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# SERUM LEVEL AND PHARMACOKINETIC PARAMETERS OF SINGLE ORAL DOSE OF AMOXICILLIN IN TYPE 2 DIABETIC PATIENTS

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**ABSTRACT**
Many pathophysiological processes can affect the pharmacokinetic properties of drugs in people with diabetes. The present study was designed to evaluate the influence of diabetes mellitus on the pharmacokinetic parameters of amoxicillin administered as single oral dose. Twelve healthy volunteers and twelve diabetic patients were enrolled in the present study. On day 1, a single oral dose of amoxicillin 500 mg was administered orally to all participants at 9:00 am after a 10-hour fasting. Over the following 24 hours, blood samples were taken at frequent intervals and serum amoxicillin concentrations were measured by a high-performance liquid chromatography method for assessment of pharmacokinetics of amoxicillin**.** The values of $C_{max}$, $AUC_{total}$, $AUC_{last}$ were significantly decreased in diabetic patients compared to healthy subjects. At the same time, $T_{max}$ and $K_{elim.}$ were non-significantly affected compared to healthy subjects, while $T_{½}$ was significantly increased. In conclusion, diabetes mellitus affects some of the pharmacokinetic values of orally administered amoxicillin, an event that point to the requirement for dose monitoring of some drugs in such cases.
**Key words**: diabetes mellitus, amoxicillin, oral absorption, pharmacokinetics

## INTRODUCTION

Many pathophysiological processes can affect the pharmacokinetic properties of drugs in people with diabetes (Yu *et al*., 2005). Patients with diabetes have higher rates of cardiovascular, renal, gastrointestinal, neurological, and thyroid diseases and ophthalmological complications compared with individuals without diabetes. All may increase the chance of having drug-disease interactions (White and Campbell, 2000). Some physiological disorders, such as gastroparesis, decreased plasma albumin level, elevated plasma free fatty acid level, glycosylation of plasma proteins and changes in the hepatic microsomal cytochrome P-450 (CYP) contents were reported to occur in diabetes mellitus patients (Kim *et al*., 2005); these changes could alter the pharmacokinetics and hence the pharmacodynamics of drugs in such patients (Gwilt *et al*., 1991). Absorption of many orally administered drugs, such as metoclopramide and tolazoamide, was affected in diabetic patients with gastroparesis and autoimmune neuropathy (Gwilt *et al*., 1991; Jing *et al*., 2009; O'Connel *et al*., 1987; Chung *et al*., 2002; Della-Coletta and Eller, 1988). Amoxicillin is oral semisynthetic penicillin structurally related to ampicillin; it is widely used for treatment of bacterial infections and its plasma level is of critical importance for diabetic patients (Luis and Rodrigo, 2003; Goodman and Gillman, 2006). There is a wealth of information regarding the pharmacokinetic parameters of amoxicillin in healthy subjects; however, limited information is available in diabetic patients. Since amoxicillin is often used to treat many types of bacterial infections in diabetics (Foroutan *et al*., 2007), the influence of the disease processes and consequent complications on the pharmacokinetic parameters of drugs, including amoxicillin, should be systematically evaluated. The present study was deigned to evaluate the influence of diabetes mellitus on the pharmacokinetics of amoxicillin administered as single oral dose.

## PATIENTS AND METHODS

### Patient's selection and design

Twelve healthy volunteers and twelve diabetic patients were enrolled in the present study; all have an age of 55.3±5.78 years and with body mass index for each of 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 have been 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.

### Blood sampling and analysis

Following a 5-day screening period, healthy volunteers and patients with type 2 diabetes were enrolled in the study. On day 1, a single oral dose of amoxicillin 500 mg (Athlone, England) was administered orally to all participants at 9:00 a. m. after a 10-hours fasting. Blood samples were taken at zero-time and at frequent intervals over a period of 24 hours following the administration of amoxicillin (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, and 24.0 hrs) and serum amoxicillin concentrations were measured by a high-performance liquid chromatography method for the assessment of pharmacokinetic of amoxicillin. Stock solution of amoxicillin (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 amoxicillin solution to get the final required serum amoxicillin concentrations (2.0, 4.0, 6.0, 9.0, and 12.0 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°C for 5 minutes, then 1 ml of dichloromethane was mixed with the supernatant; mixed and centrifuged at 10,000 rpm at 10°C for 5 minutes; then 20µl of supernatant was injected into HPLC column for determination of amoxicillin serum levels (Foroutan *et al*., 2007). 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 0.02 M disodium hydrogen phosphate buffer-methanol (10:90 vlv) adjusted to pH 3.0 at a flow rate of 1 ml/min. The wave length was set at 228nm; run time was 10min (Foroutan *et al*., 2007). Analysis of the pharmacokinetic parameters was performed using the computer software kinetica PK– PD analysis version 5.0 (Microsoft –programs).

## RESULTS

The effects of diabetes mellitus on absorption of amoxicillin was shown in table 1 and figure 1. The data showed that the values of $C_{max}$, $AUC_{total}$, $AUC_{last}$ were significantly decreased ($P$<0.05) in the serum of diabetic patients compared with that in corresponding healthy subjects. At the same time, the values of $T_{max}$, $K_{elim}$ were non-significantly affected ($P$>0.05) compared with healthy controls, while $T_{1/2}$ was significantly elevated ($P$<0.05) compared with that reported in healthy subjects.

