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Variable Omeprazole Kinetics in Healthy Jordanian Adults

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ABSTRACT: *Objectives*. The objective of this study was to examine the pharmacokinetics of orally administered omeprazole in healthy adult Jordanian men.

Method. Plasma concentrations of omeprazole were measured over a 12 h period after administration of a single oral dose of 40 mg omeprazole (Losec®, AstraZeneca, UK). Subjects were healthy adult Jordanian men age 18–38 (24 ± 4, mean $\pm$ SD). The pharmacokinetic parameters were derived from the plasma concentration-time profiles for $AUC_{0\text{-}t}$, $AUC_{0\text{-inf}}$, C_{max}, t_{max}, $t_{1/2e}$ and K_e.

Results. The pharmacokinetic of omeprazole were scattered over a wide range. The median $AUC_{0\text{-inf}}$ was 784.86 ± 1182.88 (ng·h/ml), and the median C_{max} was 521 ± 354 (ng/ml) (median $\pm$ SD). In general, most subjects showed normal distribution ($\sim$90%). Some subjects (10%) did show very high *AUC* and C_{max} compared with the reported *AUC* and C_{max} levels. These subjects had higher half-lives and lower rates of elimination.

Conclusion. Significant difference in the pharmacokinetics of omeprazole after a single dose administration was noted. Approximately 10% of the study group showed very high omeprazole plasma levels and *AUC*s. Differences in the pharmacokinetics might be due to differences in the genetic make-up of subjects.

Key words: omeprazole; kinetics; Jordanian adults

Introduction

Omeprazole is a substituted benzimidazole that belongs to a new class of antisecretory compounds. It suppresses gastric acid secretion by specific irreversible inhibition of the H^+/K^+ ATPase enzyme (proton pump) system at the secretory surface of the gastric parietal cell, thus known as a proton pump inhibitor (PPI) [1–5]. The half-life of omeprazole is <1 h in most cases, however, acid secretion suppression could last up to 12–15 h with a single dose, because it forms covalent binding with the proton pump. The degree of acid secretion is dose dependent. Due to the very short half-life of omeprazole, studies on acid secretion were related to the drug's bioavailability (*AUC*) rather than to plasma levels [6–9].

Omeprazole is successfully used in the treatment of various gastric acid-related disorders. It is generally a well-tolerated drug, even in long term treatment. Clinical doses are in the range 20–40 mg/day for the treatment of gastric and duodenal ulcers, 20–80 mg/day for reflux esophagitis, and 20–120 mg/day for Zollinger–Ellison syndrome [10,11].

Omeprazole is mainly metabolized (80%) by cytochrome P450 2C19 (CYP2C19), and to a lesser extent by cytochrome P450 3A (CYP3A). CYP2C19 is polymorphically expressed in the population. It has a mutant allele (non-functional enzyme) that constitutes the recessive trait.

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Homozygous carriers of the mutation are labeled as poor metabolizers (PMs) of omeprazole. These poor metabolizers have been shown to represent 3–4% of the Caucasian population, and 20% of the Far Eastern population [12,13]. Poor metabolizers are expected to have a low metabolizing capacity of omeprazole, and subsequently, extended half-lives of the drug and very high plasma and *AUC* levels [14,15].

Omeprazole is widely used in Jordan for the management of gastric and duodenal ulcers, as well as for other acid secretion disorders [16–18]. To our knowledge the variability in omeprazole kinetics in the Jordanian population has never been studied, and there are no studies on genotyping or phenotyping of CYP2C19. Studies from other countries in the Middle East showed that the frequency of non-functional CYP2C19*1 is around 10% [19,20].

The aim of this study was to investigate the pharmacokinetics of oral omeprazole in healthy adult Jordanian men with similar demographic data, and to see whether a correlation exists between higher peak plasma concentrations and/or *AUC* and the incidence of adverse effects.

Materials and Methods

Chemicals

Omeprazole (Losec® 20 mg capsule) was obtained from AstraZeneca UK. All other chemicals were of reagent grade and obtained commercially.

