand, increase in metformin concentration may result in hypoglycemic effects.

Keywords: Metformin, NIDDM, cimetidine, ranitidine, famotidine

INTRODUCTION

Metformin, N,N-dimethylimidodicarbonimidic diamide or 1,1-dimethylbiguanide (figure 1) is an oral hypoglycemic agent, which enhances insulin sensitivity and is not effective in the absence of insulin (The Merck Index, 1999). It lowers blood glucose level in NIDDM patients by suppressing hepatic glucose output and enhancing peripheral glucose uptake. The mechanism of action involves binding of the apolar biguanide hydrocarbon side-chain to membrane phospholipids, evoking a change in the electrostatic surface potential (Damico, 2002). Subsequently, various metabolic effects are elicited, depending on the target cell, tissue, organ, species (Hermann, 1979 and Bailey, 1985) and metabolic regulation (Hermann, 1981). The available data on the relationship of structure to hypoglycemic activity for metformin has extensively been studied (Lu *et al*., 2004; Dolzhenko *et al*., 2003; Giannoukakis, 2003; Wagstaff & Goa, 2002; Scheen, 2001; Farrar *et al*., 2001; Koyama *et al*., 1997; Dumic *et al*., 1995; Krentz *et al*., 1994; Meglasson *et al*., 1993 and Retiz *et al*., 1989).

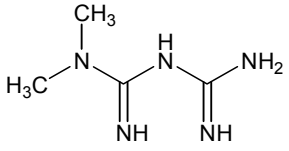

Fig. 1

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Metformin is incompletely absorbed, faecal recovery being about 30% of an oral dose (Tucker *et al*., 1981), the absorption is slower than the elimination. Oral bioavailability was 50-60% of the dose (Pentikainen *et al*., 1979; Noel, 1979 and Sirtori *et al*., 1978). The difference between absorbed and available drug may reflect minor presynaptic clearance of the drug (Tucker *et al*., 1981) or binding to the intestinal wall (Sirtori *et al*., 1978). Concomitant food intake may slightly impair metformin absorption (Melander *et al*., 1978). Metformin, because of its chemical structure, does not interact with the liver and has a short half-life (Vigneri *et al*., 1987). Higher doses may be associated with an increased incidence of gastrointestinal adverse effects (Melchior *et al*., 1996; Davidson *et al*., 1996 and Klepser *et al*., 1997).

There are relatively few interactions reported with cimetidine, while there is no interaction reported with ranitidine of famotidine. Several drug interactions of metformin reported with cimetidine are solely pharmacokinetic in origin. Very few studies have investigated the clinical relevance of such pharmacokinetic interactions by measuring pharmacodynamic responses or clinical endpoints (Plosker & Figgitt, 2004 and Somogyi & Muirhead, 1987). Aside from elevated plasma metformin levels with cimetidine and synergistic hypoglycemia with sulfonylureas, few interactions occur (Davidson & Peters, 1997). Potential adverse drug interactions include

hypoglycemia during concurrent sulfonylurea therapy and elevated metformin plasma concentrations when metformin is taken concomitantly with cimetidine (Guthrie, 1997). Finally, only very few drug interactions have been described with metformin in healthy volunteers. Plasma levels may be reduced by guar gum and alpha-glucosidase inhibitors and increased by cimetidine, but no data are yet available in the diabetic population (Scheen, 1996).

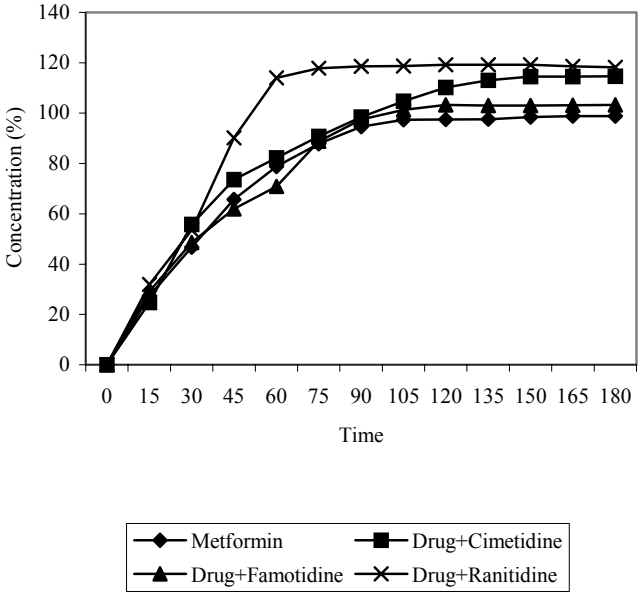

Fig. 2: Concentration of metformin (%) in presence of H_2 receptor antagonists at different time intervals in simulated gastric juice (pH 1) at 37 ºC.

