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Effect of formulation factors and food intake on the bioavailability of erythromycin stearate tablets

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Summary

The bioavailability of 3 commercial erythromycin tablet formulations: film-coated stearate, enteric-coated stearate and enteric-coated erythromycin base, was compared in a single-dose cross-over study on 15 healthy volunteers. The tablets were administered to fasted subjects and in a mode where drug administration was followed by a standardized breakfast. The bioavailability of the film-coated tablet was enhanced by food intake, whereas food impaired the bioavailability of the other two formulations. From the bioavailability study results and from the tablets' in vitro disintegration properties it was concluded that it is not necessary to protect erythromycin stearate by an enteric-coating, but with a film-coating withstanding low pH and susceptible of disintegrating rapidly at pH values above 4.5. On the basis of these results a new film-coated erythromycin stearate tablet formulation was developed which had the desired in vitro disintegration properties and showed good bioavailability when administered just prior to a standardized breakfast. It is suggested that the proposed in vitro test can be useful in controlling the production of the novel tablet formulation.

Introduction

The usefulness of the macrolide antibiotic erythromycin has been demonstrated in treating a variety of bacterial infections. Serious untoward effects are only rarely caused by erythromycin (Goodman and Gilman, 1980). Erythromycin is commer-

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cially available in oral as well as in injectable dosage forms. The erythromycin base is rapidly destroyed by gastric acid and is therefore protected by enteric coating in oral formulations. The sparingly soluble stearate salt is claimed to be more stable in gastric fluid, and hence it is produced commercially in both enteric-coated and film-coated form.

A number of bioavailability studies conducted with orally administered erythromycin preparations compare the bioavailability of different erythromycin derivatives, administered as commercial formulations, or investigate the effect of concomitant food intake on bioavailability (e.g. McDonald et al., 1977; Welling, 1977; Welling et al., 1978; Welling et al., 1979; Bechtol et al., 1979; Fraser, 1980; Malmborg, 1980; Clayton and Leslie, 1981; Mather et al., 1981). Only few study reports published so far pay attention to the role of the pharmaceutical formulation or the in vitro properties of erythromycin preparations as factors affecting bioavailability. Yakatan et al. (1979) compared the bioavailability of 5 commercial erythromycin stearate film-coated tablets, when administered to fasted subjects. Two of the products studied showed significantly greater C_{max} and AUC values than the other 3 products. DiSanto and Chodos (1981) found that bioavailability of erythromycin base or stearate is intimately dependent upon the degree of protection afforded the core tablets by a properly prepared enteric coating. Such a preparation can be administered irrespective of meals with the expectation of optimum bioavailability. The authors did not, however, include enteric-coated erythromycin stearate tablets in their study, nor was the effect of food intake immediately after the administration of the drug investigated. Malmborg (1979) made the interesting finding that the bioavailability of a specific brand of film-coated erythromycin stearate tablets was improved when the tablets were taken immediately before a meal. This observation was made by other authors, too (Clayton and Leslie, 1981). Stavchansky et al. (1980) found significant correlations between linear combinations of certain in vitro disintegration and dissolution parameters and bioavailability parameters of film-coated erythromycin stearate tablets from 5 manufacturers. The authors concluded that tablet distintegration tests similar to the ones presented in their study can be useful for monitoring erythromycin stearate tablets.

The purpose of the present study was to discover some of the pharmaceutical in vitro properties which can be connected with the good bioavailability of erythromycin stearate tablets, when the tablets are administered immediately before a meal. The study was carried out in two parts. In a preliminary study, the effect of food intake on the bioavailability of 3 commercial erythromycin tablets was tested. Based on the test results and on the in vitro properties of the formulations compared, a new erythromycin stearate tablet with the desired in vitro properties was developed. The performance of the new tablet was tested in a comparative bioavailability study in which the tablets were administered to healthy volunteers just prior to a standardized breakfast.

Experimental

The tablets studied

The different tablet brands and lots studied are indicated as follows.

