

NOTES

Influence of Food on Absorption of Erythromycin Ethyl Succinate

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Erythromycin plasma concentrations were determined in 18 subjects after a single dose (800 mg) of a new formulation of erythromycin ethyl succinate taken immediately before, immediately after, and 1 h after food. Adequate absorption occurred with all treatments, although bioavailability was best when the drug was taken before food. Absorption was delayed by food, with the highest and earliest peak plasma erythromycin levels occurring under fasting conditions.

Erythromycin is widely used for the treatment of a variety of infectious diseases, including respiratory tract infections, for which many strains of common upper and lower respiratory pathogens are inhibited by this antibiotic. However, erythromycin is sensitive to inactivation by gastric acid, and some preparations are poorly absorbed unless taken before food (1, 8, 14). Erythromycin ethyl succinate has been available as granules and a suspension for pediatric use, and studies with this preparation taken under nonfasting conditions suggest that its bioavailability is not affected by food (3, 5, 6, 9). The purpose of this study was to determine the effect of food on the absorption of a new tablet formulation of erythromycin ethyl succinate.

Methods. Eighteen healthy subjects (14 males and four females), aged from 20 to 25 years, volunteered for this study. Written consent was given by each subject after the procedure of the study had been fully explained. No antibiotic or other drug therapy had been received for 2 weeks before the commencement of or during the study period. The subjects fasted from midnight before all study days.

The formulation of erythromycin administered in this study was erythromycin ethyl succinate, 800 mg (400-mg film tablet; 5729, Abbott Laboratories). The study was a balanced, randomized Latin square design and was performed on 3 separate days at weekly intervals. The three treatments were: (i) erythromycin ethyl succinate, 800 mg, administered immediately before food; (ii) erythromycin ethyl succinate, 800 mg, administered immediately after food; (iii) erythromycin ethyl succinate, 800 mg, administered 1 h after food. A standard breakfast consisting of cereal with milk, toast, and fruit juice was

eaten over a period of 15 min. The drug was given with 120 ml of water. No other food or drinks were allowed until 4 h after drug ingestion.

Venous blood samples were collected immediately before drug ingestion and subsequently at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h after ingestion for erythromycin plasma level determination. Before drug administration, blood was also collected for a biochemical profile (electrolytes, urea, creatinine, protein, albumin, uric acid, bilirubin, alkaline phosphatase, lactic acid dehydrogenase, glutamic oxaloacetic transaminase, and glucose) and a full blood count. The subjects were asked to report any unwanted effects during the study.

The assay method for plasma erythromycin followed that described by Bell et al. (2) using a microbiological technique with *Sarcina lutea* ATTC 9341 as the test organism. The only modification was the use of large antibiotic assay plates (12 by 12 in.; ca. 30 by 30 cm), which enabled six standards and 12 samples to be set twice, each assay plate being done in duplicate. Individual levels were obtained by using linear regression of log concentration against zone diameter. The plasma levels in the results were the weighted means of the results from the two plates. Standard solutions of erythromycin were prepared, using 3.5% bovine albumin and phosphate buffer (pH 8.0) as diluent. All erythromycin assays were performed blind with the investigator having no knowledge of the experimental design.

The results were submitted to statistical analysis using the paired Student's *t* test.

Results. The means \pm standard deviations of plasma erythromycin concentrations for the

three treatments are shown in Table 1. The means \pm standard deviations of areas under the plasma erythromycin concentration-time curves, maximal plasma concentrations (C_{\max}), and times to reach maximal concentration (t_{\max}) for the three treatments are shown in Table 2.

The plasma concentrations for erythromycin administered immediately before food were significantly greater than those with erythromycin administered immediately after food (0.5 to 2 h, $P < 0.05$) and erythromycin administered 1 h after food (0.5 to 2 h, $P < 0.01$) for 2 h. The plasma concentration for erythromycin administered immediately after food was significantly greater than that for erythromycin administered 1 h after food at 1 h ($P < 0.01$) and significantly less at 4 h ($P < 0.05$).

The area under the plasma erythromycin concentration-time curve for erythromycin immediately before food was significantly greater than that for erythromycin administered immediately after food ($P < 0.05$). The C_{\max} for erythromycin administered immediately before food was significantly greater than those for erythromycin administered immediately after ($P < 0.01$) and

1 h after food ($P < 0.05$). The t_{\max} for erythromycin administered immediately before food was significantly less than those for the other treatments ($P < 0.01$), and the t_{\max} for erythromycin administered immediately after food was significantly less than that for erythromycin administered 1 h after food ($P < 0.05$).

There was one subject who reported nausea 1 to 2 h after breakfast with erythromycin administered 1 h after food on day 1 and also with erythromycin administered immediately after food at the same time on day 2. A blood glucose test performed at the time of nausea on day 2 was 45 mg/dl, and it was considered that the subject's symptoms may have been due to reactive hypoglycemia rather than to a drug effect.

