Effect of Omeprazole on Gastric Mucosa and Serum Levels of Amoxicillin in Patients with Non-Ulcer Dyspepsia

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Abstract

The aim of this study was to determine the interaction between omeprazole and amoxicillin, being common agents used in the eradication regimen for *H. pylori* infection. Amoxicillin concentrations in gastric mucosa and serum were quantitatively analysed in 12 patients with non-ulcer dyspepsia following the administration of one week duration of placebo as group I and omeprazole as group II. The study was a blind, cross-over design with a one week wash out period between the two treatment groups. Six antral gastric mucosa were biopsied 90 minutes after oral administration of amoxicillin. Blood samples were collected before and after administration at intervals up to 6 hours. All samples were analysed for amoxicillin concentration using the HPLC technique. Highly intersubject variations of amoxicillin concentrations were observed. The concentration of amoxicillin in gastric mucosa ranged from 0.00-1.74 and 0.00-1.25 μg/mg for group I and group II, respectively, with the mean concentration of 0.25±0.48 μg/mg for group I and 0.28±0.40 μg/mg for group II. The difference was not statistically significant (p=0.89). Pharmacokinetic parameters of amoxicillin in serum following regimen I and regimen II were not significantly different (p>0.05). The mean Cmax values were 14.62±5.39 and 12.65±4.76 μg/ml, the Tmax were 2.3±1.0 and 2.0±0.9 hour and the AUC_{0-6} were 40.79±13.26 and 38.75±15.04 μg/ml.h in the group I and group II, respectively. From these results, we concluded that omeprazole has no effect on gastric mucosa level nor serum levels of amoxicillin. The therapeutic efficacy of using these two agents in the eradication regimen of *H. pylori* may be related to other factors rather than pharmacokinetic interaction.

Key word : Gastric Mucosa, Amoxicillin, Omeprazole

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It is now generally accepted that *Helicobacter pylori* (*H. pylori*) plays a causal role in duodenal ulcer, gastric ulcer, chronic gastritis and gastric neoplasia[1]. Neither antisecretory drugs nor cytoprotective agents can eradicate *H. pylori* or alter the natural history of the disease since ulcer recurrence occurs after cessation of any of these treatments. Combined therapy using antisecretory agents and antimicrobial agents are more effective to cure the disease[2-5].

Amoxicillin is one of the most common antibiotics used to eradicate *H. pylori*. Although the organism is very sensitive to amoxicillin with the MIC_{90} values of 0.12 mg/l *in vitro*, the *in vivo* eradicating efficacy of this agent alone is disappointing[6]. However, using amoxicillin in combination with omeprazole, a potent antisecretory drug, can eradicate *H. pylori* infection in 60-80 per cent[7-10]. Its synergistic mechanism remains unknown. Various hypotheses have been speculated including: omeprazole induced hypoacidity enhances the antibacterial activity of amoxicillin, increased amoxicillin stability and enhancing amoxicillin level in gastric mucosa[7]. The recently available data has been controversial and thus can not be concluded.

The aim of this study was to examine the effect of omeprazole on gastric mucosa and serum levels of amoxicillin. Omeprazole may enhance amoxicillin concentration in target site and systemic circulation and this may explain how omeprazole potentiates the effect of amoxicillin on *H. pylori* eradication.

MATERIAL AND METHOD

Amoxicillin trihydrate (ASEAN reference standard) was donated by the Department of Medical Science, Ministry of Public Health, Thailand. Cefadroxil, used as the internal standard, was purchased from Sigma Chemical Co.ltd.. Sodium acetate trihydrate, phosphate buffer saline solution , 70 per cent perchloric acid, acetonitrile and methanol HPLC grade were used in the analytical procedure. Amoxil-Bencard® 500 mg capsule batch NO.362032F and Omeprazole 20 mg capsule (Losec®) batch. NO. VI 6162 were used in the clinical experiment.

Apparatus

HPLC apparatus is composed of a model 510 pump (Waters Associates, Milford, MA, USA), fixed loop injector (Rheodyne 7125 injection port, Rheodyne California, USA), lambda-Max Model 481 LC-spectrophotometry detector and Waters 740 data module. Analytical column, bondapak C18, was used in the analytical experiment.

Subjects and Procedure

The study was carried out in 12 patients with non-ulcer dyspepsia, 3 males and 9 females, 22-45 years of age, with a body weight ranging from 40-70 kg. All subjects were not known to have allergy to penicillin and none of these patients had a history of liver or renal dysfunction. Written informed consent was obtained from each patient and the study was approved by the Faculty Ethics Committee.

