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THE INFLUENCE OF FOOD ON THE BIOAVAILABILITY OF NEW FORMULATIONS OF ERYTHROMYCIN STEARATE AND BASE

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1 The effect of food on the bioavailability of two new formulations of erythromycin, 1) erythromycin stearate, 500 mg (Erythrocin, 250 mg capsule-shaped tablets) and 2) erythromycin base, 500 mg (Eryc, 250 mg capsules containing enteric-coated pellets) was studied in 16 healthy subjects.

2 The study was a balanced, randomized Latin square design and was conducted on 4 days. The four treatments were erythromycin stearate immediately before (EB) and after (EA) breakfast and erythromycin base immediately before (eB) and after (eA) breakfast.

3 The mean ± s.d. maximal plasma erythromycin concentrations were 2.09 ± 1.06, 0.37 ± 0.40, 1.84 ± 1.15 and 1.91 ± 1.57 μg/ml and the mean ± s.d. times at which these occurred were 1.3 ± 0.7, 2.3 ± 0.9, 4.4 ± 1.9 and 4.3 ± 1.1 h for EB, EA, eB and eA respectively.

4 The mean ± s.d. areas under the curves (0 to 8 h) were 4.99 ± 2.41, 1.04 ± 1.57, 4.93 ± 2.98 and 4.98 ± 3.17 for EB, EA, eB and eA respectively.

5 The bioavailability of erythromycin stearate was significantly reduced by the prior administration of food, whereas the absorption of the base was not inhibited by food.

Introduction

Erythromycin is an effective antibiotic for the treatment of a wide variety of infectious diseases. However, many erythromycin formulations are poorly absorbed particularly when administered with food (Blough, Hall & Hong, 1960; Griffith & Black, 1964; Bell, 1971; McDonald, Mather & Story, 1977). Erythromycin base is susceptible to inactivation by gastric acid and *in vitro* has been shown to dissociate readily from the stearate salt (Boggiano & Gleeson, 1976). Erythromycin estolate is associated with higher plasma levels than the stearate, but this may be explained by increased protein binding (Wiegand & Chun, 1972). Also, the estolate does not produce significant antibacterial activity until conversion to the base, but this occurs slowly and incompletely (Stephens, Pugh, Davis, Hoehn, Ralston, Sparks & Thompkins, 1969). Erythromycin estolate has been associated with cholestatic jaundice (Cooksley & Powell, 1977). Recently, consistent absorption has been demonstrated following administration of a new formulation of erythromycin base one hour before food (McDonald *et al.*, 1977) and of erythromycin stearate taken immediately before food (Berend, Rutland & Marlin, 1978). The purpose of this study was firstly to compare the plasma concentrations of these two preparations after a single oral administration and secondly to determine whether food interferes with their bioavailability.

Methods

Subjects and study design

Sixteen healthy subjects (fourteen males and two females), aged from 21 to 30 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 prior to the commencement of or during the study period. The subjects fasted from midnight before all study days.

The formulations of erythromycin administered in this study were: (1) erythromycin stearate, 500 mg (Erythrocin, 250 mg, capsule-shaped tablets, C946, Abbott Laboratories Pty. Ltd.)

(2) erythromycin base, 500 mg (Eryc, 250 mg, capsules containing enteric coated pellets, F. H. Faulding & Co. Ltd). The study was a balanced, randomized Latin square design and was performed on 4 days separated from each other by a period of 1 week. The four treatments were:

(1) erythromycin stearate, 500 mg, before breakfast (EB)

(2) erythromycin stearate, 500 mg, after breakfast (EA)

(3) erythromycin base, 500 mg, before breakfast (eB)

(4) erythromycin base, 500 mg, after breakfast (eA)