A1: Abboticin 250 mg Filmtabs, Abbott Laboratories, lot 88021 TF, analyzed content 265.7 mg erythromycin as the stearate;

A2: Abboticin 250 mg Filmtabs, Abbott Laboratories, lot 22005 PD, analyzed content 273.8 mg erythromycin as the stearate;

E: Etromycin 250 mg enteric-coated tablets, Orion Pharmaceuticals, Finland, lot DH7, analyzed content 242.6 mg erythromycin base;

R1: Resibion 250 mg enteric-coated tablets, Leiras Pharmaceuticals, Finland, lot DL01, analyzed content 258.2 mg erythromycin as the stearate;

R2: Resibion 250 mg enteric-coated tablets, Leiras Pharmaceuticals, Finland, lot FK03, analyzed content 265.8 mg erythromycin as the stearate; and

RN: Resibion 'New' film-coated tablets, Leiras Pharmaceuticals, Finland, trial batch 181280, analyzed content 278.2 mg erythromycin as the stearate.

The in vitro disintegration time of the tablets was determined by using an apparatus corresponding to the specifications of the European Pharmacopoeia. Two different disintegration tests were performed. In Method 1, the tablets were run in simulated gastric fluid, pH 1.2 (USP XX), at 37°C for 1 h whereafter the medium was replaced by simulated intestinal fluid, pH 7.5 (USP XX), and the test was continued until all the 6 tablets had disintegrated. In Method 2, the same equipment was used, but initially the tablets were run in simulated gastric fluid at 37°C for only 30 min and then the medium was replaced by a phosphate buffer solution containing 0.7 g of monobasic potassium phosphate and 30.4 ml of 1 N NaOH, adjusted to pH 4.5 with concentrated hydrochloric acid, and water to 1000 ml.

Bioavailability studies

Bioavailability and the effect of food intake on the bioavailability of different erythromycin tablet formulations was studied in two separate trials, Study 1 and Study 2.

Study conditions

The bioavailability studies were conducted under medical supervision at the Research Laboratories of Huhtamäki Oy, Leiras Pharmaceuticals. The subjects participating in the study were healthy volunteers. All subjects were found by medical examination to be in good physical condition, and all subjects were given detailed information about the purpose of the study. The study design was cross-over with a 1-week wash-out period between the treatments. After an overnight fast the subjects were given 2 tablets, corresponding to 500 mg of erythromycin base (label claim), in randomized order. The dose was swallowed with 150 ml of water. Blood samples of 10 ml were drawn from the cubital vein prior to administration and at fixed time intervals following administration of the drug. Intake of food was allowed 3 h after drug intake. In the other case, a standardized breakfast was taken within 20 min of administration of the drug. The breakfast included one 50 g wholemeal bread

TABLE 1

COMPOSITION OF THE STANDARDIZED BREAKFAST

Energy (kJ)	Energy (kcal)	Protein (g)	Fat (g)	Carbohydrate (g)	Ca (g)	Mg (mg)	Fe (mg)	A vitamin (mg)	Thiamine (mg)	Riboflavin (mg)	Niacin (mg)	C vitamin (mg)
3560	850	27	44	85	0.3	90	5.4	0.7	0.5	1.0	4.4	38

TABLE 2

MEAN SERUM CONCENTRATIONS OF ERYTHROMYCIN (mg/l) AFTER SINGLE-DOSE ADMINISTRATION OF TWO 250 mg TABLETS, MEAN PEAK CONCENTRATION, C_{max} (mg/l) TIME TO PEAK, t_{max} (h) AND MEAN AUC 0–7.5 h (h·mg/l). BIOAVAILABILITY STUDY 1 (n = 15). NUMBERS IN PARENTHESES REPRESENT S.D.