Each subject received both regimens, placebo as group I and omeprazole as group II with an interval of 1 week as a wash out period between the two groups. Six subjects received regimen I followed by regimen II whereas the other 6 subjects received the reverse. Placebo or omeprazole 20 mg twice daily were given 7 days before administration of a single oral dose of 1000 mg amoxicillin capsule. The study was designed as blind, randomized and cross-over.

Six biopsies were taken from antral gastric mucosa 90 minutes after oral administration of amoxicillin. Blood samples were collected before administration and at 0.5, 1, 1.5, 2, 4, and 6 h following administration of amoxicillin. All samples were analyzed for amoxicillin level by the HPLC technique.

Amoxicillin Assay

Six antral biopsied samples were rinsed within 5 seconds with 1 ml of phosphate buffer saline (pH 7) to wash drugs and gastric contents coating the gastric mucosa then suspended in 1 ml of phosphate buffer saline solution (pH 7) with 10 µl of cefadroxil solution 2 mg/ml. The mucosa was homogenized with ultrasonic homogenizer for 1 min and centrifuged at 15,000 rpm for 1 h[11]. All the procedures were done at the temperature of 4°C. The supernatant was then assayed for amoxicillin concentration by HPLC with the method described in USPNF[12]. Intra-day and inter-day precisions of this assay were ranged within 0.20-3.31 per cent and 2.74-6.47 per cent RSD, respectively. Mean of analytical recovery was 96.36± 10.34 per cent. The linearity was ranged at the concentration of 1-100 ug/ml with r^2 = 0.9989.

Serum sample preparation was modified from the method of Charles B et al[13]. Each serum sample (500 µl) was deproteinized with 50 µl of 5 per cent perchloric acid and 650 µl of methanol containing 10 µl/ml of cefadroxil. Each sample was vortex-mixed for 30 seconds, then centrifuged for 20 minute at 3000 rpm. The supernatant was then injected to HPLC[12]. Intra-day and inter-day precisions of this assay ranged within 1.24-7.35 per cent and 5.52-12.26 per cent RSD, respectively. Mean analytical recovery was 90.49±7.60 per cent. The linearity ranged at the concentration of 1-40 µg/ml with r^2=0.9965.Omeprazole did not produce an interfering peak with these assays.

Pharmacokinetic and Statistical Analysis

Standard curve was set up in each of the analysis of amoxicillin in gastric mucosa. Linear regression analysis was used to calculate the value. Concentration of amoxicillin in each gastric mucosa was calculated in microgram per milligram weight of 6 antral biopsy samples. The results are expressed as means ± standard deviation. The unpaired T test was used to test for significant differences between concentrations of amoxicillin after regimen I and II with consideration at the significant level of 0.05.

Amoxicillin concentrations in serum were also calculated from linear regression analysis of standard curve. The serum concentration-time profile of amoxicillin was plotted. Peak serum concentration (Cmax) and time to peak serum (Tmax) were determined from the data. The serum AUC was calculated by the linear trapezoidal rule. The means of serum pharmacokinetic parameters were compared between group I and II with unpaired T test at the significant level of 0.05.

RESULTS

Amoxicillin levels in Gastric Mucosa

Amoxicillin concentrations in gastric mucosa after 90 min of oral administration in twelve non-ulcer dyspepsia patients who received regimen I as placebo control group and regimen II as omeprazole group are shown in Table 1. Highly intersubject variations were observed among them. In each individual data, amoxicillin level in gastric mucosa was increased with the omeprazole treatment in 4 of 12 patients. The concentrations in 3 patients were

Table 1. Comparison of amoxicillin in gastric mucosa in twelve patients with non-ulcer dyspepsia after being treated with regimen I (Placebo) and II (Omeprazole).

Subject No.	Amoxicillin level in gastric mucosa (µg/ml)		Gastric mucosal weight (mg)		Amount of amoxicillin in gastric mucosa (µg/mg)	
	Placebo[1]	Omeprazole[2]	Placebo[1]	Omeprazole[2]	Placebo[1]	Omeprazole[2]
1	0.00	2.39	19.9	18.1	0.00	0.13
2	34.49	2.00	19.8	28.7	1.74	0.07
3	2.68	0.00	25.5	28.4	0.11	0.00
4	3.29	1.36	32.5	20.4	0.10	0.07
5	4.35	0.00	21.0	23.5	0.21	0.00
6	0.00	0.00	30.8	28.8	0.00	0.00
7	0.00	16.06	26.0	12.9	0.00	1.25
8	4.62	20.78	33.6	23.5	0.14	0.88
9	10.72	14.25	18.0	21.6	0.60	0.66
10	4.96	6.87	39.1	25.7	0.13	0.27
11	0.00	0.20	32.3	31.8	0.00	0.01
12	0.00	0.00	34.1	25.9	0.00	0.00
				Mean	0.25	0.28
				SD	0.48	0.40
				Unpaired T-test	NS (p = 0.89)	