As metformin is prescribed for a long-term therapy, it may be coadministered with commonly used H_2 receptor antagonists. The later drugs compete with histamine for H_2 receptors and block gastric acid secretion and some cardiovascular effects of histamine. In the present paper, we describe the *in vitro* availability of metformin in presence of H_2-receptor antagonists like, cimetidine, ranitidine and famotidine. These studies were carried out in simulated gastric juices, simulating empty and full stomach (pH 1 & 4), simulated intestinal juice (pH 9) and buffers of pH 7.4 simulating blood pH at 37°C on a B.P. 2003 dissolution test apparatus.

MATERIALS AND METHODS

Materials

Metformin hydrochloride (Neodipar 500 mg) and its reference standard were gift from Aventis Limited. The H_2 receptor antagonists used in the studies were cimetidine (Ulcerax 400 mg), ranitidine (Nulcer 150 mg) and famotidine (Hiler 20 mg) of Sami Pharmaceuticals (Pvt.) Ltd., Bosch Pharmaceuticals (Pvt.) Ltd. and Getz Pharma Pakistan (Pvt.) Ltd. Respectively, which were purchased from the market. All these drugs had an expiry of not less than 365 days at the time of study.

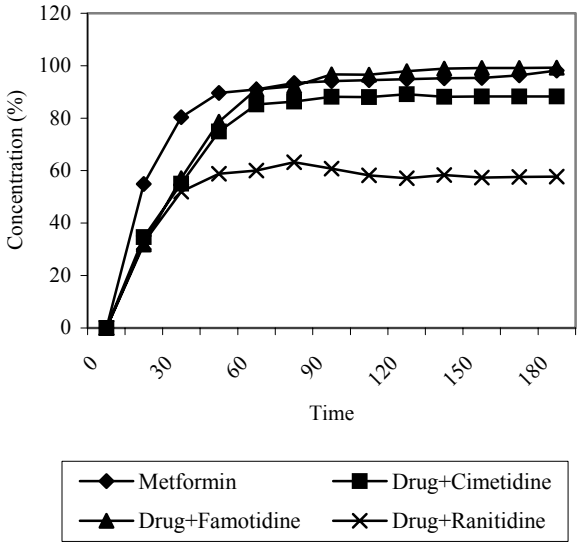

Fig. 3: Concentration of metformin (%) in presence of H_2 receptor antagonists at different time intervals in buffer pH 4 at 37 ºC.

Methods

Buffers of pH 1, 4, 9 and 7.4 simulating gastric and intestinal juices and blood pH were prepared according to standard procedures given in BP 2003. *In vitro* availability of metformin and the interacting drugs were individually studied in absence of each other in these buffers at 37ºC on a modified dissolution equipment the details of which have been described earlier (Arayne *et al*., 2005). During these experiments, metformin 0.5 gm was added to the dissolution medium at zero time, while H_2 receptor antagonists (cimetidine 0.4 g, famotidine 0.02 g, ranitidine 0.15 g) were added after 15 minutes time interval, separately in each set of experiment. Aliquots of 0.5 ml were withdrawn at every 15 minutes time interval for 180 minutes and assayed for both the drug contents after appropriate dilution, if required. The analysis of metformin and interacting drugs was carried out by measuring the absorbance at 233 nm for metformin and at 216, 224 and at 266 nm for cimetidine, ranitidine and famotidine respectively and by employing simultaneous equation.

RESULTS AND DISCUSSION

The results of the effects of H_2 receptor antagonists on the *in vitro* availability of metformin at different time intervals, in buffers of pH 1, 4, 7.4 and 9 at 37ºC are mentioned in table

1. Buffers of pH 1, 4, 7.4 and 9 simulated empty stomach, full stomach, blood pH and intestinal juice respectively, while human body temperature was also maintained. Graphs were plotted (figures 1-4) for the first order dissolution rate constant of drug in each set of experiment in presence and absence of H_2 receptor antagonists. The first order dissolution rate constants (K) values of metformin in presence of H_2 receptor antagonists and variations observed in dissolution times (T_{50} and T_{90}) are given in table 2.