Subjects and study protocol

This was an open-label, randomized study of the bioavailability of single dose of 40 mg enteric coated omeprazole. The drug was given after at least 10 h fasting, and lunch was served 4 h after drug ingestion. Venous blood samples were collected in heparinized tubes before dosing (0.00 h) and at the following times after the dose: 0.33, 0.66, 1.00, 1.33, 1.66, 2.00, 2.33, 2.66, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00 and 12.00 h. The plasma samples separated after centrifugation at $1500 \times \mathbf{g}$ for 10 min were stored frozen at -20°C until analysis.

Medical histories and demographic data, including name, sex, age, body weight (kg), height (m), race and tobacco use were recorded for each subject. None of the subjects had hepatic or renal dysfunction or had taken any medication, including alcohol or over the counter drugs for at least 1 week before or during the study.

Inclusion criteria

Healthy males, age 18–45 years, body weight within 15% of ideal weights for height. Laboratory tests are within the normal range. Subject does not have allergy to the drugs under investigation.

Exclusion criteria

Presence of medical history, vital signs and/or physical examination with evidence of clinically significant deviation from normal medical condition.

Written informed consent was obtained from all subjects before the study commenced. This research was carried out in accordance with conditions stipulated by International Clinical Research Guidelines, and was approved by The Institutional Review Board of the hospital in advance.

HPLC assay

The HPLC system consisted of LC-10ADvp pump, a manual injector (rheodyne, USA), a UV-VIS detector SPD-10AVvp, a Lichrospher 60 RP-Select B (5 μm) (250 × 4 mm) HPLC cartridge column, a SCL-10Avp system controller and Class-VP Software Version 5.03 (Shimadzu Co., Japan).

Plasma samples were spiked with 100 μl of lansoprazole working solution (8.00 μg/ml) and vortexed for about 30 s. 200 μl of 0.5 M sodium carbonate buffer (pH 9.8) was added and vortexed for 30 s. 7 ml of the extraction solvent (ethyl acetate) was added and vortexed for a further 1 min. The samples were centrifuged for 5 min at a speed of 3000 rpm. The organic layer was evaporated to complete dryness in a water bath at a temperature of 40°C under a gentle stream of nitrogen gas. The intra-day accuracy of the method for omeprazole ranged from 88.33%

to 103.90%, while the intra-day precision ranged from 2.18% to 10.61%. The inter-day accuracy ranged from 94.58% to 103.61%, while the inter-day precision ranged from 2.73% to 16.78%, the absolute recovery of amoxicillin was 101.25% and the absolute recovery of the internal standard (lansoprazole) was 88.85%, while the relative recovery of omeprazole ranged from 82.02% to 85.15%.

Pharmacokinetic analysis

The area under the plasma concentration time curve (*AUC*) was calculated using the linear trapezoidal rule from 0 to infinity. The maximum plasma concentration (C_{max}) was obtained graphically. The apparent first-order elimination or terminal rate constant K_e was calculated by linear least-squares regression analysis of the terminal log-linear portion of plasma concentration-time profile. The elimination or terminal half-life $t_{1/2e}$ was calculated as $0.693/K_e$. Pharmacokinetic parameters were calculated using the Kinetica™ 2000 Computer Program.

Statistical analysis

The values are expressed as the mean value $\pm$ SD. The data were analysed through a computerized program SPSS (Statistical Package for Social Science). Values of $p < 0.05$ were considered statistically significant.

Results

A total of 48 subjects aged 18–38 years (24 ± 4, mean $\pm$ SD) were enrolled in the study. Their body mass index was within the normal range (23.73 ± 2.46, mean $\pm$ SD). All the subjects were healthy and none were taking any medication. All of them had laboratory data within normal ranges, the data are presented as mean $\pm$ SD; serum creatinine 0.95 ± 0.11 mg/dl, AST 16.73 ± 12.87 (units), and ALT1 8.02 ± 11.86 (units). Variations in age, weight, body mass index, renal function and liver function were negligible as represented by mean and standard deviation. In a stepwise regression performed between *AUC* (0-t and 0-infinity) and C_{max} against age, weight, body mass index, serum creatinine, liver enzyme levels, none achieved statistical significance. Variations in the measured omeprazole kinetics are represented in Table 1. Details of the five subjects presenting with the highest *AUC*s levels are shown in Table 2.