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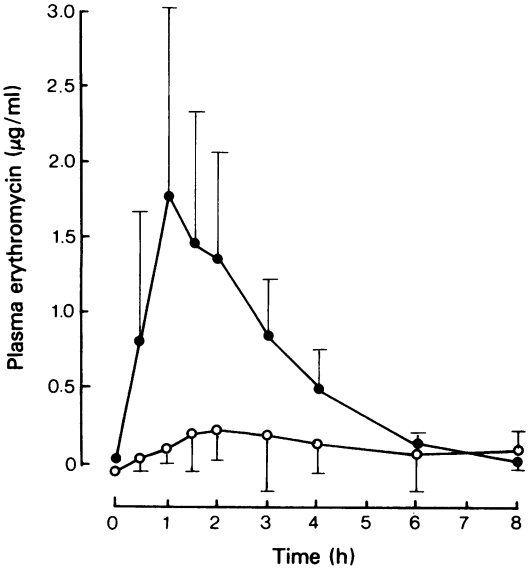

Figure 1 The mean ± s.d. erythromycin plasma concentrations after 500 mg erythromycin stearate taken immediately before (●) and after food (○) for the sixteen subjects.

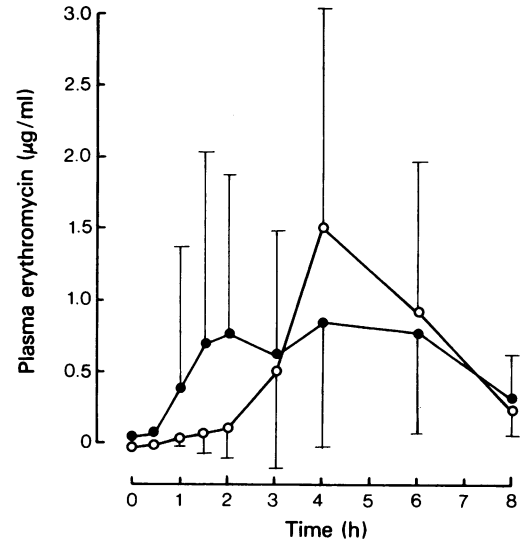

Figure 2 The mean ± s.d. erythromycin plasma concentrations after 500 mg erythromycin base taken immediately before (●) and after food (○) for the sixteen subjects.

The drug was administered either immediately before or after a standard breakfast which was eaten over a period of 15 min. The breakfast consisted of cereal with milk, fruit juice and toast. Other food and drinks were not restricted but were not taken until 2 h following drug ingestion. The drug was given with 50 ml of water.

Venous blood samples were collected immediately before drug ingestion and subsequently at 0.5, 1, 1.5, 2, 4, 6 and 8 h for erythromycin plasma level determination. Before drug administration blood was also collected for a biochemical profile (electrolytes, renal and hepatic function, blood sugar) and a full blood count. The subjects were asked to report any side-effects during the study.

Assay method for erythromycin concentration

The assay method for plasma erythromycin concentration followed that described by Bell, Hamman & Grundy (1969) using a microbiological technique with *Sarcina lutea* ATTC 9341 as test organism. The only modification was the use of large 12 × 12 inch antibiotic Assay plates which enabled six standards and twelve samples to be set on each plate. Each standard and sample was set twice and each assay plate was done in duplicate. Individual plasma levels were obtained using linear regression of log concentration against zone diameter. The plasma levels in the calculations were the weighted means of the results from the two plates. 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 mean ± s.d. plasma concentrations for EB and EA are shown in Figure 1 and for eB and eA in Figure 2. The areas under the plasma drug concentration/time curve (AUC), the maximal plasma concentrations (C_{max}) and the times to reach maximal concentration (t_{max}) for all subjects with the mean ± s.d. results are shown in Table 1.

