Bioavailability of Erythromycin Acistrate from Hard Gelatin Capsules Containing Sodium Bicarbonate

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Erythromycin acistrate is a new prodrug of erythromycin. Its bioavailability from hard gelatin capsules containing the drug with or without sodium bicarbonate was studied in healthy volunteers. The plasma levels of erythromycin, anhydroerythromycin, and acetylerythromycin were measured using an HPLC method. Addition of sodium bicarbonate to the capsule markedly enhanced the plasma level of the microbiologically active substance, erythromycin, doubling the C_{max} and AUC values ($P < 0.05$). At the same time, the lag time in the absorption curve was shortened to one-third. No changes in the plasma levels of the inactive metabolite anhydroerythromycin were noted. It is concluded that adding sodium bicarbonate to an erythromycin acistrate formulation enhances its bioavailability.

KEY WORDS: erythromycin acistrate; erythromycin; bioavailability; sodium bicarbonate; high-performance liquid chromatography (HPLC).

INTRODUCTION

Erythromycin acistrate has better gastrointestinal absorption characteristics than erythromycin, and it lacks the hepatotoxic effect of erythromycin estolate. Chemically it is the stearate salt of 2′-acetylerythromycin (1). However, like other erythromycin derivatives, a small amount of erythromycin acistrate metabolizes in the acidic content of the stomach to anhydroerythromycin. This inactivation can be avoided by means of an enteric coating. The systemic conversion of erythromycin acistrate to anhydroerythromycin or anhydro-2′-acetylerythromycin is negligible (2,3). Because of the water sensitivity of erythromycin acistrate, water-based coating dispersions for enteric coating cannot be used. The use of organic solvents, on the other hand, may cause toxicological and environmental problems.

Sodium bicarbonate is an effective antacid. It is also a pharmaceutical additive used especially in effervescent tablets and in water-soluble tablets as a disintegrant. Hard gelatin capsules containing sodium bicarbonate have been shown to disintegrate in the human stomach in 2–3 min, bringing the gastric pH to about 7 (4).

The aim of the present study was to determine whether sodium bicarbonate could be used to prepare a rapidly disintegrating hard gelatin capsule formulation that would increase the gastric pH and the gastric emptying rate to such an extent that the resulting plasma anhydroerythromycin level would be markedly lower and the erythromycin level higher than those after administration of erythromycin acistrate alone.

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MATERIALS AND METHODS

Capsule Formulations

Size 0 hard gelatin capsules (Posilock, Capsugel AG, Switzerland) were used. Formulation I contained 340 mg of erythromycin acistrate (Fermion, Orion Corporation Ltd., Finland). Formulation II contained 340 mg of erythromycin acistrate and 200 mg of sodium bicarbonate (Ph.Eur.), premixed manually in a mortar. The capsules were filled by weighing. The amount of erythromycin acistrate used corresponds to 200 mg of erythromycin.

Formulation I disintegrated in 0.1 *M* hydrochloric acid, without stirring, in 90 to 120 sec. The respective time for formulation II was 60 to 80 sec.

Absorption Study

Six healthy female volunteers aged 20–35 years and weighing 53–72 kg were informed about the risks and side effects of the study and their written consent was obtained. The Ethical Committee of Orion Pharmaceutica approved the experimental protocol. Routine clinical tests showed all subjects to have values within the normal ranges.

In a randomized crossover study the volunteers took two capsules (corresponding to 400 mg of erythromycin) with 100 ml of tap water at 8 AM after an overnight fast. Food was subsequently withheld for 3 hr. Blood (10 ml) was sampled just before and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hr after capsule administration. Plasma was separated and stored at −18°C until analyzed. The washout period between the administrations was 1 week.

Erythromycin, anhydroerythromycin, and acetylerythromycin were assayed in plasma using a high-performance liquid chromatographic method based on coulometric detection (5). The limit of quantitation (with CV less than 20%) was 0.05 μg/ml for each analyte (2′-acetylerythromycin, erythromycin, and anhydroerythromycin). The calibration curves were constructed daily after analyzing samples containing 0.25, 0.5, 1.0, 2.0, 3.0, and 5.0 μg/L of each analyte. The curves were linear (typically $r = 0.999$) over the range and passed close to the origin. The recovery and precision of the methods were tested with spiked plasma samples of 1.0 μg/ml ($n = 6$). The mean recovery was 99.6 to 103.6%, with relative standard deviations of 3.3 to 4.4%.

Pharmacokinetic calculations were carried out using a Siphar computer program (Simed, France) and the following parameters were calculated: absorption lag time (lag time), absorption half-life ($t_{1/2a}$), maximum plasma level (C_{max}), time to peak concentration (t_{max}), area under the concentration/time curve from 0 to 8 hr (AUC_{0-8h}) and extrapolated to infinity ($AUC_{0-\infty}$), elimination half-life ($t_{1/2el}$), and mean residence time (MRT). The AUC values were calculated according to the linear trapezoidal rule and the absorption parameters (lag time and $t_{1/2a}$) according to the Wag-

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ner–Nelson method. The nonparametric Wilcoxon test was used in the statistical evaluation.

