Effects of Two Oral Erythromycin Ethylsuccinate Formulations on the Motility of the Small Intestine in Human Beings

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Fourteen-membered macrolides are known to produce alterations in digestive tract motor activity; these include the induction of strong gastric contractions and a decrease in the motility of the small intestine. The aim of the study was to compare the effects of two different formulations of erythromycin ethylsuccinate (EE) on duodenojejunal motility. Compared with the more commonly used crystalline formulation of EE (CEE), the amorphous formulation (AEE) has previously been described to have greater bioavailability and to induce significantly fewer gastrointestinal side effects when given at therapeutic and what have been considered to be equivalent oral doses (i.e., CEE, 1,000 mg every 12 h; AEE, 500 mg every 12 h). In a crossover double-blind study, duodenojejunal manometric recordings were performed for 10 volunteers treated with placebo, CEE at 1,000 mg, or AEE at 500 mg. Recordings for each volunteer were obtained for a fed period after a standard dinner and then for a nocturnal fasting period. When compared with the placebo, CEE significantly decreased the motility index of the duodenum during the 30 min after the peak serum erythromycin concentrations, shortened the duration of the fed state, and had no effect during the fasting state. In contrast, AEE did not significantly modify any motility parameter. Because AEE produced significantly lower concentrations in serum than CEE, these results do not necessarily imply that the two formulations of EE act differently on the motility of the small intestine.

Changes in gastrointestinal motility have previously been invoked to explain, at least in part, the digestive intolerance to macrolides (9). In human beings, as well as in animals, erythromycin frequently causes nausea, vomiting, abdominal pain, or diarrhea (1, 9, 25). Disturbances of digestive motility have also been reported; these appear to be dependent on the route of administration, the dose used, the level of the gastrointestinal tract studied, and whether subjects are fed or fasting (9, 17, 21, 25). Given intravenously at subtherapeutic doses, erythromycin has been shown to induce premature migrating motor complexes, i.e., propagated contractions which are initiated in the stomach and which migrate along the small intestine (21). Given intravenously at therapeutic doses, erythromycin acts differently in the stomach and in the small intestine: erythromycin significantly increases the antral motility, inducing both during the fed state and the fasting state contractions of high amplitude and long duration; by contrast, erythromycin significantly decreases the duodenojejunal motility during the fed state and has no effect during the fasting state (18, 21).

It has been shown that there is a relationship between the structure of macrolides and their ability to induce changes in gastrointestinal motility. In contrast to erythromycin and other compounds with 14 atoms in their lactone ring, 16-membered macrolides such as josamycin, midecamycin, or spiramycin have not been shown to influence motility and rarely cause gastrointestinal side effects (10, 17). The effects of the different erythromycin derivatives on motility vary from one compound to another.

The crystalline formulation of erythromycin ethylsuccinate has been used as an antimicrobial agent for many years. More recently, an amorphous formulation of erythromycin ethylsuccinate has become available. The two formulations are chemically identical, but they differ in their physical states. Pharmacokinetic studies have shown that the amorphous form has greater bioavailability; 500 mg of this formulation provided areas under the plasma drug concentration-versus-time curves (AUCs) equivalent to those achieved with 1,000 mg of the crystalline formulation when both are given orally (4, 5). In a comparative study evaluating the effects of different macrolide antibiotics in the treatment of respiratory tract infections, the incidence of gastrointestinal side effects was significantly lower with a regimen of 500 mg of amorphous erythromycin ethylsuccinate every 12 h than with a regimen of 1,000 mg of crystalline erythromycin ethylsuccinate every 12 h (0 of 30 versus 5 of 31 patients, respectively) (16).

Scintigraphic and manometric techniques are two complementary methods that can be used to investigate the digestive motor activity in human beings: the scintigraphic method allows recording of the transit time, but it fails to assess the contractions; conversely, the manometric method allows assessment of the contractions, but it fails to record the transit time. Studying gastric motility in human volunteers using a scintigraphic technique, we have recently shown that a single oral dose of either of the two formulations of erythromycin ethylsuccinate, amorphous (500 mg) or crystalline (1,000 mg), had the same effect on gastric emptying, inducing a statistically significant acceleration for both the solid and the liquid phases when compared with that after administration of a placebo (4).
TABLE 1. Pharmacokinetic parameters for crystalline formulation of ethylsuccinate erythromycin after administration of a single oral dose of 1,000 mg and for amorphous formulation of ethylsuccinate erythromycin after administration of a single oral dose of 500 mg