The erythromycin concentrations with EB were significantly greater than those with EA for 4 h ($P<0.01$), with eB for 2 h (1.5 ($P<0.05$); 0.5, 1 and 2 ($P<0.01$)), and with eA for 2 h ($P<0.01$), whereas they were significantly less than those with eB at 6 and 8 h ($P<0.01$) and with eA from 4 to 8 h (4 ($P<0.05$); 6 and 8 ($P<0.01$)). The only significant difference between treatments eB and eA was at 2 h when the concentration with eB was greater ($P<0.05$). Erythromycin levels with EA from 4 to 8 h were significantly less than those with eB (4 and 8 ($P<0.05$); 6 ($P<0.01$)) and eA (4 and 6 ($P<0.05$); 8

Table 1 The individual and mean ± s.d. areas under the erythromycin plasma concentration curves (plasma AUC), the maximal plasma concentration (C_{max}) and the times at which these occurred (t_{max}) for the sixteen subjects after treatments EB, EA, eB and eA.

	Plasma AUC (μg ml^{-1} h)				*C_{max} (μg)*				*t_{max} (h)*			
Subject	*EB*	*EA*	*eB*	*eA*	*EB*	*EA*	*eB*	*eA*	*EB*	*EA*	*eB*	*eA*
1	4.62	0.35	7.23	10.51	1.96	0.09	1.83	4.56	2.0	2.0	4.0	6.0
2	8.00	0.74	5.83	6.91	2.88	0.18	1.49	2.24	1.0	3.0	4.0	3.0
3	3.92	1.10	7.31	2.62	0.99	0.44	3.10	1.02	3.0	4.0	6.0	6.0
4	4.49	0.49	1.35	3.06	1.89	0.37	0.64	1.13	1.0	2.0	6.0	4.0
5	0.18	0.50	6.22	3.66	0.06	0.14	2.54	1.22	3.0	1.0	4.0	4.0
6	6.49	0.75	7.09	5.24	3.33	0.42	2.54	1.92	1.0	2.0	3.0	3.0
7	10.02	1.11	10.31	11.66	4.68	0.62	4.58	6.35	1.0	1.5	1.5	4.0
8	2.46	0.26	2.90	5.01	1.31	0.08	1.02	1.48	1.0	3.0	1.5	4.0
9	2.94	1.28	2.11	0.79	1.54	0.51	1.03	0.33	1.5	1.5	6.0	6.0
10	6.65	0.01	6.97	3.29	2.77	0.00	1.94	1.11	0.5	4.0	3.0	4.0
11	7.29	1.33	9.17	6.20	2.53	0.49	3.23	2.05	1.0	1.5	2.0	4.0
12	3.55	0.32	4.77	6.28	1.85	0.17	2.23	2.00	1.0	2.0	4.0	4.0
13	5.23	0.47	0.72	0.14	1.87	0.17	0.30	0.14	1.0	1.5	6.0	3.0
14	4.89	0.25	1.59	7.65	2.13	0.20	1.10	2.47	1.0	1.5	8.0	4.0
15	6.07	6.73	2.49	2.58	2.45	1.69	0.69	0.70	1.5	3.0	6.0	6.0
16	3.02	0.97	2.85	4.06	1.19	0.34	1.14	1.92	1.0	3.0	6.0	4.0
Mean	4.99	1.04	4.93	4.98	2.09	0.37	1.84	1.91	1.34	2.28	4.44	4.31
s.d.	2.41	1.57	2.98	3.17	1.06	0.40	1.15	1.57	0.27	0.93	1.92	1.08

EB: erythromycin stearate, 500 mg, before breakfast
EA: erythromycin stearate, 500 mg, after breakfast
eB: erythromycin base, 500 mg, before breakfast
eA: erythromycin base, 500 mg, after breakfast

($P<0.01$)), although the level with EA at 1 h was significantly greater than that with eA ($P<0.05$).

There were no significant differences between the AUCs and C_{max} for treatments EB, eA and eB, but all were significantly greater than for EA ($P<0.01$). The t_{max} values for both eB and eA were significantly greater than those for EB and EA ($P<0.01$) and also the t_{max} for EA was significantly greater than for EB ($P<0.01$). The mean $\pm$ s.d. elimination half-life for erythromycin was 1.33 ± 0.31 h.

