A Comparison of the Gastrointestinal Side Effects of Two Forms of Erythromycin

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Background. The gastrointestinal (GI) side effects of erythromycin frequently limit therapy and compliance. PCE Dispertab, a more expensive brand of erythromycin, has been promoted as a well-tolerated new dosage form; however, no studies compare its GI side effects with those of other forms of erythromycin. We compared erythromycin PCE (particles-in-tablet) with E.E.S. (erythromycin ethylsuccinate) to determine whether there is a difference in the incidence and severity of GI side effects.

Methods. This was a multicenter, prospective, single-blind, randomized trial. Observers, but not participants, were blinded to the brand of erythromycin taken until after data analysis. We enrolled ambulatory patients who were at least 18 years old and weighed at least 90 lb for whom erythromycin had been prescribed at a dosage of 1.0 g/d. Subjects were given either the particles-in-tablet form, 333 mg three times daily, or the ethylsuccinate form, 400 mg four times daily, for 10 days and asked to report efficacy, compliance, and the frequency and severity of four GI symptoms (abdominal pain, nausea, vomiting, and diarrhea) in a daily diary.

Results. There were no significant differences between the particles-in-tablet and ethylsuccinate forms in incidence of GI side effects (63% and 61%, respectively), average daily GI symptom severity score (0.62 and 0.68, respectively), and GI-related discontinuations (8.5% and 8.2%, respectively). The incidence of moderate or severe nausea was 5% for the particles-in-tablet form and 25% for the ethylsuccinate form ($P < .001$).

Conclusions. Although ethylsuccinate caused a higher incidence of moderate to severe nausea, there were no differences in the three main outcome measures: incidence of GI side effects, average daily GI-symptom severity score, and GI-related discontinuations. Therefore, we support prescribing erythromycin ethylsuccinate as a first line of treatment because it costs less.

Key words. Erythromycin; gastrointestinal diseases; drug costs; cost control. *J Fam Pract 1992; 35:517-523.*

With over 30 million prescriptions annually, erythromycin is one of the most frequently prescribed oral antibiotics.[1–3] Gastrointestinal (GI) side effects commonly occur, however, with a reported incidence of 13% to 71%.[4,5] These symptoms, including nausea, vomiting, diarrhea, and abdominal pain, can lead to discontinuation rates ranging from 4% to 25%.[4,6] Erythromycin causes gastrointestinal side effects primarily by its motilin agonist activity on smooth muscle receptors in the gut.[7]

Pharmaceutical manufacturers have developed different erythromycin salts (eg, ethylsuccinate, stearate, estolate) and delivery forms in an effort to reduce the GI side effects. Erythromycin ethylsuccinate is generally better tolerated than erythromycin base.[4–6] Ellsworth et al[8] recently compared erythromycin base with ERYC, which is an enteric-coated pellet form of erythromycin base (Parke-Davis, Morris Plains, NJ), and found only minimal differences in GI side effect profiles.

PCE 333 Dispertab, a polymer-coated erythromycin particles-in-tablet form (Abbott Laboratories, Abbott Park, Ill), which was introduced in 1986, has been promoted as a "well-tolerated" new dosage form. There are, however, no published studies that compare the GI side effects, efficacy, or compliance rates of PCE with those of other forms of erythromycin.

According to the 1990 National Prescription Audit, the three most frequently prescribed brands of erythromycin are E.E.S. (erythromycin ethylsuccinate, Abbott Laboratories), PCE 333 Dispertab, and ERYC.[9] The

Submitted, revised, July 8, 1992.

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ISSN 0094-3509

average wholesale price of a 10-day course of PCE is $21.41, as compared with $8.77 for E.E.S.[10] Given the frequent use of these two brands and the $12.64 cost difference between them, it is important to know whether there is a clear clinical advantage in the more expensive preparation. This study prospectively compares the incidence and severity of GI side effects experienced with equivalent doses of PCE (particles in tablets) and E.E.S. (ethylsuccinate).