Sample (h)	Formulation A1		Formulation E		Formulation R1	
	Fasted	Breakfast	Fasted	Breakfast	Fasted	Breakfast
0	0	0	0	0	0	0
0.5	0.15 (0.31)	0.71 (0.50)	0	0.17 (0.46)	0	0.02 (0.04)
1	0.70 (0.74)	2.23 (1.24)	0	0.39 (0.85)	0.17 (0.23)	0.37 (0.39)
1.5	1.17 (0.85)	2.02 (0.81)	0.04 (0.12)	0.47 (0.85)	0.48 (0.50)	0.60 (0.85)
2	1.58 (0.81)	1.74 (0.74)	0.32 (0.15)	0.34 (0.62)	0.72 (0.50)	0.63 (0.81)
2.5	1.47 (0.81)	1.40 (0.62)	0.46 (0.74)	0.26 (0.50)	0.87 (0.46)	0.61 (0.70)
3	1.30 (0.46)	1.11 (0.46)	0.81 (0.74)	0.25 (0.46)	0.82 (0.39)	0.64 (0.70)
4	0.90 (0.39)	0.77 (0.31)	1.29 (0.77)	0.16 (0.31)	0.92 (0.43)	0.70 (0.70)
6	0.48 (0.19)	0.35 (0.19)	0.79 (0.35)	0.32 (0.66)	0.51 (0.31)	0.38 (0.35)
7.5	0.28 (0.15)	0.22 (0.15)	0.48 (0.27)	0.32 (0.58)	0.32 (0.19)	0.19 (0.15)
C_{max}	1.80 (0.70)	2.50 (1.05)	1.54 (0.70)	0.91 (1.08)	1.27 (0.35)	1.18 (0.89)
t_{max} (median)	2	1	4	1.5	2.5	4
AUC	5.91 (2.17)	6.83 (2.56)	4.70 (2.21)	2.04 (2.67)	4.27 (1.32)	3.48 (2.56)

roll, 10 g butter, 20 g cheese with 40% fat, 1 boiled egg, 100 ml orange juice, 1 Danish pastry, 150 ml of coffee with 2 lumps of sugar and 200 ml milk. The calculated composition and energy content of the meal are given in Table 1.

Bioavailability Study 1

The effect of food intake on the bioavailability of 3 commercial erythromycin tablets, indicated A1, E and R1, was studied. The subjects participating in the study were 6 females and 9 males, 19–46 years of age (mean 32), 56–83 kg weight (mean 67) and 160–184 cm height (mean 170).

Bioavailability Study 2

On the basis of the results of Study 1, a new film-coated erythromycin stearate tablet was developed, designated here as RN. It was apparent from Study 1 that good bioavailability was achieved especially when film-coated tablets were administered just prior to food intake. Therefore, the bioavailability of the new formulation was tested in Study 2, in which drug administration was followed by intake of a standardized meal (Table 1). The formulations compared were A2, R2 and RN. The subjects participating in the study were 2 females and 10 males, 19–23 years of age (mean 20), 60–85 kg weight (mean 69) and 170–195 cm height (mean 177).

Erythromycin assay in serum

Serum was separated from blood by centrifugation. To 2 ml of freshly separated serum 2 ml of phosphate buffer, pH 9.2, and 5 ml of diethyl ether were added in a centrifugation tube. After shaking, an aliquot part of the ether layer was withdrawn and evaporated to dryness. The dry residue was stored at −18°C until analysis. The antibiotic activity of the serum extracts was quantified microbiologically by the cylinder plate agar diffusion method, using Antibiotic Medium 1, pH 8.0 (Difco), seeded with Sarcina lutea ATCC 9341.

Data analysis

From individual serum erythromycin levels at given times the following pharmacokinetic parameters were determined: peak serum erythromycin concentration, C_{max}, time to peak concentration, t_{max}, and area under the serum–concentration time curve, AUC, calculated by the trapezoidal rule. The mean C_{max} and AUC values from each treatment were compared by the paired *t*-test.

Results and Discussion

Erythromycin serum concentration data from Study 1 demonstrate good bioavailability of the film-coated erythromycin stearate formulation A1 (Tables 2–4). Bioavailability (mean AUC 0–7.5 h) of formulation A1 was enhanced when drug administration was followed by food intake, and the mean C_{max} value was statistically significantly higher ($P < 0.05$). The opposite was observed with both the enteric-coated formulations, E and R1. Here, food intake decreased bioavailability.