Discussion. The bioavailability of this erythromycin ethyl succinate formulation was best when administered immediately before food, when rapid absorption occurred. The presence of food delayed the absorption of the drug. However, when the drug was taken immediately or 1 h after food, bioavailability remained satisfactory and compared favorably with other recent formulations of erythromycin stearate and base (10, 12, 14). Malmborg (10) demonstrated a mean peak plasma erythromycin level of 2.8 $\mu\text{g/ml}$ with the stearate taken immediately before food. Rutland et al. (14) reported a mean peak plasma erythromycin level of 2.1 $\mu\text{g/ml}$ with the stearate taken immediately before food and also levels of 1.84 and 1.91 $\mu\text{g/ml}$ for the base taken immediately before and after food, respectively. Plasma erythromycin levels with erythromycin estolate given either before or after food are of a similar range (1, 8), but this formulation has been associated with cholestatic jaundice. The minimal inhibitory concentrations for common respiratory pathogens are 0.02 to 0.2 $\mu\text{g/ml}$ for beta-hemolytic *Streptococcus* spp., 0.01 to 0.2 $\mu\text{g/ml}$ for *Streptococcus pneumoniae*, 0.01 to 1.6 $\mu\text{g/ml}$ for *Staphylococcus aureus*, 0.4 to 3.0 $\mu\text{g/ml}$ for *Haemophilus influenzae*, and 0.005 to 1.5 $\mu\text{g/ml}$ for *Mycoplasma pneumoniae* (7, 11, 13).

TABLE 1. Erythromycin plasma levels in 18 healthy subjects at various times for 8 h after administration of 800 mg of erythromycin ethyl succinate

Time (h)	Erythromycin plasma level ($\mu\text{g/ml}$) ^a		
	Immediately before food	Immediately after food	1 h after food
0.5	1.60 \pm 1.00	0.27 \pm 0.45	0.08 \pm 0.02
1.0	2.23 \pm 1.32	0.54 \pm 0.75	0.35 \pm 0.75
1.5	2.17 \pm 1.28	0.94 \pm 0.93	0.51 \pm 0.83
2.0	1.65 \pm 1.06	1.06 \pm 1.11	0.67 \pm 0.68
3.0	1.14 \pm 0.74	1.04 \pm 0.76	1.48 \pm 0.86
4.0	0.78 \pm 0.46	0.80 \pm 0.52	1.15 \pm 0.76
6.0	0.37 \pm 0.22	0.37 \pm 0.24	0.52 \pm 0.34
8.0	0.18 \pm 0.11	0.19 \pm 0.14	0.27 \pm 0.20

^a Mean \pm standard deviation. Erythromycin: 1 $\mu\text{g/ml}$ = 1.36 $\mu\text{mol/liter}$.

TABLE 2. Areas under the erythromycin plasma concentration curves (AUC), the maximal plasma concentrations (C_{\max}), and the times at which these occurred (t_{\max}) for the 18 subjects after receiving 800 mg of erythromycin ethyl succinate

Treatment	AUC ^a	C_{\max} ($\mu\text{g/ml}$) ^a	t_{\max} (h) ^a
Immediately before food	7.48 \pm 3.98 (0.62-15.63)	2.71 \pm 1.34 (0.43-4.47)	1.28 \pm 0.79 (0.5-4.0)
Immediately after food	4.85 \pm 3.28 (1.07-11.25)	1.54 \pm 1.05 (0.38-4.03)	2.39 \pm 0.93 (1.0-4.0)
1 h after food	5.51 \pm 3.06 (1.09-10.79)	1.72 \pm 0.89 (0.30-3.13)	2.97 \pm 0.81 (1.0-4.0)

^a Mean \pm standard deviation. Range of values is shown within parentheses.

Plasma levels achieved with the single dose of erythromycin ethyl succinate in this study compared favorably with these minimal inhibitory concentrations, and, moreover, higher plasma levels would be expected under steady-state conditions.

Welling et al. (15) recently demonstrated that when erythromycin stearate was taken with 250 ml of water on a fasting stomach, higher C_{max} values were obtained than when the drug was taken with only 20 ml of water. The large volume of water would assist in transporting the drug rapidly into the intestine and also dilute any gastric acid present which might reduce acid degradation. In the present study, the volume of water taken with the drug might have increased the rate and degree of absorption when taken before food. Gastric motility reaches peak activity immediately before food. Gastric motility reaches peak activity immediately before food, and transit time in the stomach for the drug is reduced to a few minutes. These factors would explain the higher C_{max} and shorter t_{max} values when erythromycin ethyl succinate was taken immediately before food. The water taken with the drug would not have the same effect on its absorption when food was present in the stomach.

Coyne et al. (5) have demonstrated in two different groups of pediatric patients (aged 6 to 65 months) that the absorption of erythromycin ethyl succinate granules was enhanced by food when compared with administration of the drug 1 h before food. No explanation for these results was given, although the time of food administration may have influenced the erythromycin levels obtained. Malmberg (10) has shown better absorption of erythromycin stearate when it is administered immediately before than when administered 3 h before food. Chun and Seitz (3) have also demonstrated good absorption of erythromycin ethyl succinate suspension in adults under nonfasting conditions both after a single dose and during steady state. The present study demonstrates considerable variability within and among subjects in the absorption of erythromycin. This emphasizes the need to use large numbers of subjects and comparisons within subjects of different treatments for a valid assessment of the pharmacokinetics of this drug.

In summary, this study demonstrates adequate absorption of a new formulation of erythromycin ethyl succinate whether taken before or after food, but for rapid absorption and high peak plasma levels, drug ingestion immediately before food would be preferred.

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