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# Effect of Acarbose on the Bioavailability and Pharmacokinetics of Metronidazole in Healthy and Diabetic Subjects

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## ABSTRACT

Although drug interactions with Acarbose are uncommon, there is a possibility for interference with the pharmacokinetic behaviors of concomitantly administered drugs. The present study was designed to evaluate the possible drug interactions between Acarbose and orally administered MTZ. Twelve healthy volunteers and twelve diabetic patients were enrolled in a randomized controlled crossover study. The effect of Acarbose (single 100mg dose) on the pharmacokinetics of MTZ was evaluated, while the effect of multiple doses was evaluated only in diabetic patients. In both groups, 5ml blood samples were collected into plane tubes at 0, 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0 and 48.0 hrs; serum levels of MTZ were evaluated using HPLC technique. The results showed that diabetes mellitus significantly altered the pharmacokinetic parameters of orally administered MTZ compared to healthy subjects. Moreover, both single and multiple doses of Acarbose significantly changed the pharmacokinetic parameters of MTZ when used concomitantly. The pharmacokinetics of orally administered MTZ was significantly affected by both diabetes mellitus and concomitant use of single or multiple doses of Acarbose.

*Keywords: Acarbose; metronidazole; type 2 DM; drug interactions.*

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## ABBREVIATIONS

*MTZ: Metronidazole; DM: diabetes mellitus; AUC: area under the curve.*

## 1. INTRODUCTION

The influence of diabetes on drug disposition has received relatively little attention. The pathophysiological changes and alteration in glucose homeostasis associated with diabetes mellitus may have fundamental effects on basic cellular processes, resulting in altered handling of many drugs. While little information is available on the effect of diabetes mellitus on the oral absorption of drugs (Gwilt et al., 1991), it has shown that glipizide has 100% oral systemic availability in type 2 diabetes (Chung et al., 2002; Wahlin-Boll et al., 1982). Acarbose is an oral hypoglycemic agent that acts by reversible competitive inhibition of alpha-glucosidase in the intestinal mucosa (Campbell et al., 1996). The main action of Acarbose is to reduce the postprandial monosaccharide absorption and hyperglycemia (Santeusanio and Compagnucci, 1994). Drug interactions with Acarbose are uncommon, the most frequent being augmentation of the hypoglycemic effect of oral hypoglycemic drugs. Acarbose has not been found to interact with nifedipine, propranolol or ranitidine, and did not change the pharmacokinetic profile of glibenclamide in patients with non-insulin-dependent diabetes mellitus (Gerard et al., 1984). Meanwhile, Acarbose has been shown to reduce the bioavailability of metformin in healthy subjects (Scheen et al., 1994), and also reported to increase INR values in patients treated with warfarin, possibly due to the increased absorption of warfarin (Morreale and Janetzky, 1997). While an association between Acarbose and low plasma levels of digoxin was suspected in four case reports (Ben-Ami et al., 1999; Nagai et al., 2000), two studies in small groups of volunteers showed conflicting results (Hillebrand et al., 1981; Miura et al., 1998). There are many other reports about the interaction of Acarbose with other concomitantly administered drugs including prometazine (Oba et al., 2001), sodium valproate (Serrano et al., 1996) and metformin (Scheen et al., 1994); however, the general clinical relevance of these cases is uncertain. The present study was designed to investigate the possible influence of single or multiple doses of the orally administered Acarbose on the bioavailability and pharmacokinetics of concomitantly orally administered metronidazole in both healthy subjects and patients with type 2 diabetes mellitus.

## 2. MATERIALS AND METHODS

### 2.1 Patient's Selection and Design

Twelve healthy volunteers (with age range 53±4.1 years) and twelve diabetic patients (with age range 56.3±5.2 years) were enrolled in a randomized controlled crossover study performed in Baquba Teaching Hospital and the Graduate Studies Laboratory of the college of Pharmacy, University of Baghdad, Iraq; the body mass index (BMI) for each group was 20.1±1.38 and 25.58±2.6 respectively. All healthy volunteers show normal medical history and revealed no pathological abnormalities on clinical and biochemical examination. Meanwhile, all patients were selected for having type 2 diabetes mellitus for at least 5 years and already treated with single daily dose of glibenclamide 5mg and metformin 500mg three times daily. All patients had serum transaminase concentrations less than twice the upper limit of the laboratory reference range and a normal serum creatinine (<120 mmol/L). Written

informed consent was obtained from each subject and the clinical protocol was approved by the Human Ethics Committee of the Iraqi Ministry of Health. All subjects were nonsmokers and were instructed not to drink caffeine or alcohol containing beverages for at least 10 hours before and during the study day. The study was performed according to an open, randomized clinical study design.