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pharmacokinetic parameter</th>
<th>Crystalline formulation</th>
<th>Amorphous formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg · ml&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>AUC (µg · h · ml&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Crystalline formulation</td>
<td>1.10 ± 0.21</td>
<td>2.3 ± 0.6</td>
<td>7.03 ± 1.79</td>
</tr>
<tr>
<td>Amorphous formulation</td>
<td>0.88 ± 0.32</td>
<td>1.7 ± 0.66</td>
<td>4.77 ± 1.65</td>
</tr>
</tbody>
</table>

* Values represent means ± standard deviations.
* Significantly different from results for crystalline formulation (P < 0.05).
* Significantly different from results for crystalline formulation (P < 0.02).

The aim of the present study was to evaluate, by using a manometric recording, the effects of the two formulations of erythromycin ethylsuccinate on duodenojejunal motility in human volunteers during both the fed and the fasting states.

**MATERIALS AND METHODS**

**Subjects.** Ten healthy male volunteers (ages, 18 to 40 years) were included in the study. No subject was taking any medicine or had any history of gastrointestinal symptoms or surgery. The study was approved by the Ethical Committee of the Medical University of Saint Germain en Laye, France, and written informed consent was obtained from each subject.

**Study design.** During the present randomized controlled double-blind study, each subject underwent three manometric recording sessions with a washout period of at least 1 week between sessions. Over the course of the study, each subject received, in random order, a single dose of 500 mg of amorphous erythromycin ethylsuccinate, 1,000 mg of crystalline erythromycin ethylsuccinate, and an equivalent amount of placebo, with the three regimens being identical in appearance (Laboratory Belmac, Valbonne, France). Medications were taken by mouth at 6 p.m. with a standard dinner. Manometric recordings were started just before dinner and were then continued for a total of 14 h, until 8 a.m. the following morning. During the recording, the subjects remained in the supine position and were allowed to read and to watch television. Oral intake was strictly limited to the standard dinner and to the tablets of antibiotics or placebo. Each dinner consisted of one hard-boiled egg, minced beef, beans, mashed potatoes, one yogurt, apple compote, and water. The composition of the dinners remained constant: 750 kcal, 50% carbohydrate, 30% fat, and 20% protein.

**Antibiotic assays.** Serum erythromycin concentrations were determined at each session. Five milliliters of blood was collected before drug intake and at 0.25, 0.5, 1, 2, 3, 4, 6, and 12 h after intake. Immediately after centrifugation, plasma samples were stored at −80°C to prevent degradation until they were assayed. Erythromycin concentrations were determined by the agar diffusion method by using Micrococcus luteus ATCC 9341 as the test organism. Standards and samples were run in triplicate. The lower limit of detection was 0.05 µg/ml.

The calibration curves were linear for concentrations up to 2 µg/ml. Samples with concentrations higher than 2 µg/ml were diluted and assayed again. Intraday and interday coefficients of variation were less than 5%.

**Pharmacokinetic analysis.** The fitting procedure was performed with the non-linear Aipst pharmacokinetic software (8). The best fitting was obtained with a monophasic elimination with first-order absorption. The apparent elimination half-life (t<sub>1/2</sub>) was calculated as 1 ln2/β, where β is the constant terminal elimination.

The AUC was extrapolated to infinity. The maximum concentration in plasma (C<sub>max</sub>) and the time to reach C<sub>max</sub> (T<sub>max</sub>) were read directly from the observed data.

**Manometric recording.** Intraluminal pressures were recorded from four side-holes cut into an assembly of four polyvinyl tubes (internal diameter, 0.8 mm), as reported previously (3, 7). The sensors were located 3, 15, 25, and 35 cm from a rubber stop containing 2 ml of mercury and fixed to the tip of the tube to facilitate positioning. Radiopaque marks were inserted into the catheters at the tip and near the side holes in order to check the position of the assembly fluoroscopically. The probe was advanced so that the two proximal sensors were below the ligament of Treitz, i.e., in the jejunum. This probe was then fixed to the subject’s nose to avoid migration during the recording period. Recording lumens were continuously perfused with distilled water by using a low-compliance hydraulic infusion system. Pressures were measured by transducers (Gould Statham P23 ID) and were digitized with a frequency of 5 Hz per channel to be stored in the hard disk of a computer (AT; International Business Machines).