TABLE 3

SIGNIFICANCES OF DIFFERENCES OF C_{max} AND AUC MEANS IN BIOAVAILABILITY STUDY 1 (*P*-VALUE BY STUDENT'S *t*-TEST)

Comparison Study condition	Formulations A1/E		Formulations A1/R1		Formulations E/R1	
	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
Fasted	N.S.	0.05	0.005	0.01	N.S.	N.S.
Breakfast	0.001	0.001	0.001	0.001	N.S.	N.S.
Fasted/Breakfast	Formulation A1		Formulation E		Formulation R1	
	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
	0.05	N.S.	N.S.	0.02	N.S.	N.S.

In the case of formulation E, the observed decrease was statistically significant ($P < 0.02$). This different effect of food ingestion immediately after drug administration on bioavailability of film-coated and enteric-coated erythromycin tablets is in accord with literature data (Malmborg, 1979; Clayton and Leslie, 1981). To describe the differences between individual bioavailability data after administration of each formulation, two arbitrary, qualitative criteria were used to denote failure of a given formulation to be absorbed: observed $C_{max} < 1$ mg/litre, or AUC < 3 h · mg/l (Table 4). These criteria are only technical, and are not intended to implicate non-compliance with accepted MIC-levels of erythromycin or failure in a clinical situation. According to criterion C_{max}, there was failure in only one subject in connection with formulation A1. According to criterion AUC, there was failure in one other subject receiving formulation A1. In both the formulations E and R1, the bioavailability-decreasing effect of food intake was very pronounced. Food intake seemed to have a dual effect on the absorption of formulation E. On the other hand, absorption was accelerated, as reflected by the observed median for t_{max} at 1.5 h. On the other hand, in 8 out of 15 subjects no erythromycin activity was found in serum samples up to 7.5 h following administration. (It is a pure coincidence that all 'absorption failures' according to the C_{max} criterion in Table 4, in connection with formulation E and breakfast, are at the same time 'zero absorbers' during the observation period of 7.5 h.) Food intake in connection with formulation R1

TABLE 4

NUMBER OF SUBJECTS HAVING C_{max} LESS THAN 1 mg/litre, AND NUMBER OF SUBJECTS HAVING AUC LESS THAN 3 h·mg/l AFTER SINGLE-DOSE ADMINISTRATION OF TWO 250 mg TABLETS. BIOAVAILABILITY STUDY 1 (n = 15)

	Formulation A1		Formulation E		Formulation R1	
	Fasted	Breakfast	Fasted	Breakfast	Fasted	Breakfast
C_{max}	1	1	3	8	3	7
AUC	1	1	3	10	4	8

retarded the observed median for t_{max} from 2.5 to 4 h and doubled the number of absorption failures. These bioavailability results after single-dose administration are, however, not very conclusive. Then in several studies a good and uniform bioavailability of enteric-coated erythromycin base preparations has been demonstrated, and the importance of multiple-dose testing in assessing the bioavailability of erythromycin and erythromycin stearate preparations is stressed (e.g. Yakatan et al., 1980; DiSanto and Chodos, 1981).

Technical characteristics and in vitro disintegration times of the tablet formulations studied are presented in Table 5. Test results demonstrate that formulation E is an enteric-coated tablet of very good pharmaceutical and technical quality. The coating is resistant to simulated gastric fluid and to phosphate buffer, pH 4.5. But the tablets disintegrate rapidly in simulated intestinal fluid, pH 7.5. The single-dose bioavailability of this formulation was, however, poor, a problem often encountered with enteric-coated tablets. The pharmaceutical quality of the enteric-coated formulations, R1 and R2, which are different manufacturing lots of the same brand, appears not to be as good as that of formulation E, as reflected by the longer in vitro disintegration time observed when using Method 1. However, the observed 'technical failure', i.e. disintegration already at lower pH (pH 4.5 in Method 2), could at least partially explain the relatively good absorption of formulation R2 in bioavailability Study 2; tablets entering the small intestine disintegrate quite rapidly and release the drug for absorption. Formulations A1 and A2 which are different lots of the same brand, disintegrated very rapidly in both the tests performed, and the film-coating itself in some tablets disintegrated already during the period in simulated gastric fluid. Thus, the film-coating used in this formulation appears to have some degree of resistance to gastric acid, but giving free access to fluids of higher pH values.