## DISCUSSION

The data of the present study strongly indicated that diabetes mellitus alters some of the pharmacokinetic parameters of orally administered amoxicillin. The mechanism by which diabetes mellitus alters the pharmacokinetics of amoxicillin may be due to alterations in gastric emptying time induced by gastroparesis; since altered gastric emptying can modify the pharmacokinetic/pharmacodynamic profile of many orally administered drugs (Preston and Epstein, 1999). Erah in 2007 shows that alteration in body position which causes changes in gastric emptying time reduce the absorption of orally administered metronidazole and amoxicillin in rabbits (Erah, 2007)**.** Symptoms of diabetic gastroparesis include early satiety, nausea, vomiting, heart burn, anorexia, and severe gastric stasis may ultimately lead to gastric bezoars, bacterial over growth, and gastric candidiasis; this will lead to alter secretion of GI hormones, poor glycemic control, acidosis, and electrolyte disturbances (Preston and Epstein, 1999). These factors may alter the pH of stomach to a value of 5 which may alter the solubility of amoxicillin. Absorption of amoxicillin is less affected by changes in pH of GIT because of it is being a Zwitter ion with p*Ka* values of 2.68 (carboxylic acid), 7.49 (amine) and 9.63 (phenolic hydroxyl); it is often ionized across the whole range of pH in the GIT (Erah, 2007). Amoxicillin is not susceptible to hepatic metabolism; also about 60% of an oral dose of amoxicillin is excreted unchanged in the urine within 6 hours by glomerular filtration and tubular secretion**.** Depending on the stage of diabetes, the glomerular filtration rate may be increased, normal, or decreased. In addition, a variety of renal tubular secretory abnormalities arise in both type 1 and type 2 diabetes that could potentially influence pharmacokinetics as well (Parving *et al*., 1998; Hebden *et al*., 1998). It has been previously reported that benzylpenicillin clearance was significantly higher in diabetic children than in controls and serum concentration of kanamicin, bekanamicin and amikacin were lower, and the half-life shorter, in diabetic children than in non diabetic children, and studies in adults are more equivocal (Gwilt *et al*., 1991)**.** Twenty to 30% of diabetics develop abnormal gastric motility, resulting in disordered gastric emptying or gastroparesis (Gwilt *et al*., 1991). Although the etiology of altered gastric motility remains obscure, many factors appear to be important including poorly controlled diabetes, and others (Marangos *et al*., 1995). Absorption of many orally administered drugs may or may not affected by the presence of diabetes; the extent of absorption of metoclopramide administered orally to diabetic patient with gastroparesis fell within the range of values reported in healthy subjects (Gwilt *et al*., 1991). Meanwhile, absorption of tolazamide was 26% slower in diabetic patients with asymptomatic autonomic neuropathy than in healthy subjects (Gwilt *et al*., 1991), and a 26% decrease in the extent of absorption of orally administered ampicillin was reported compared with non-diabetics controls (Nicolan and Estein, 2010). Therefore, it appears that diabetes can influence the gastrointestinal absorption of drugs, but the extent of influence of the disease on drug absorption may depend on the severity, duration and type of the disease (Preston and Epstein, 1999). Also, Daniyan *et al*. showed that diabetes induces an alteration in the pharmacokinetics of halofantrine and its major metabolite, especially the $C_{max}$, drug absorption parameters, and binding to plasma components (Daniyan *et al*., 2008). In conclusion, the pharmacokinetic parameters of amoxicillin absorption after oral administration were altered in diabetic patients compared to healthy subjects. Therefore, the effect of diabetes mellitus on the pharmacokinetic parameters of drugs should be carefully evaluated to avoid clinical insignificance.

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**Table 1. The pharmacokinetic parameters of orally administered amoxicillin in type 2 diabetic patients compared to healthy subjects**

| Pharmacokinetic Parameters | Healthy subjects | Diabetic patients |
|---|---|---|
| $C_{max}$ (µg/ml) | 8.68 ± 0.05 | 8.51 ± 0.09* |
| $T_{max}$ (hr) | 2.5 ± 0.01 | 2.5 ± 0.01 |
| $AUC_{last}$(µg. $mL^{-1}$. hr) | 21.97 ± 1.18 | 20.83 ± 0.94* |
| $AUC_{tot}$ (µg. $mL^{-1}$. hr) | 21.99 ± 1.19 | 20.85 ± 0.94* |
| $K_{elim}$ ($hr^{-1}$) | 0.41 ± 0.38 | 0.41 ± 0.37 |
| $T_{½}$ (hr) | 2.17 ± 0.60 | 2.21 ± 0.64* |

Values are presented as mean ± S. D.; * significantly different compared to healthy subjects.

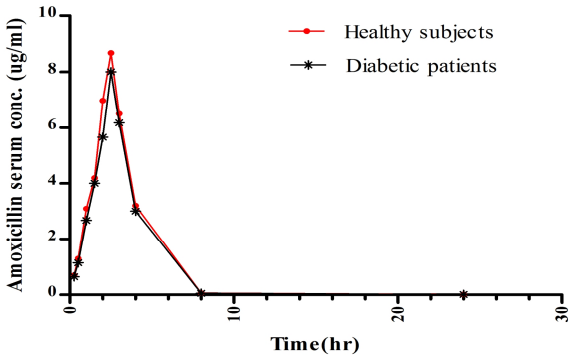


**Figure 1. Serum–time profile of amoxicillin after 500 mg single oral dose in healthy subjects and patients with type II diabetes mellitus.**

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