Methods

Recruitment and Entry Criteria

Our target population consisted of ambulatory patients of at least 18 years of age, weighing at least 90 lb, for whom erythromycin was prescribed at a dosage of 1.0 g/d (base equivalent). We enrolled patients from five ambulatory care offices in a metropolitan setting. Four offices were traditional group practices; the fifth was an urgent care center. All offices were staffed primarily with family physicians.

We excluded patients with any of the following: true allergy to erythromycin; potential for drug interaction (those taking theophylline, carbamazepine, warfarin, and digoxin); active GI disease or vomiting within the previous 24 hours; gastrointestinal motility disorders; prior GI bypass surgery; concomitant initiation of other medications with known GI side effects (eg, codeine in analgesic doses, nonsteroidal anti-inflammatory drugs, or aspirin); and pregnancy or lactation. Patients taking oral contraceptives agreed to use a barrier method of contraception during therapy and for the remainder of the menstrual cycle. Patients who had experienced previous nonallergic adverse effects from erythromycin were not excluded from the study. This study was approved by our institutional review board. All patients signed an informed consent before enrollment.

Study Design

This was a randomized, single-blind (for the investigator and prescriber), parallel, multicenter, prospective study. Subjects were told that the intent of the study was to determine patient response to two forms of erythromycin. They were not told that the specific study purpose was to compare the GI side effects of the two preparations.

The following baseline data were collected at the time of enrollment: age, weight, sex, education level, and diagnosis. Subjects were randomized in a 1:1 fashion using a computer-generated random list.

Subjects received either erythromycin particles in tablets, PCE Dispertab 333, three times a day (Abbott) or erythromycin ethylsuccinate, E.E.S. 400 Filmtab, four times a day (Abbott), for 10 days. Daily dosages in each group were equivalent to 1 g of erythromycin base. Subjects received a sealed envelope labeled with their study number. Each envelope had an inner prescription vial appropriately labeled containing either PCE 333 Dispertab #30 (labeled "Take 1 tablet 3 times a day for 10 days") or E.E.S. 400 Filmtab #40 (labeled "Take 1 tablet 4 times a day for 10 days"). Each vial had two auxiliary labels, "Take with food" and "Finish all this medication unless otherwise directed by prescriber." Tablets were not changed in any way from their standard appearance. A daily symptoms diary and postage-paid return mailer were also enclosed.

Study Instrument

We created a daily diary to collect serial self-reports on the following GI symptoms: nausea, vomiting, abdominal pain, and diarrhea. Four distractor symptoms (fever, chills, headache, and cough) were also included.[11] We asked subjects to rank the severity of each symptom daily using the following scale: none = symptom not present; mild = awareness of symptom but easily tolerated; moderate = discomfort enough to cause interference with usual activity; or severe = incapacitating with inability to do work or usual activity. Subjects were instructed to record any acute medications taken to relieve their symptoms. Subjects received verbal and written instructions to fill out one diary page for each day they took the medication. Day 1 was defined as the first day they took medication.

Subjects reported other study measures on a summary page at the end of the diary. We used this information to assess the number of medications taken for chronic conditions; the number of GI discontinuations; the number of GI-related calls to the physician; patient compliance; and erythromycin efficacy. Self-reported pill counts were verified by counting the number of returned tablets. To ensure compliance in returning the diary, two reminder cards, a telephone call, and a personalized letter were used when necessary. If diaries were returned incomplete, every attempt was made to contact the subject by telephone or letter to obtain the additional information needed.