[1] One week pretreated with placebo + single dose 1000 mg of amoxicillin

[2] One week pretreated with omeprazole 20 mg twice daily + single dose 1000 mg of amoxicillin

NS = non significant

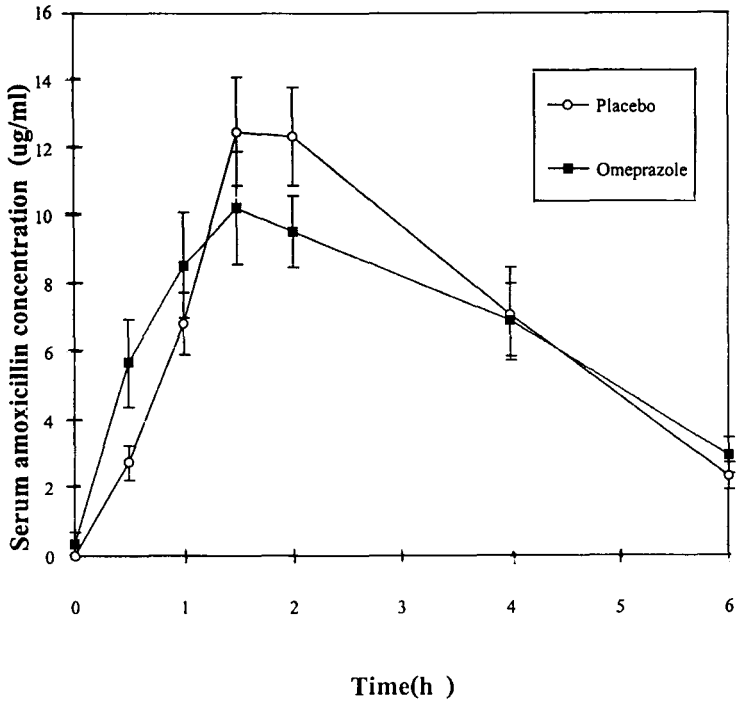

Fig. 1. Mean concentrations of amoxicillin in serum *versus* time profile in regimen I (placebo) and II (omeprazole).

Table 2. Comparison of pharmacokinetic parameters of amoxicillin in regimen I (placebo) and II (omeprazole) in twelve patients with non ulcer dyspepsia.

Subject No.	AUC (μg/ml.h)		Cmax (μg/ml)		Tmax (h)	
	Placebo[1]	Omeprazole[2]	Placebo[1]	Omeprazole[2]	Placebo[1]	Omeprazole[2]
1	32.45	33.92	13.28	14.97	1.5	2.0
2	61.51	31.73	18.97	10.67	4.0	4.0
3	47.28	77.32	18.79	21.88	1.5	1.5
4	38.49	42.95	12.90	13.19	2.0	2.0
5	38.63	19.25	17.78	14.52	2.0	1.5
6	49.16	38.56	18.13	11.92	1.5	1.0
7	17.33	22.59	4.83	8.00	2.0	1.5
8	28.36	56.00	14.32	21.16	1.5	1.0
9	61.49	45.78	20.26	12.77	1.5	4.0
10	24.00	35.42	5.45	6.68	4.0	2.0
11	49.35	32.54	21.37	7.74	2.0	2.0
12	41.43	28.90	9.37	8.25	4.0	2.0
Mean	40.79	38.75	14.62	12.65	2.3	2.0
SD	13.26	15.04	5.39	4.76	1.0	0.9
SE	3.83	4.34	1.56	1.37	0.3	0.3
Unpaired T-test	NS (p = 0.74)		NS (p = 37)		NS (p = 0.55)	

[1] One week pretreated with placebo + single dose 1000 mg of amoxicillin
[2] One week pretreated with omeprazole 20 mg twice daily + single dose 1000 mg of amoxicillin

NS = non significant

decreased under omeprazole treatment and in another 3 patients, the amoxicillin level was equal in both regimens. No amoxicillin levels were detected 90 minutes after administration of both regimens in the other patients. The amount of amoxicillin in gastric mucosa ranged within 0.00-1.74 μg/mg and 0.00-1.25 μg/mg in group I and group II, respectively. The average amounts were 0.25±0.48 μg/ml and 0.28±0.40 μg/ml, respectively, in which no statistically significant difference was observed between the groups with the P value of 0.89.