Peak plasma levels of omeprazole occurred within 1 to 5 h of administration. All measured

Table 1. Summary of studied group pharmacokinetic (48 subjects)

Measured parameters	Median	Mean	SD	Minimum	Maximum
$AUC_{0\text{-}t}$ (ng/h.ml)	762.92	1126.78	1273.75	190.45	6871.86
$AUC_{0\text{-}inf}$ (ng/h.ml)	784.86	1182.88	1425.83	199.35	8230.71
C_{max} (ng/ml)	521	597	354	183	2029
t_{max} (h)	1.66	1.8	0.7	1.00	5.00
$t_{1/2e}$ (h)	0.72	0.90	0.67	0.41	4.81
K_e (1/h)	0.93	0.94	0.33	0.14	1.69

Table 2. Pharmacokinetics details of the five subjects with lowest excretion rate and highest *AUCs*

Subject #	Age (years)	BMI (kg/m^2)	$AUC_{0\text{-}t}$ (ng/h.ml)	C_{max}(ng/h.ml)	t_{max} (h)	$t_{1/2e}$ (h)
1	26	26.4	2154.2	771	1.66	1.2
2	19	22.6	2629.7	1091	2.00	1.03
3	26	26.5	3379.3	1313	1.33	1.61
4	21	19.8	5983.7	2029	1.66	2.29
5	20	23.4	6871.9	1403	1.66	4.81

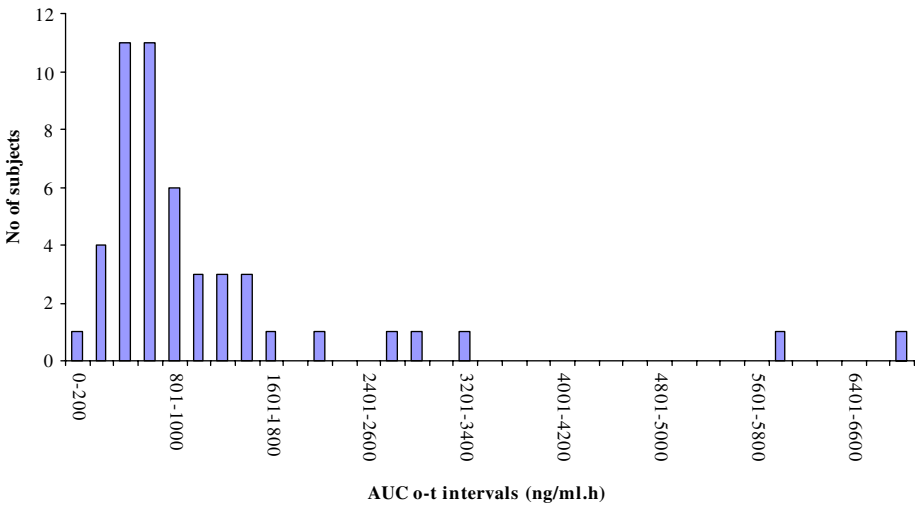

Figure 1. Distribution of subjects as a function of $AUC_{0\text{-}t}$

parameters showed wide variations as shown by the wide range of data, and standard deviations (see Table 1). Most variability was noted in *AUC*. Figure 1 shows the $AUC_{0\text{-}t}$-time curve of the 48 subjects after 40 mg omeprazole administration. Normal distribution of subjects is seen at *AUC* levels less than 1200 ng/h.ml. Some subjects showed very high *AUC* levels ranging from 3–4 fold the level of the median (three subjects) and 8–9 fold the level of the median (two subjects).