## 2.2 Blood Sampling and Analysis

Twelve diabetic patients (6 males and 6 females) and twelve healthy subjects received orally a single 500mg tablet of Metronidazole (MTZ) in the first part of the experiment; then after a washing period of one week, the same patients received orally 500mg single tablet of MTZ (Aventis, France) and 100mg Acarbose tablet (Bayer, Germany) in the second part. After one week second washing period, the patients only treated with Acarbose tablet (100mg) once daily for one week, and then given MTZ tablet (500mg) as a single oral dose in the eighth day. During each part and after each drug treatment, the diabetic patients were hospitalized at 10 p.m., and after 12 hours fasting, they received a single oral dose of MTZ (as mentioned previously) with 200 ml tap water. Four hours after drug administration, they received a standardized meal. An indwelling venous catheter was then introduced and kept patent by injection of diluted heparin solution. In all groups, 5ml blood samples were collected into plane tubes at 0, 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0 and 48.0 hours; samples were centrifuged at 4000 rpm at room temperature for five minutes, then serum was removed and frozen until time of assay. Serum MTZ concentrations were measured by a high-performance liquid chromatography method for the assessment of the pharmacokinetic parameters. Stock solution of MTZ (reference standard, 1mg/ml) was prepared by dissolving 100mg in 100ml of methanol. Working standard solutions were prepared from the stock solution by sequential dilution with methanol to yield final concentrations of 2.0, 4.0, 6.0, 9.0, and 12.0µg/ml. Samples for the preparation of standard curve were prepared by mixing blank serum (specially prepared for this purpose) with different concentrations of standard MTZ solution to get the final required serum concentrations (0.15, 1.5, 7.5, 15.0, 22.5, and 30.0 µg/ml). Calibration standards were obtained by addition of 300µl of acetonitril to 100µl of blank serum, then centrifuge at 10,000 rpm at 10℃ for 5 minutes, then 1 ml of dichloromethane was mixed with the supernatant; mixed and centrifuged at 10,000 rpm at 10℃ for 5 minutes; then 20µl of supernatant was injected into HPLC column for determination of MTZ serum levels (Emami et al., 2006). Analyses were performed using an HPLC system (Knauer, Germany) composed of a smartline pump 1000 and smartline U.V detector 2500 connected to smartline manager 5000. The separation was performed on a waters symmetry C19, 5µm (4.6 x150 mm) column. The drug analysis data were acquired and processed using CLASS-VP (v.6.2) software running under Windows 98 on a Pentium PC. The mobile phase was a mixture of 0.02M disodium hydrogen phosphate buffer-methanol (10:90 v/v) adjusted to pH 3.0 at a flow rate of 1 ml/min. The wave length was set at 276nm; run time was 10min (Mustapha et al., 2006). Analysis of the pharmacokinetic parameters was performed using the computer software Kinetica PK–PD analysis version 5.0 (Microsoft programs).

## 3. RESULTS

### 3.1 Effect of Single Dose Acarbose on Oral Absorption of MTZ in Healthy Subjects

Serum MTZ levels profile is shown in figure 1; the data presented in table 1 indicated that the values of $C_{max}$, $AUC_{tot}$, $AUC_{last}$, and $t_{½}$ were significantly decreased (60.42%, 52.545%, 46.164%, and 43.170% respectively) ($P$<0.05) in healthy subjects administered single dose of Acarbose compared with those not taking Acarbose. At the same time, the values of $T_{max}$ and $K_{elim}$ were significantly increased (27.5% and 39.17% respectively) ($P$<0.05) compared with those administered MTZ only.