TABLE 5

TECHNICAL CHARACTERISTICS AND DISINTEGRATION TIMES OF THE TABLET FORMULATIONS STUDIED

	Tablet formulation					
	A1	A2	E	R1	R2	RN
Form	round biconvex	round biconvex	round biconvex	round biconvex	round biconvex	capsule-formed
Weight (mg)	760	775	650	820	805	820
Hardness [a] (kg)	10	10	over 16	15	12 to over 16	over 16
	Disintegration time [b] (min)					
Method 1 (n = 6)	2–3	5–7	14–20	28–33	22–28	6–8
Method 2 (n = 6)	6–8	9–11	180	36–40	46–64	11–14

[a] Pfizer Hardness Tester.

[b] Manesty Tablet Disintegration Tester, Mark III. The time recorded is minutes in simulated intestinal fluid (Method 1) or in phosphate buffer, pH 4.5 (Method 2).

Not only the erythromycin base but also the stearate readily dissolves in and is inactivated by acidic solutions (Boggiano and Gleeson, 1976). It was therefore felt that erythromycin stearate should be made up in a form which gives some protection from gastric acid. From the good bioavailability of formulation A1 and from the tablets' disintegration properties in simulated gastrointestinal fluids it was concluded that: (a) erythromycin stearate does not require a protective enteric coating; and (b) that rapid disintegration of tablets at pH values lower than that of simulated intestinal fluid may be essential for good and regular in vivo absorption. Finally, a novel formulation, RN, was developed with the intention of achieving two essential in vitro properties: rapid disintegration of the tablet core in water, and, by means of a protective film-coating, the power to withstand low pH but susceptible of dissolving or disintegrating rapidly at about pH 4.5, a value thought to represent the transient pH-range from gastric to intestinal environment. The protective film-coating contained hydroxypropylmethylcellulose-phthalate, hydroxypropylmethylcellulose and polyethylene glycol. The in vitro disintegration properties of formulation RN are comparable to those of formulations A1 and A2 (Table 5).

The results of Study 2 demonstrate that formulation RN is markedly better absorbed than the older, enteric-coated formulation R2 of the same brand (Fig. 1 and Tables 6 and 7). Unexpectedly, its absorption appeared to be even better than that of formulation A2 ($P < 0.05$). The technical and in vitro disintegration proper-