RESULTS

The plasma levels of the active drug, erythromycin, are shown in Fig. 1 and the corresponding pharmacokinetic data in Table I. Adding sodium bicarbonate to the capsule markedly enhanced the plasma level of the microbiologically active moiety, doubling the C_{max} and AUC values ($P < 0.05$). The addition of bicarbonate also shortened the lag time in the absorption curve to one-third.

The plasma levels of the acidic degradation product, anhydroerythromycin, are shown in Fig. 2. No statistically significant differences were found between the two formulations.

The concentrations of the prodrug form, acetylerythromycin, are given in Fig. 3 and the calculated pharmacokinetic parameters in Table II. Formulation II, which contained sodium bicarbonate, tended to enhance the bioavailability of acetylerythromycin; however the differences were not statistically significant. On the other hand, the lag time and t_{max} values were significantly ($P < 0.05$) shorter when sodium bicarbonate was added to the formulation.

Table I. Pharmacokinetic Parameters of Erythromycin After Oral Administration of Erythromycin Acistrate in Hard Gelatin Capsules (Dose Corresponding to 400 mg of Erythromycin): Means ± SD, $n = 6$

Parameter	Capsule I, drug	Capsule II, drug + $NaHCO_3$	Statistics,[a] $P <$
Lag time (hr)	0.77 ± 0.42	0.23 ± 0.12	0.05
$t_{1/2a}$ (hr)	0.55 ± 0.22	0.65 ± 0.15	NS
C_{max} (mg · L^{-1})	0.46 ± 0.24	0.86 ± 0.51	0.05
t_{max} (hr)	2.42 ± 0.66	2.71 ± 1.32	NS
AUC_{0-8h} (mg · L^{-1} · hr^{-1})	2.23 ± 1.35	4.62 ± 2.86	0.05
$AUC_{0-\infty}$ (mg · L^{-1} · hr^{-1})	2.87 ± 1.74	5.90 ± 3.75	0.05
$t_{1/2el}$ (hr)	3.05 ± 0.56	3.27 ± 1.08	NS
MRT (hr)	5.82 ± 0.91	5.57 ± 1.15	NS

[a] Nonparametric Wilcoxon test; NS, not significant.

DISCUSSION

The present results show that the problems presented in the introduction (formation of anhydroerythromycin and use of water or toxic solvents in manufacture) can be solved by adding sodium bicarbonate to hard gelatin capsules of erythromycin acistrate. Although the amount of anhydroerythromycin did not decrease in absolute terms, there was a marked decrease in relation to the amount of the active moiety. The C_{max} and AUC values of anhydroerythromycin are about 50% of those of erythromycin in formulation I but only about 25% of those in formulation II (Figs. 1 and 2). Thus in therapy the dose of erythromycin acistrate can be halved and still produce the same erythromycin plasma levels. In addition, the filling procedure for hard gelatin capsules is much simpler than enteric coating utilizing organic solvents.

Sodium bicarbonate clearly has a biphasic mechanism of action. It first causes rapid disintegration of the capsule, which is seen both in the *in vitro* disintegration times and in the shortened absorption lag times of both erythromycin and acetylerythromycin (Tables I and II). The corresponding absorption rate parameters ($t_{1/2a}$) did not change, which means that sodium bicarbonate does not accelerate the actual absorption rate of these drugs, but it can be imagined that sodium bicarbonate causes an effective spreading of the capsule content to the stomach. This is in accordance with the previous findings, with ibuprofen capsules containing sodium bicarbonate as an additive leading to effective disintegration of the capsule and to a shorter absorption lag time (6).

Second, sodium bicarbonate raises the gastric pH. This diminishes the rate of metabolism of erythromycin to anhydroerythromycin. It has been proved that formation of anhydroerythromycin takes place just in the acidic environment of the stomach, because after administration of enteric-coated erythromycin acistrate tablets, the plasma levels of anhydroerythromycin are negligible (2,3). Thus sodium bicarbonate has diminished the presystemic formation of anhydroerythromycin. Of course the tendency for enhanced

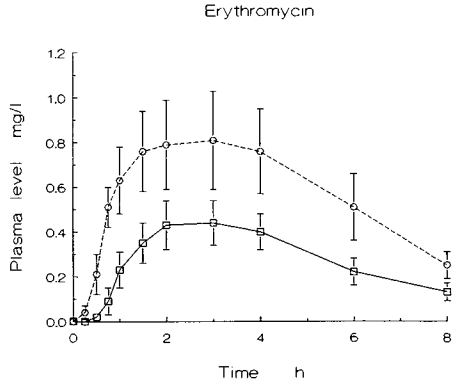

Fig. 1. Effect of sodium bicarbonate on the bioavailability of erythromycin from erythromycin acistrate capsules; single dose corresponding to 400 mg of erythromycin. (□) Capsules containing the drug alone; (○) capsules containing the drug and 200 mg of sodium bicarbonate. Means ± SE; $n = 6$.