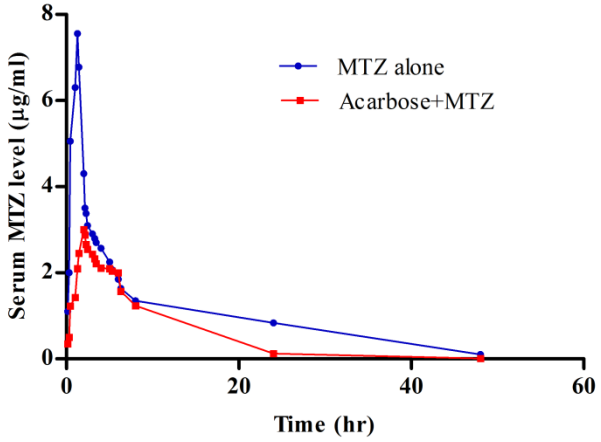


**Figure 1. Effects of single dose of Acarbose on the plasma level profile of orally administered Metronidazole (MTZ) in healthy subjects.**

**Table 1. Effect of single oral dose of Acarbose on the pharmacokinetic parameters of orally administered Metronidazole (MTZ) in healthy subjects**

| Pharmacokinetic Parameters | Single MTZ (500mg) only | Acarbose+500mg MTZ |
|---|---|---|
| $C_{max}$ (µg/ml) | 7.58 ± 0.38 | 3.0 ± 0.03* |
| $T_{max}$ (hr) | 1.45 ± 0.16 | 2.0 ± 0.01* |
| $AUC_{last}$ (µg $hr^{-1}ml^{-1}$) | 44.19 ± 16.63 | 23.79 ± 3.22* |
| $AUC_{tot}$ (µg $hr^{-1}ml^{-1}$) | 50.30 ± 10.73 | 23.87 ± 3.22* |
| $K_{elim}$ ($hr^{-}1$) | 0.073 ± 0.016 | 0.12 ± 0.003* |
| T½ (hr) | 10.03 ± 2.57 | 5.70 ± 0.15* |

*Values are presented as mean ± SD; n=12 subjects; * significantly different compared to MTZ only*

### 3.2 Effect of Single Dose Acarbose on Oral Absorption of MTZ in Diabetic Patients

The effect of single dose of Acarbose on the serum level profile and the pharmacokinetic parameters of orally administered of MTZ was shown in figure 2 and table 2. The data presented in table 2 indicated that the values of $C_{max}$, $AUC_{tot}$, $AUC_{last}$, $t_{½}$ were significantly decreased (58.8%, 81%, 79.9%, 35.99% respectively; $P$<0.05) in diabetic patients as a

result of concomitant administration of single oral dose of Acarbose compared with that reported in diabetic patients who not received Acarbose. Meanwhile, the values of $T_{max}$ and $K_{elim}$ were significantly increased (22.22% and 37.5% respectively; $P<0.05$) compared to its levels without co-administration of Acarbose.

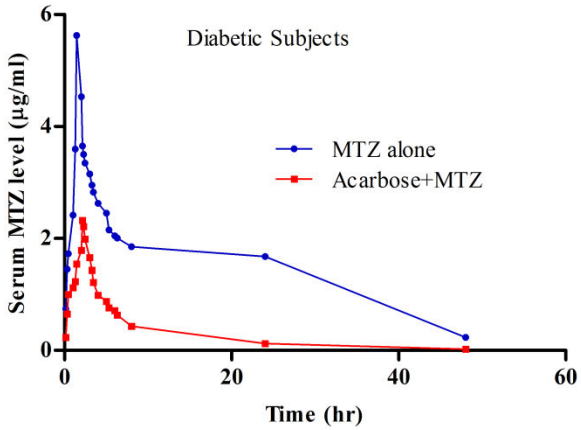


**Figure 2. Effects of single dose of Acarbose on the plasma level profile of orally administered Metronidazole (MTZ) in diabetic patients.**