There were no side-effects reported during the study. Haematological and biochemical profiles were all normal before and during the study and the blood sugar measurements before EB and eB confirmed the fasting state of the subjects.

Discussion

Both erythromycin preparations when taken immediately before food demonstrated equivalent bioavailability. However, the rate of absorption of the stearate was significantly faster than the base which may be explained by the slow release of drug from the enteric-coated pellets of the base preparation. There was less variation in the t_{max} with the stearate resulting in higher mean plasma levels during the first two hours after administration. Other factors have been shown to affect the absorption of erythromycin stearate when taken before food. Welling, Huang, Hewitt & Lyons (1978) have recently demonstrated in healthy subjects a C_{max} mean value of 3.0 μg/ml after 500 mg erythromycin stearate (two 250 mg film-coated tablets) taken with 250 ml of water on a fasting stomach compared with 1.7 μg/ml when the drug was taken with only 20 ml of water. Malmborg (1978) has shown a higher mean C_{max} value (2.8 μg/ml) which was reached 1 h earlier, when 500 mg erythromycin stearate was given immediately before food, than when taken on a fasting stomach, food being withheld for a further 3 h (1.3 μg/ml).

The rate of intestinal absorption of a drug, which is not absorbed from the stomach, is influenced by the rate of gastric emptying. For drugs which are unstable in gastric fluid, bioavailability and therapeutic efficacy depend upon residence time in the stomach. There is great variability in gastric emptying time in man and this is influenced by many factors including age, physical activity, posture, and the physical and chemical properties of gastric contents, e.g. composition, volume, osmotic pressure, viscosity, acidity and temperature (Hunt, 1959, Levine, 1970; Davenport, 1971; Prescott, 1974). Gastric volume in fasting man may be 50 ml or less and during fasting gastric motility increases, mediated by vagal impulses (Davenport, 1971). Thus, transfer of a drug into the intestine may be rapid, occurring within minutes, if the drug is taken on a fasting stomach.

Gastric motility may reach peak activity associated with neural influences immediately before food, which would explain the findings of Malmborg (1978). The administration of erythromycin stearate with a large volume of water on a fasting stomach may assist in transporting the drug rapidly into the intestine. The large water volume might also improve the dissolution of the erythromycin which has low water solubility and dilute gastric acid which might reduce acid degradation. In the present study erythromycin stearate was given with a small volume of water only. Administration of a larger volume may have resulted in improved absorption. The effect of the time interval before food and the volume of water taken with the drug has not been investigated with the base preparation.

The bioavailability of the stearate when taken immediately after food was markedly reduced, although the absorption of the base was not impaired. Transfer of the stearate when given before food from stomach to duodenum must have been extremely rapid to have escaped acid degradation. The enteric-coated base formulation offered some protection against acid degradation, although as expected its absorption was delayed by the presence of food in the stomach. During the study further fluid and food intake was permitted after 2 h had elapsed following drug ingestion. Fluid intake after this time which coincided with the t_{max} for this formulation may have improved absorption of the base. Thus the conditions at the time of absorption of the two preparations were not identical with respect to fluid intake. There was considerable intrasubject and intersubject variation in absorption of erythromycin. Although the content of the breakfast was standardized throughout the study, other factors known to influence gastric emptying rate, such as activity and posture, were not controlled.

In conclusion, this study demonstrated that food may have a profound effect on drug absorption. Further studies are required to determine the extent to which food will affect the bioavailability of these erythromycin formulations during steady state conditions in patients receiving normal meals. The erythromycin stearate preparations should be given immediately before food for consistent and rapid absorption. In this study food did not appear to affect the bioavailability of the erythromycin base preparation. When erythromycin is prescribed, it is important that precise instructions be given to the patient regarding the timing of drug intake with respect to meals and volume of water taken with the drug.

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