Subjects were monitored for side effects throughout the trial. Of the 48 subjects enrolled in the study, 15 reported side effects. These side effects were reported with the following frequency: headache (12 subjects), epigastric pain (two subjects), nausea (one subject), dizziness (one subject) and drowsiness (one subject). Some subjects reported more than one side effect. There was no correlation between the frequency of occurrence of side effects and the C_{max} or the *AUC* values.

Discussion

This study provides evidence that omeprazole metabolism in Jordanian adults undergoes wide inter-individual variations. Although the mean and median adult *AUC* values were within the range reported by other studies [21–23], in this study, the measured pharmacokinetic parameters were scattered over a wide range; the lowest *AUC* was about 4-fold lower than the median, and the highest *AUC* was about 9-fold higher than the median. One subject having the highest C_{max}, presented with up to a 36-fold increase in *AUC* when compared with the subject with the lowest C_{max}.

In a bioavailability study assessment, C_{max} usually serves to assess the rate of drug absorption, while *AUC* is the most reliable reflection of the extent of relative bioavailability. In the case of omeprazole *AUC* is a reflection of efficacy since the extent of acid secretion correlates with *AUC* rather than plasma level [1,9].

The variability in omeprazole kinetics is consistent with the fact that omeprazole metabolism is mainly through CYP2C19 which undergoes polymorphism [14–15,20]. A study from Egypt showed that the frequencies of the non-functional CYP2C19 alleles was about 11% in the Egyptian population [19]. The present data showed that about 10% of our sample had very high *AUC*s and long half-lives of omeprazole. Although this might suggest that about 10% of our sample are poor metabolizers, the conclusion regarding CYP2C19 similar to that of the Egyptian population still awaits further genotyping studies.

Kinetics variability can also be attributed to extremes of age [22], after the first year of life,

children exhibit apparent metabolic rates that are several fold higher than those observed in adults, and decline as the children reach puberty. In this study, the age range was narrow [18–38 years], so the effect of age cannot be a contributing factor for kinetics variability. Thus, differences in the rates of metabolism during adulthood, and consequently pharmacokinetics parameters can be attributed to differences in the activity of the CYP2C19 enzyme [13–14, 22–24].

From a therapeutic prospective, patients with very low omeprazole *AUC*s are at risk of a lower rate of treatment success. This has been demonstrated for omeprazole use in the eradication regimens for the management of *H. pylori* [25–29]. *Helicobacter pylori* infection is common in dyspeptic Jordanian patients. Males are affected more than females. About 70–80% of patients with upper gastrointestinal symptoms have *H. pylori* infection, this rate is similar to that seen in other developing countries with infections occurring at a younger age and with the annual infection rate being double that seen in developed countries [16–18]. If the patient is an extensive metabolizer, the healing rate and efficacy of omeprazole in decreasing acid pH would be affected. About 10% of our studied sample had *AUC* values $\geqslant$2-fold lower than the median. These individuals are probably at higher risk of treatment failure.

In theory, the increase in omeprazole plasma and *AUC* levels would be associated with an increased incidence of side effects, especially in patients with liver impairment [30]. Common side effects of omeprazole therapy include: headache or dizziness, rash, diarrhea, abdominal pain, nausea, vomiting, constipation or taste perversion, muscle weakness or back pain, upper respiratory infection or cough. About 30% of the study group reported side effects. However, the reported side effects were minor, and did not have any correlation with *AUC* or C_{max} values. This can be explained by the fact that all the subjects enrolled were healthy volunteers, and they were exposed to a single dose of the drug.

In conclusion, when omeprazole is used in adult Jordanians, a wide variation in response is expected. Some patients will be at higher risk of developing side effects, especially if higher doses are used. Others probably will not see an improvement in their gastric acidity due to rapid metabolism and excretion of the drug. Individualization of the dose, and careful monitoring of the clinical improvement and side effects are recommended. Further studies on genotyping for polymorphism of CYP2C19 are recommended in the Jordanian population.

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