Amoxicillin Levels in Serum

The mean serum concentration versus time profiles of amoxicillin in both groups are illustrated in Fig. 1. The pharmacokinetic parameters determined as Cmax, Tmax and AUC_{0-6} are concluded in Table 2. The mean Cmax values were 14.62±5.39 and 12.65±4.76 μg/ml, the Tmax were 2.3±1.0 and 2.0±0.9 h, and the AUC_{0-6} were 40.79±13.26 and 38.75±15.04 μg/ml.h in group I and II, respectively. All parameters showed no statistically significant difference between the groups at the significant level of 0.05.

DISCUSSION

The increased level of amoxicillin in gastric mucosa and systemic circulation with omeprazole combination therapy is one of the possible mechanisms for the potentiating effect of omeprazole on amoxicillin therapy in *H. pylori* eradication. Our study was designed to determine whether omeprazole can affect local and systemic bioavailability of amoxicillin in this combination regimen. Each subject received a one week treatment of omeprazole 20 mg twice daily to assure an optimal gastric acid suppression prior to administration of 1000 mg single oral dose of amoxicillin. Omeprazole is a potent H^+/K^+ ATPase inhibitor, which has a long duration of action and once daily dosing with omeprazole, 20 mg, substantially reduces gastric acidity, causing about a 90 per cent reduction in the 24-hour intragastric acidity[14].

Amoxicillin concentrations in gastric mucosa and serum were measured in this study. Gastric mucosal biopsies were taken at 90 min after ingestion because of the poor dissolution of amoxicillin capsule. A 1 g dose of amoxicillin requires about 370 ml of water for dissolution[15]. The optimal time to represent the peak concentration of amoxicillin in gastric mucosa was variable: 30 min, 60 min and 90 min, have been observed in other reports[16-18]. Inhibitory antimicrobial concentration detected in gastric biopsy specimens may be due to locally absorbed drug or systemic circulation after absorption elsewhere in the gastrointestinal tract[17]. We previously determined the peak level of gastric mucosal concentration of amoxicillin and have found that 90 min is the optimal time. However, considerable variability in levels from subject to subject was observed. Variable gastric emptying may be an important factor which could account for the inter- and intra-subject variability[17]. Hence, variation of amoxicillin levels in gastric mucosa was observed and its level can not be detected in some subjects. The results of gastric mucosa and serum amoxicillin levels showed no significant differences between combined therapy and the placebo group. This study showed that the target site concentration and systemic bioavailability of amoxicillin were not increased by the prior administration of a one week treatment of omeprazole and confirmed that omeprazole had no effect on gastric mucosa concentration and serum pharmacokinetic characteristics of amoxicillin.

The enhancement of clindamycin concentrations in gastric mucosa of guinea pigs by cimetidine, the H_2 receptor antagonist, was previously shown in a prior study[11]. Due to the fact that clindamycin is a weak base, increasing intragastric pH would be expected to increase its uptake. Amoxicillin is an acid stable antibiotic that contains three ionized groups with three pKa values[19]. The drug exists in an ionized form for the entire pH range. Accordingly, the lipophilicity of amoxicillin is relatively low[19]. No significant correlation was found between gastric juices pH and amoxicillin levels in serum[18]. It seems likely that amoxicillin penetration does not increase by lowering intragastric acidity. The synergistic effect of omeprazole and amoxicillin in eradicating *H. pylori* is not due to a pH dependent increase in amoxicillin uptake. Other investigators also reported that high dose omeprazole (40 mg bid) did not alter the serum profile of amoxicillin[20]. These results are in agreement with our study.

The other possible mechanisms for the synergistic effect of this combined therapy need to be further established. Other recent hypotheses have been proposed, including the direct effect of omeprazole on *H. pylori*. Omeprazole therapy on its own may lead to a change in the nature of the orga-