For each recording, two successive periods were considered for analysis: a fed (i.e., postprandial) state and a fasting (i.e., interdigestive) state. With the exception of phase 3 (defined below) measurements, duodenal and jejunal leads were analyzed separately. For each period and each lead, motor activity was studied over successive periods of 0.5 h each, according to methodologies described previously (14, 24). A computer program (system 2ERL; Society Lomatech, Rennes, France) was used to count the contractions and to calculate the area under the motility tracing curve (expressed in millimeters of mercury · second).

To allow comparison between recordings, a motility index was defined as the ratio of the area under the motility tracing curve (AUC) divided by time (in minutes) and expressed in millimeters of mercury · second · minute<sup>−1</sup> (1 mm Hg = 133.3 Pa).

The fed state was defined as irregular contractile activity observed in all leads, beginning with the onset of dinner and ending with the return of the first phase 3 (defined below) after the meal (12). Three parameters were analyzed: the duration of the period (in hours), the number of contractions (per half hour), and the motility index (as defined above).

The fasting state extended from the return of phase 3 after the meal to the end of the resting. The three phases of migrating motor complexes that characterized this period were recognized visually. Phase 1 was defined as a period of quiescence without visible contractions. Phase 2 was defined as intermittent motor activity occurring between phases 1 and 3. Phase 3 was characterized by a burst of uninterupted rhythmic and regular contractions lasting at least 2 min and migrating down the intestine at least over the two distal pressure sensors (12). Phases 1 and 2 were analyzed together by using the computer program to determine the number of contractions (per half hour) and the motility index. Phases 3 were analyzed manually, and the frequency (per hour), duration (in minutes), amplitude (in millimeters of mercury), and propagation velocity (in centimeter · minute<sup>−1</sup>) were calculated.

**Statistical analysis.** In this report, all values are expressed as means ± standard deviations. Pharmacokinetic parameters were compared by the Student t test (two-tailed) for paired values. Comparison of manometric parameters between the three groups was performed by using nonparametric tests for paired data; a Friedman test to look for an overall difference between all groups and then a Wilcoxon test when significance was observed. The statistical significance was assessed at a level of 0.05.

**RESULTS**

**Antibiotic assays.** The values of the pharmacokinetic parameters of the two formulations of erythromycin ethylsuccinate are provided in Table 1. Compared with the crystalline formulation, the amorphous formulation resulted in similar values of T<sub>max</sub> and t<sub>1/2</sub> but statistically significant lower values of C<sub>max</sub> and AUC.

**Manometric recordings.** The duration of the fed state was significantly shorter with the crystalline erythromycin ethylsuccinate formulation (4.37 ± 1.34 h) than with either the amorphous formulation (6.12 ± 2.68 h; P < 0.05) or the placebo (6.28 ± 2.07 h; P < 0.05); the difference between the last two regimens was not significant. During the fourth half hour of the fed state, the number of contractions as well as the motility index in the small intestine were lower with the crystalline erythromycin ethylsuccinate regimen than with the placebo regimen. The difference reached statistical significance only in the duodenal leads (Fig. 1 and 2). In contrast, there was no clear difference in the effects of amorphous erythromycin ethylsuccinate and placebo on duodenal and jejunal motility during any period of the fed state (Fig. 1 and 2).

During the fasting state, no motility parameter was significantly modified by either the crystalline or the amorphous erythromycin ethylsuccinate when compared with the placebo. Indeed, the number of contractions (Fig. 3), the motility index...
(Fig. 4), as well as the characteristics of the phases 3 (Table 2) were in the same range for each drug.

**Side effects.** Three subjects complained of episodes of abdominal pain; in each case, symptoms occurred during the crystalline erythromycin ethylsuccinate session. No other adverse reactions were described. No side effect was related to a particular motor event.

**DISCUSSION**

The aim of the study described here was to evaluate the effects of two different formulations of erythromycin ethylsuccinate on duodenojejunal motility during the fed and fasting states in human beings. For this purpose, a manometric recording, which is a safe and well-described method (24), was used. Because of important variations in motility in normal small intestines from one subject to another (14), each subject was considered his own control. A double-blind study was designed in order to avoid any subjectivity in the analysis of the motor patterns.

The two formulations of erythromycin ethylsuccinate were given by mouth with food because this method of administration is usually recommended for macrolide antibiotics, especially for those known to cause gastrointestinal side effects (1). To our knowledge, no previous data on the effect of erythromycin, given orally with food, on the small intestine are available. Prior motor studies have been done with subjects receiving the drug either intravenously (2, 18, 21, 23) or orally...
without food (19, 20). Since it has been shown that gastrointestinal motility can be affected after the administration of a single intravenous dose of erythromycin (18), sessions were not preceded by a treatment period and recordings were performed during the first oral administration. To increase the probability of observing digestive disorders, the highest recommended unit dose (i.e., 1,000 mg) of crystalline erythromycin ethylsuccinate was used; this was based on a dose relationship for the adverse effects of the drug (1).