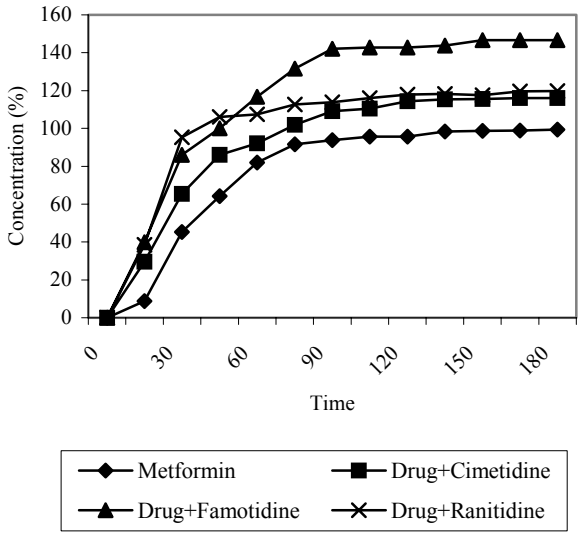

Fig. 4: Concentration of metformin (%) in presence of H_2 receptor antagonists at different time intervals in buffer pH 7.4 at 37ºC.

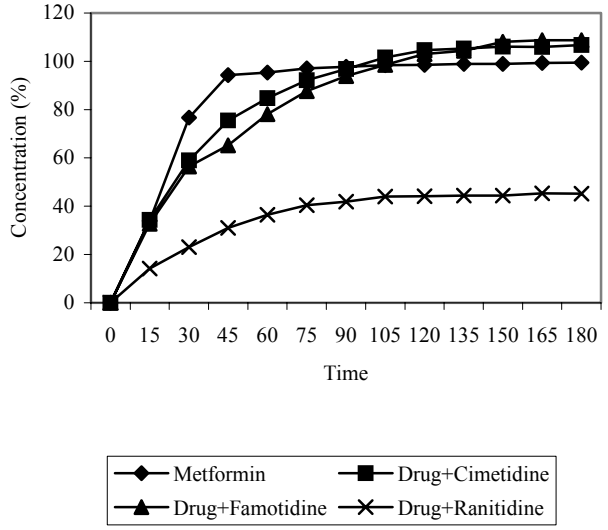

Fig. 5: Concentration of metformin (%) in presence of H_2 receptor antagonists at different time intervals in buffer pH 9 at 37ºC.

During metformin-H_2 receptor antagonists interaction studies carried out in simulated gastric juice (pH 1), the drug was quantitated at 233 nm, which showed that all H_2 receptor antagonists increase the availability of metformin particularly in case of ranitidine where 118.2% drug was available at the end of experiment. The increase of *in vitro* availability of metformin is presented in table 1 and is plotted in figure 1. The T_{50} of metformin in presence of all three H_2 receptor antagonists were almost same at 30 min i.e., 55.76%, 48.65% and 53.61% respectively but after that time graph shows a sudden increase in the %availability of metformin which ends up to 118.2% at the end of experiment.

Similarly, the availability of metformin increases (control <cimetidine<ranitidine<famotidine) in buffer pH 7.4 in presence of all H_2-receptor antagonists as compared to control. Archambeaud- Davidson and Peters (1997) reported that metformin cimetidine interactions resulted in elevated metformin plasma levels. In another studies the same result occurred, when metformin was taken concomitantly with cimetidine; an elevated metformin plasma concentration resulted (Scheen, 1996). The availability of metformin was found maximum in presence of famotidine (146.72%) at the end of experiment, which is indicative of complex formation. The increased availability of famotidine at this pH reveal potential circumstances of formation of charge transfer complex. These results indicate that when metformin is taken concurrently with famotidine, the patient may undergo severe hypoglycemia. Whereas the same drug i.e., famotidine does not exert any effect at pH 4 and the availability of metformin remains same. On the other hand, cimetidine and ranitidine decreases the availability of metformin at this pH up to 88.30% and 57.71% respectively. The most significant decline in the availability of metformin was observed in presence of ranitidine at pH 9 and so, it can be concluded that ranitidine should not be concurrently administered with metformin as it decreases the availability of metformin at both pH 4 and 9. The values of $T_{50\%}$ and $T_{90\%}$ were found to be 207.19% and 688.55% respectively.