nism, such that it may retire to sanctuary sites or change an organism into a coccoid form[14]. The synergistic effect may be due to the enhancement of host defense mechanisms accompanying acid suppression by omeprazole[21]. Previous studies have shown that omeprazole has a specific inhibitory effect on *H. pylori* urease[22]. With *in vitro* study, the growth rate of *H. pylori* affects antibiotic susceptibility. Omeprazole may exert a synergistic effect with amoxicillin by improving growth conditions for *H. pylori* and thus improving the conditions for antibacterial action *in vivo*[23]. The hypothesis stating that improved amoxicillin activity at higher pH is still controversial. The activity of amoxicillin was not significantly decreased at the low pH. Its activity against *H. pylori* is not pH dependent[24]. In contrast, raising the gastric pH from 3.5 to 5.5 increases the *in vitro* effectiveness of amoxicillin more than 10 fold[25]. Recent studies have suggested that amoxicillin exerts a topical or intraluminal antibacterial activity against *H. pylori*. The effect of omeprazole on intraluminal concentration of amoxicillin is likely to elucidate the mechanism of synergistic action. Other investigators showed that omeprazole increases intraluminal concentration of amoxicillin partly by reducing gastric juice volume. Thus, omeprazole may potentiate amoxicillin treatment of *H. pylori* by increasing its concentration in the lumen[19].

Based on the findings of our and other studies, it could be concluded that omeprazole does not affect the gastric mucosa and serum concentrations of amoxicillin. Further study is required to explain the synergistic interaction between omeprazole and amoxicillin used in the combination therapy for *H. pylori* eradication.

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ผลของออมมิพราโซลต่อระดับอะมอกซีซิลลินในเยื่อบุกระเพาะอาหารและซีรั่มของผู้ป่วย NUD

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การวิจัยนี้เพื่อศึกษาการเกิดปฏิกิริยาสัมพันธ์ระหว่างยาออมมิพราโซลกับอะมอกซีซิลลิน ซึ่งยาทั้งสองนี้มักให้ร่วมกันเพื่อเสริมฤทธิ์การกำจัดเชื้อ *H. pylori* โดยทำการทดลองข้ามแบบสุ่มให้ระยะห่างของการทดลองเป็นเวลา 1 สัปดาห์และผู้ป่วยไม่ทราบว่าได้รับยาใด ผู้ป่วยจะได้รับยาหลอกจัดเป็นกลุ่มหนึ่งของยาออมมิพราโซลจัดเป็นกลุ่มสองเป็นเวลา 1 สัปดาห์ จากนั้นให้อะมอกซีซิลลินขนาดเดียว แล้วทำการตัดชิ้นเนื้อเยื่อบุกระเพาะอาหาร 6 ชิ้นที่เวลา 90 นาทีหลังได้รับยาและเก็บตัวอย่างเลือดเมื่อเวลาก่อนและหลังได้รับยาอะมอกซีซิลลินจนถึง 6 ชั่วโมง วิเคราะห์หาระดับยาอะมอกซีซิลลินด้วยวิธี HPLC ผลการทดลองพบความแปรปรวนของระดับยาอะมอกซีซิลลินในเยื่อบุกระเพาะอาหาร กลุ่มหนึ่งมีระดับยาอยู่ในช่วง 0.00–1.74 ไมโครกรัม/มิลลิกรัม กลุ่มสอง 0.00–1.25 ไมโครกรัม/มิลลิกรัม ค่าเฉลี่ยที่ได้เท่ากับ 0.25±0.48 ไมโครกรัม/มิลลิกรัม และ 0.28±0.40 ไมโครกรัม/มิลลิกรัม ตามลำดับ ระดับยาอะมอกซีซิลลินในเยื่อบุกระเพาะอาหารของทั้งสองกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญ ค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของอะมอกซีซิลลินในซีรั่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญ โดยกลุ่มหนึ่งและกลุ่มสองมีค่าเฉลี่ยความเข้มข้นของระดับยาสูงสุดเท่ากับ 14.62±5.39 และ 12.65±4.76 ไมโครกรัม/มิลลิลิตร ค่าเฉลี่ยเวลาที่ระดับยาสูงสุดเท่ากับ 2.3±1.0 และ 2.0±0.9 ชั่วโมง ค่าพื้นที่ใต้กราฟของระดับยากับเวลาเท่ากับ 40.79±13.26 และ 38.75±15.04 ไมโครกรัม/มิลลิลิตร-ชั่วโมง ตามลำดับ สรุปได้ว่าออมมิพราโซลไม่มีผลเพิ่มระดับยาอะมอกซีซิลลินทั้งในเยื่อบุกระเพาะอาหารและซีรั่ม ผลการเสริมฤทธิ์ในการกำจัดเชื้อ *H. pylori* ของยาทั้งสองนี้น่าจะมาจากปัจจัยอื่นมากกว่าผลทางเภสัชจลนศาสตร์

คำสำคัญ : เยื่อบุกระเพาะอาหาร, อะมอกซีซิลลิน, ออมมิพราโซล

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