The amorphous formulation was given at a dose of 500 mg, which has previously been considered to be at least equivalent to 1,000 mg of the crystalline formulation (4, 5). Indeed, the only two studies before this one that compared the pharmacokinetics of the two formulations both showed that, when compared with a 1,000-mg dose of the crystalline formulation, a 500-mg dose of the amorphous formulation provided similar AUCs and higher Cmax. Unfortunately, the serum erythromycin levels (Cmax and AUC) observed in our 10 volunteers were significantly lower for the amorphous form than for the crystalline form. We found no clear explanation for these unexpected results.

Our findings indicate that the crystalline formulation of erythromycin ethylsuccinate given in a single therapeutic oral dose with food decreased the duration of the fed pattern, decreased duodenal motility during the fourth half hour following ingestion, but had no significant effect during the fasting state. These results are in accordance with those presented in the literature (2, 18, 20, 21). Indeed, Sarna et al. (18) and Tack et al. (21) have previously shown that an intravenous infusion of either 200 or 500 mg of erythromycin lactobionate given during the fed state in healthy volunteers shortens the duration of the fed pattern and reduces the number of small bowel contractions for periods of 10 and 30 min after the start of infusion for the 200- and 500-mg doses, respectively. Interestingly, the inhibition of small intestinal motor activity during the fed state was observed in the two previous studies, as well as in ours, only shortly after the erythromycin concentrations peaked, i.e., immediately after infusion or about 1.5 h after ingestion. This suggests that the effect of erythromycin on the small intestine depends upon the level of the drug in serum.

The fact that only the duodenal motility index was modified during the session with the crystalline form of the drug is in agreement with previous data showing that an oral regimen of erythromycin of 500 mg administered every 8 h induced no changes in jejunal contractions during either the fed or the fasting state (20).

Several studies have demonstrated that erythromycin and other 14-membered macrolides stimulate propagated gastric motor activity by stimulating motilin receptors (6, 11, 15). The decrease in the duration of the fed state observed in our volunteers receiving the crystalline formulation has two possible explanations. The drug might influence duodenojejunal motility, e.g., via the same motilin-like mechanism; alternatively, the change in the motor pattern might be indirectly related to the acceleration of gastric emptying that we have shown previously (4). The mechanism of the inhibition of small intestinal motility remains unknown. Whatever the mechanism, the decrease in the duration of the fed period might contribute to an acceleration of transit, analogous to what is described in patients having undergone vagotomy for ulcer disease, in which the fed state is significantly shorter in those suffering from diarrhea after surgery than in those without diarrhea (22).

The duodenojejunal recordings failed to show specific motor patterns in our three subjects complaining of episodes of abdominal pain during the crystalline formulation session. Giant migrating or retrograde contractions in the small intestine have been described in dogs vomiting after receiving an oral or intravenous dose of erythromycin (13). In volunteers receiving an intravenous infusion of erythromycin lactobionate, no giant contractions or other specific patterns in the small intestine have been observed, while the sensations of abdominal pain and bloating were correlated with the occurrence of strong antral contractions (18). On the basis of these results, we postulate that the abdominal pain described by our subjects receiving the oral crystalline formulation of erythromycin ethylsuccinate was not related to any particular small intestinal motor pattern, but was more likely due to the stimulation of gastric motility shown previously (4).

One final important result was that the amorphous formulation of erythromycin ethylsuccinate given in a single oral dose of 500 mg induced no significant change in the duodenojejunal pattern compared with the pattern observed after administration of the placebo regimen. Two hypotheses can be raised to explain this result. The two formulations might act differently on the motility of the small intestine; however, it must be emphasized that, when given to healthy volunteers at the same doses used in the present study, the two forms have previously been shown to induce a similar dramatic acceleration of gastric emptying (4). Assuming a dose relationship for the effects of erythromycin on the motility of the small intestine, we cannot exclude the possibility that the amorphous formulation produced levels in the serum of our 10 volunteers that were too low, especially at the peak, to induce significant changes in the motor patterns.

In conclusion, the present study demonstrated that, when given orally with food at single therapeutic doses, the crystalline formulation of erythromycin ethylsuccinate induces changes in duodenal motility during the fed state, while the amorphous formulation does not.

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