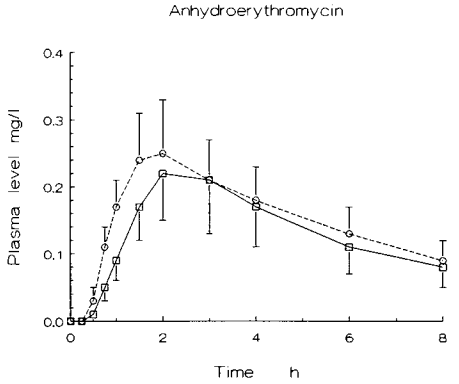

Fig. 2. Effect of sodium bicarbonate on anhydroerythromycin plasma levels after administration of erythromycin acistrate (corresponding to 400 mg of erythromycin) in hard gelatin capsules. (□) Capsules containing the drug alone; (○) capsules containing the drug and 200 mg of sodium bicarbonate. Means ± SE; $n = 6$.

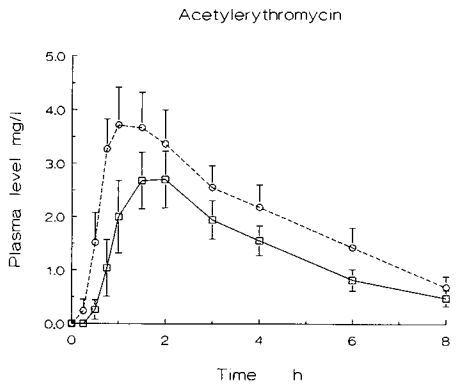

Fig. 3. Effect of sodium bicarbonate on acetylerythromycin plasma levels after administration of erythromycin acistrate (corresponding to 400 mg of erythromycin) in hard gelatin capsules. (□) Capsules containing the drug alone; (○) capsules containing the drug and 200 mg of sodium bicarbonate. Means ± SE; $n = 6$.

absorption of acetylerythromycin (Fig. 3) might have increased the systemic formation of erythromycin.

The anhydro form of acetylerythromycin is also formed from erythromycin acistrate in an acidic environment (2,3) and its formation can also be affected by sodium bicarbonate. This, however, was not examined because the main goal of the present study was to find a way to enhance the plasma level of the clinically active entity of erythromycin acistrate.

The mean apparent elimination half-life of erythromycin in the present study was 3.07–3.27 hr. The $t_{1/2el}$ values usually reported for erythromycin are 1.5 to 2 hr (7,8). This discrepancy can be explained by the fact that in the body acetylerythromycin forms a drug reservoir which releases erythromycin by hydrolysis until the reservoir is depleted. Thus the effect of a single erythromycin dose may be prolonged.

Table II. Pharmacokinetic Parameters of Acetylerythromycin After Oral Administration of Erythromycin Acistrate in Hard Gelatin Capsules (Dose Corresponding to 400 mg of Erythromycin): Means ± SD, $n = 6$

Parameter	Capsule I, drug	Capsule II, drug + $NaHCO_3$	Statistics,[a] $P <$
Lag time (hr)	0.54 ± 0.20	0.23 ± 0.12	0.05
$t_{1/2a}$ (hr)	0.41 ± 0.15	0.41 ± 0.27	NS
C_{max} (mg · L^{-1})	2.86 ± 1.29	3.91 ± 1.66	NS
t_{max} (hr)	1.83 ± 0.26	1.29 ± 0.46	0.05
AUC_{0-8h} (mg · L^{-1} · hr^{-1})	10.82 ± 5.54	16.38 ± 7.34	NS
$AUC_{0-\infty}$ (mg · L^{-1} · hr^{-1})	12.72 ± 7.28	19.40 ± 10.6	NS
$t_{1/2el}$ (hr)	2.40 ± 0.57	2.65 ± 0.72	NS
MRT (hr)	4.49 ± 0.83	4.36 ± 0.85	NS

[a] Nonparametric Wilcoxon test; NS, not significant.

The present results concerning the effect of an antacid on the bioavailability of an erythromycin derivative differ from those obtained by studying the effect of antacids on the pharmacokinetics of the stearate salt of erythromycin (9). In that study no significant differences in absorption characteristics were noted.

It is concluded that the extent of bioavailability of erythromycin from erythromycin acistrate can be greatly enhanced by adding sodium bicarbonate to the capsule formulation; however, the stability of this formulation needs to be studied.

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