In general, a number of drug interactions have been reported with biguanides in the literature, in which metformin is reported to interact with other drugs (Hermann, 1979; Bailey, 1985; Hermann, 1981; Nestler *et al*., 1994; Crave *et al*., 1995; Carpentier *et al*., 1976 and Carlsen *et al*., 1997). Use of a biguanide concomitantly with other drugs that lower blood sugar concentrations increases the risk of hypoglycemia, while drugs that increase blood glucose may reduce the effect of biguanide therapy. During one of these studies, it was suggested that cimetidine caused a 60% increase in metformin peak plasma and whole blood concentrations and a 40% increase in plasma and whole blood AUC (Beaven, 1978; Kathleen, 1587 and Korolkovas & Burckhalter, 1976). Cationic drugs that are eliminated by

Table 1: Concentration of metformin (%) in presence of H_2 receptor antagonists at different time intervals

Sample	Time [min]												
	0	15	30	45	60	75	90	105	120	135	150	165	180
Simulated gastric juice													
Metformin	0.0	27.3	46.7	65.7	78.7	87.7	94.3	97.3	97.5	97.5	98.4	98.8	98.8
Metformin + Cimetidine	0.0	24.7	55.7	73.6	82.1	90.8	98.4	104.7	110.2	113.04	114.4	114.5	114.5
Metformin + Ranitidine	0.0	31.9	53.6	90.1	114.0	117.8	118.5	118.7	119.2	119.1	119.1	118.6	118.2
Metformin + Famotidine	0.0	29.1	48.6	61.9	70.8	88.7	97.4	101.2	103.2	102.9	102.9	103.1	103.3
Buffer of pH 4													
Metformin	0.0	54.9	80.3	89.6	91.0	93.4	94.1	94.4	94.8	95.2	95.3	96.3	98.1
Metformin. + Cimetidine	0.0	34.6	55.0	74.8	85.2	86.3	88.1	88.0	89.1	88.2	88.2	88.3	88.3
Metformin. + Ranitidine	0	32.6	51.9	58.8	59.9	63.1	60.7	58.1	57.0	58.2	57.2	57.6	57.7
Metformin. + Famotidine	0.0	31.8	57.0	78.6	91.0	92.4	96.7	96.5	97.9	98.9	99.1	99.1	99.2
Buffer of pH 7.4													
Metformin	0.0	8.8	45.3	64.2	82.0	91.5	93.7	95.6	95.6	98.3	98.7	98.8	99.4
Metformin. + Cimetidine	0.0	29.4	65.3	86.0	92.0	101.9	109.1	110.4	114.3	115.4	115.6	116.0	116.0
Metformin + Ranitidine	0.0	38.5	95.2	106.7	107.4	112.7	113.9	116.1	117.9	118.2	117.6	119.6	119.8
Metformin + Famotidine	0.0	39.9	86.0	100.9	116.8	131.7	142.1	142.8	142.7	143.7	146.7	146.5	146.7
Buffer of pH 9													
Metformin	0.0	33.9	76.7	94.3	95.3	97.1	97.8	98.4	98.5	98.9	99.0	99.4	99.5
Metformin. + Cimetidine	0.0	34.2	58.9	75.5	84.7	92.1	96.8	101.6	104.7	105.3	106.0	105.9	106.7
Metformin + Ranitidine	0.0	14.1	23.0	31.0	36.3	40.4	41.8	43.9	44.1	44.3	44.4	45.2	45.2
Metformin + Famotidine	0.0	32.7	56.4	65.1	78.1	87.6	93.9	98.5	103.1	104.3	108.1	108.7	108.7

Table 2: Dissolution times ($T_{50\%\ and}\ T_{90\%}$) and first-order dissolution constants in the presence of H_2 receptor antagonists