**Table 2. Effect of single oral dose of Acarbose on the pharmacokinetic parameters of orally administered Metronidazole (MTZ) in diabetic patients.**

| Pharmacokinetic Parameters | Single MTZ (500mg) only | Acarbose+500mg MTZ |
|---|---|---|
| $C_{max}$ (µg/ml) | 5.63 ± 0.42 | 2.32 ± 0.07* |
| $T_{max}$ (hr) | 1.75 ± 0.01 | 2.25 ± 0.01* |
| $AUC_{last}$ (µg $hr^{-1}ml^{-1}$) | 66.57 ± 9.24 | 13.41 ± 2.31* |
| $AUC_{tot}$ (µg $hr^{-1}ml^{-1}$) | 71.99 ± 9.26 | 13.66 ± 2.39* |
| $K_{elim}$ ($hr^{-}1$) | 0.05 ± 0.01 | 0.08 ± 0.015* |
| T½ (hr) | 13.42 ± 3.03 | 8.59 ± 1.24* |

*Values are presented as mean ± SD; n=12 patients; * significantly different compared to MTZ only.*

## 3.3 Effect of Multiple Acarbose Doses on Oral Absorption of MTZ in Diabetic Patients

The effect of long-term use of Acarbose on the serum level profile and pharmacokinetic parameters of orally administered Metronidazole was shown in figure 3 and table 3. The data presented in table 3 indicated that the values of $C_{max}$, $AUC_{tot}$, $AUC_{last}$, $t_{½}$ were significantly decreased (4.085%, 22.89%, 23.509%, and 3.65% respectively; $P<0.05$) in diabetic patients treated for 7 days with 100 mg/day of Acarbose compared with those not using Acarbose . However, the values of $T_{max}$ and $K_{elim}$ were not significantly changed ($P<0.05$) with respect to those reported in diabetics not using Acarbose.

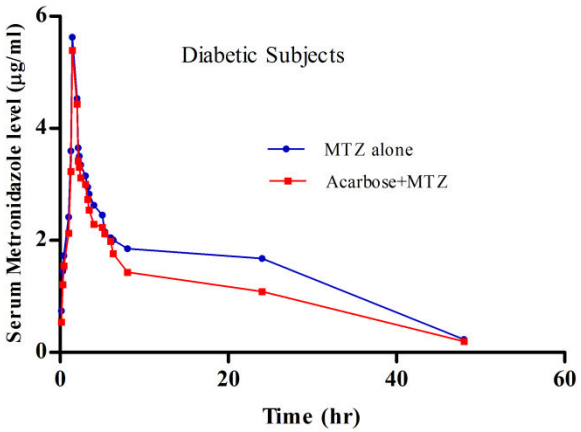


**Figure 3. Effects of multiple doses of Acarbose on the plasma level profile of orally administered Metronidazole (MTZ) in diabetic patients.**

**Table 3. Effect of long-term use of oral Acarbose on the pharmacokinetic parameters of orally administered Metronidazole (MTZ) in diabetic patients**

| Pharmacokinetic Parameters | Single MTZ (500mg) only | Acarbose+500mg MTZ |
|---|---|---|
| $C_{max}$ (µg/ml) | 5.63 ± 0.42 | 5.40 ± 0.12* |
| $T_{max}$ (hr) | 1.75 ± 0.01 | 1.75 ± 0.01 |
| $AUC_{last}$ (µg $hr^{-1}ml^{-1}$) | 66.57 ± 9.24 | 50.92 ± 6.55* |
| $AUC_{tot}$ (µg $hr^{-1}ml^{-1}$) | 71.99 ± 9.26 | 55.52 ± 10.61* |
| $K_{elim}$ ($hr^{-}1$) | 0.05 ± 0.01 | 0.056 ± 0.01 |
| $T_{½}$ (hr) | 13.42 ± 3.03 | 12.93 ± 2.94* |

*Values are presented as mean ± SD; n=12 patients; * significantly different compared to MTZ only.*