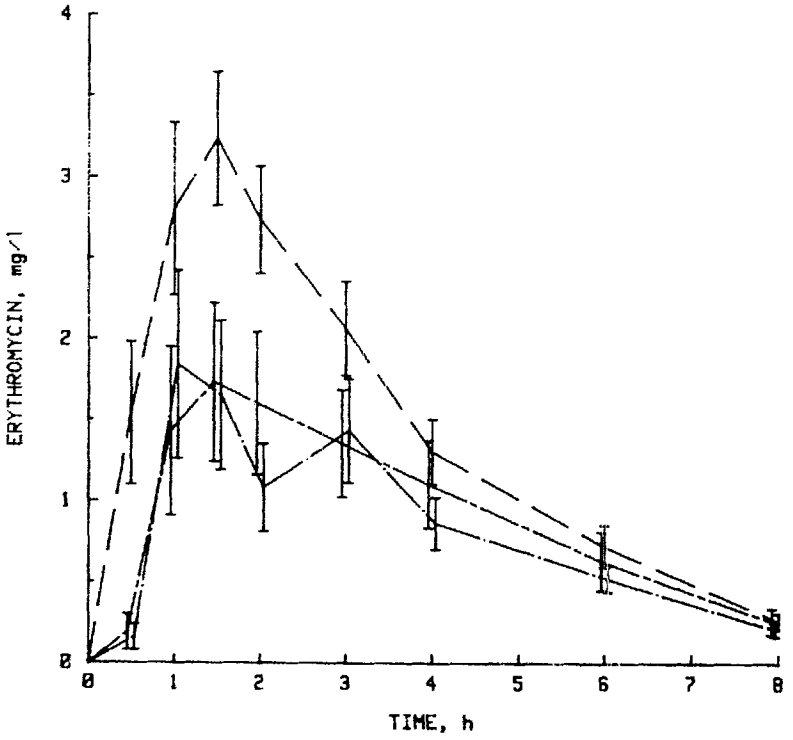

Fig. 1. Mean serum concentrations of erythromycin (±S.E.) after single-dose administration of two 250-mg tablets of the formulations RN (— — —), A2 (- — - — -), and R2 (· - · - ·) in bioavailability Study 2 (n = 12).

TABLE 6

MEAN SERUM PEAK CONCENTRATIONS OF ERYTHROMYCIN, C_{max} (mg/l) TIME TO PEAK, t_{max} (h) AND, MEAN AUC 0–8 h (h·mg/l) IN BIOAVAILABILITY STUDY 2. NUMBERS IN PARENTHESES ARE S.D.

	Formulation RN	Formulation A2	Formulation R2
C_{max}	3.50 (1.61)	2.45 (1.63)	2.49 (1.80)
t_{max} (median)	1.5	2	3
AUC	11.55 (5.22)	7.40 (5.57)	6.61 (4.21)

ties do not explain this bioavailability test result. When Studies 1 and 2 are compared, it is found that the observed apparent bioavailability (AUC) of the two different lots of the same brand, A1 and A2, is about the same in both studies. This is in accordance with the equal in vitro properties of the two lots. The apparently better relative bioavailability of R2 as compared to R1 is difficult to explain. Most probably it is due to different subject populations participating in the studies, and to intra- and interlot variations in some of the technical properties of the tablets, like dissolution, which were not detected in the in vitro tests with only a few tablets.

The study results demonstrate that erythromycin stearate tablet formulations showing good bioavailability also perform well in the both in vitro disintegration tests. When a tablet is administered just prior to food ingestion, like in this study, it is proposed that disintegration test Method 2 more properly simulates the pH-environment around the tablet proceeding in the gastrointestinal tract. And this disintegration test can be used to control production batches of the formulation RN. The study results and the proposed in vitro test are possibly valid only for the formulations studied then, as stated by Malmborg (1979), the results from one study only are valid for the preparation used and not for the substance in general, and, the in vitro tests that optimally predict bioavailability for one small sample (of erythromycin stearate tablet formulations) may not be the best independent variables for a sample of altered composition (Stavchansky et al., 1980). Further, the demonstrated good bioavailability of formulation RN in a single-dose study has to be verified in a multiple-dose study where tablets are administered just prior to food ingestion.

TABLE 7

SIGNIFICANCES OF DIFFERENCES OF C_{max} AND AUC MEANS IN BIOAVAILABILITY STUDY 2 (*P*-VALUE BY STUDENT'S *t*-TEST).

Comparison	Formulations RN/A2		Formulations RN/R2		Formulations A2/R2	
	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
	0.05	0.05	N.S.	0.02	N.S.	N.S.

Conclusions

From the qualitative connection observed between the technical in vitro properties and the bioavailability of the tablet formulations studied, the following conclusions were drawn.

(1) Oral solid dosage forms containing erythromycin stearate do not require an enteric coating. However, because of degradation of the drug by acid, the core has to be protected by a coating which will resist aqueous solutions of lower pH values than about 4.5.

(2) The solid core itself must disintegrate rapidly when coming into contact with an aqueous solution.

(3) Formulations having the above technical properties show good bioavailability, especially when administered just prior to food intake.

(4) The proposed in vitro disintegration test may be useful in controlling the production of the novel tablet formulation RN.

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