Sample	simulated gastric juice			pH 4			pH 7.4			pH 9		
	$T_{50\%}$	$T_{90\%}$	K_{233nm}	$T_{50\%}$	$T_{90\%}$	K_{233nm}	$T_{50\%}$	$T_{90\%}$	K_{233nm}	$T_{50\%}$	$T_{90\%}$	K_{233nm}
Metformin	28.80	95.71	0.024	31.90	106.01	0.021	25.16	83.62	0.027	24.33	0.84	0.028
Metf. + Cimetidine	15.04	49.99	0.046	58.13	193.18	0.011	16.40	54.49	0.042	17.98	59.76	0.038
Metf. + Famotidine	16.99	56.46	0.040	25.55	84.90	0.027	10.50	34.88	0.066	17.15	57.00	0.040
Metf. + Ranitidine	3.47	44.76	0.051	144.94	481.66	0.004	1.34	70.91	0.032	207.19	688.55	0.0033

tubular secretion may compete with metformin for elimination and this may result in clinically significant interactions. For example, cimetidine competes with metformin for elimination, resulting in increased serum concentrations of metformin. However, it does not appear to alter the kinetics of cimetidine when these drugs are used concurrently. Thus patients taking metformin with other cationic drugs (procainamide, quinidine, trimethoprim, vancomycin) that may compete for elimination should be monitored carefully (Lebech *et al*., 1990). On the other hand a number of drug interactions of H_2-receptor antagonists have been reported with other drugs (Iftikhar *et al.,* 2005) in which these drugs were shown to form charge transfer complexes. A number of other cationic drugs which interfere with the elimination mechanism may involve in such interactions (Sultana *et al.*, 2005, 2005a, 2004, 2002, 2002a, 2001; Arayne *et al.,* 2004a, 2002, 2001).

The inhibitory of effect cimetidine on the metabolic activity of CYP2C9, 2C19, 2D6 and 2A was investigated in human

liver microsomes and it was observed the cimetidine inhibited each of CYP subfamily enzymes. Grape fruit juice containing CYP3A had the similar type of activity and retard the excretion of a number of drugs (Arayne *et al*., 2005a).

An overview of metformin in the treatment of type II diabetes mellitus was studied by Davidson and Peters (1997). Unlike sulphonylureas, metformin does not stimulate insulin secretion, aggravate hyperinsulinemia, or cause hypoglycemia or weight gain. Isolated cases of hypoglycemia have been seen with gliclazide/cimetidine and glibenclamide/ranitidine but marked changes in the control of diabetes in patients on most sulfonylureas when given either cimetidine or ranitidine seem to be unusual. There have been reports of *in vitro* interactions of glibenclamide and gliclazide with antacids, in which the availability of these drugs were increased resulting in a synergistic behaviour, which may have implications in hypoglycemia if the dose is not reduced (Arayne *et al*., 2003, 2004). Marked hypoglycemia was seen in patients on glibenclamide when treated with ranitidine (Lee *et al*., 1987) and another report briefly describes hypoglycemia in two patients given cimetidine, and two others given ranitidine, while taking un-named sulfonylureas (Girardin *et al*., 1992). One study shows that gliclazide develop very low blood sugar level after starting treatment with cimetidine (Archambeaud-Mouveroux *et al*., 1987). A possible exception is glipizide with cimetidine. Cimetidine appears to reduce the clearance of metformin. Another study reported that the hypoglycemic effect was reduced by cimetidine and ranitidine (Guthrie, 1996). Studies described above clearly show that hyperglycemic patients taking H_2 receptor antagonist can have unavoidable consequences. In view of the potential interactions, which may ultimately be hazardous due to long term therapy of metformin with H_2-receptor antagonists, the present study is focused on drug interactions of metformin with almost all the commonly prescribed H_2-receptor antagonists at human body temperature.

CONCLUSION

In conclusion, it can be inferred that availability of metformin can be altered in presence of most of the H_2 receptor antagonists studied except in presence of famotidine at pH 4 where the drug remains same throughout the experiment. The availability of metformin was increased in simulated gastric juice, pH 7.4 and pH 9 (except ranitidine at pH 9) whereas the decrease in availability was observed in presence of cimetidine and ranitidine at pH 4 and ranitidine at pH 9. On the basis of these results, it is can be suggested that metformin should be used with caution along with H_2 receptor antagonists especially in case of ranitidine, although chances of adverse reactions are rare but decrease availability of metformin may result in delayed effect. On the other hand, increase in metformin concentration may result in hypoglycemic effects, while contradictory reports appear in literature regarding metformin cimetidine interactions.

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