## 4. DISCUSSION

Although the effect of the disease state (type 2 DMM) on the Pharmacokinetics of orally administered MTZ was previously reported in our laboratory (Kurji et al., 2011), the present study also strongly indicated that diabetes mellitus alters the pharmacokinetic parameters of orally administered MTZ through a mechanism that may be related to alterations in gastric emptying time induced by gastroparesis. Altered gastric emptying can affect the pharmacokinetic/pharmacodynamic profile of orally administered drugs (Preston and Epstein, 1999). Erah in 2007 showed that alteration in body position which modifies gastric emptying time reduces the absorption of orally administered MTZ in rabbits (Erah, 2007). Moreover, many pathophysiological factors may alter the pH of stomach to a value of 5, which may consequently alter the lipophilicity of MTZ with favorable formation of ionized form; this may decrease absorption in the GIT as reported in the results mentioned above. The changes in the pharmacokinetic parameters of MTZ produced by concomitant administration of Acarbose might be due to the delay in gastric emptying time. Kawagishi et al. examined the relationship between gastric emptying and the efficacy of an α-glucosidase inhibitor in type 2 diabetic patients, and found a strong correlation between the rate of gastric emptying and the efficacy of voglibose (α-glucosidase inhibitor) during therapy of type 2 diabetic patients (Kawagishi et al., 1997). Acting within the gut lumen, Acarbose can affect bioavailability of MTZ by two different mechanisms; first, by delaying digestion of sucrose

and starch, Acarbose may cause a disturbance in gastrointestinal transit as well as loose stools; it is possible that this increase in intestinal motility leads to a decrease in MTZ absorption, just like what has been reported previously with metoclopramide (Serrano et al., 1996). Second, Acarbose (being an oligosaccharide, MW 645 daltons) may adhere to MTZ molecules, inhibiting absorption of the bound molecules (Serrano et al., 1996); in this respect, it is found that in healthy volunteers, Acarbose (100mg) induced moderate but significant reductions in $C_{max}$ and AUC of orally administered metformin (Andreas and Winfried, 2009). Adsorption could be expected to directly alter the absorption kinetics of Co-administered agents by altering either the primary absorption of drugs or secondary absorption (Miller et al., 2001). This was clearly defined when the area under the concentration-time curve from time zero to infinity for rosiglitazone was found lower during co-administration of Acarbose and was accompanied by an approximate 1hr (23%) reduction in terminal elimination half-life $t_{1/2}$ (4.9 hrs versus 3.8 hrs) in healthy volunteers. This small decrease in $AUC_{0-X}$ appears to be due to an alteration in systemic clearance of rosiglitazone and not changes in absorption (Miller et al., 2001). These data support our results about the effect of a single dose of Acarbose on MTZ pharmacokinetics. Long-term treatment with Acarbose increases colonic bacterial mass, particularly of lactobacteria (Scheppach et al., 1988). This may impair carbohydrate absorption and cause increased bacterial carbohydrate fermentation and fecal acidification. In patients with liver cirrhosis and porto-systemic encephalopathy, this action of Acarbose partially mimics the effect of lactulose or lactitol (Morgan et al., 1994). Moreover, Acarbose has been reported to lower serum levels of β-hydroxybutyrate significantly, and to reduce hyperammonaemia and gut pH. Considerable interest has recently focused on the incretin type of GIT hormones; Acarbose inhibits the postprandial release of gastric inhibitory polypeptide (GIP) in the duodenum and jejunum and increases the response of GLP-1 in the distal intestine, ileum and colon during the late postprandial period (60 to 240 min) (Goke et al., 1994). Clinical studies with Acarbose have shown that the gastrointestinal adverse events associated with α-glucosidase inhibition are generally benign in nature and correspond to initiation and up titration of the drug (Mertes, 2001; Mertes, 1998). Importantly, the side effects are transient, and their incidence decreases to normal with the induction of α-glucosidases in the lower intestine and readaptation of gut flora to the new levels of carbohydrate exposure. Therefore, the effect of Acarbose on concomitantly administered drugs may decrease with continuous use, but this not means that the effect on the pharmacokinetic parameters of drugs will be abolished, rather it may be decreased. Accordingly, the reported difference between the effects of single and long-term use of Acarbose on the pharmacokinetic parameters of orally administered MTZ can be explained.

## 5. CONCLUSION

Administration of Acarbose concomitantly with MTZ, as a single dose approach or long-term use, significantly changes the pharmacokinetic properties of this anti-infective agent in both normal subjects and diabetic patients.

## ACKNOWLEDGEMENT

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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