To calculate a GI symptom severity score, we assigned the following numerical values to each self-reported GI symptom: none = 0, mild = 1, moderate = 2, and severe = 3. Next, each subject's total score was summed for the entire study. This total was then divided by the number of days the subject took the medication to

Table 1. Baseline Comparison of Treatment Groups for Subjects Returning Diaries

Characteristics	Treatment Group: Erythromycin Particles-in-Tablet (n = 131)	Treatment Group: Erythromycin Ethylsuccinate (n = 121)	*P* Value
Women, No. (%)	91 (69)	69 (57)	.040
Age, y (± SD)	41.5 (14.7)	40.1 (13.9)	.453
Weight, lb (± SD)	165.3 (37.7)	170.1 (38.7)	.325
No. (%) of subjects with			.993
Bronchitis	74 (56)	69 (57)	
Pharyngitis/tonsillitis	25 (19)	22 (18)	
Sinusitis	15 (11)	13 (11)	
Pneumonia	5 (4)	6 (5)	
Other	12 (9)	11 (9)	
No. (%) of subjects taking medications for chronic conditions	53 (40)	47 (39)	.755
Average number of medications taken (range)	1.0 (0–10)	0.72 (0–6)	.144
No. (%) of subjects at each level of education			.427
≥ College	75 (57)	77 (64)	
High school graduate	41 (31)	34 (28)	
< High school graduate	15 (11)	9 (7)	

determine the GI symptom severity score. This allowed us to calculate a severity score even for those subjects who did not complete the 10-day course of therapy. We piloted this diary with 20 subjects to confirm subjects' ability to use the instrument.

Statistical Analysis

A sample size calculation showed that 120 subjects per group would be sufficient to detect a decrease in the GI side-effect rate from 30% in the ethylsuccinate group to 15% in the particles-in-tablet group with a power of .80 and alpha equal to .05. Allowing for the 20% lost-to-follow-up rate that we incurred in our pilot study, we increased the sample size to 144 patients in each group.

Standard statistical methods were used.[12] For comparing interval scale measurements between the two groups, the Student's *t* test was used when the data were normally distributed. For data that did not have a normal distribution, such as number of medications for chronic conditions, daily severity scores, and percentage of pills taken, the Wilcoxon rank-sum test was employed. For categorical data, the chi-square test was used. When analyzing dichotomous outcome variables (eg, incidence of any GI side effect, discontinuation of the medicine, and incidence of any moderate or severe side effect), stepwise logistic regression (computer program BMDP2L) was used to adjust for baseline differences.[13] For all analyses, a *P* value of less than .05 was considered statistically significant.

Results

Subjects

A total of 288 patients (144 in each group) were enrolled in the study from January to June, 1991. Four subjects from the ethylsuccinate group and three subjects from the particles-in-tablet group were excluded from analysis because they did not meet the enrollment criteria. This left an initial enrollment of 141 subjects in the particles-in-tablet group and 140 subjects in the ethylsuccinate group. Ninety percent of those enrolled returned diaries. Nineteen subjects in the ethylsuccinate group and 10 in the particles-in-tablet group ($P = .074$) did not return their diaries. This left 121 (86%) diaries in the ethylsuccinate group and 131 (93%) diaries in the particles-in-tablet group for analysis. Four of these diaries were only partially complete (three in the particles-in-tablet group and one in the ethylsuccinate group).

There were no demographic differences between the groups we intended to treat; however, when all diaries were returned, there were significantly more women in the particles-in-tablet group ($P = .04$). Table 1 compares the treatment groups at baseline for the 252 subjects who returned diaries.

Gastrointestinal Symptoms and Side Effects

There were no significant differences between groups in any of the following: incidence of GI side effects, daily

Table 2. Gastrointestinal Outcome, by Treatment Group

Response	Treatment Group: Erythromycin Particles-in-Tablet (n = 131)	Treatment Group: Erythromycin Ethylsuccinate (n = 121)	*P* Value
Subjects with any GI side effect, No. (%)	82 (63)	73 (60)	.343
GI-related discontinuations, No. (%)	11 (8.4)	10 (8.3)	.970
Daily severity score			.890
Mean (± SD)	0.616 (0.93)	0.685 (1.133)	—
Median	0.3	0.3	—
Subjects telephoning MD with GI-related side effects, No. (%)	2 (2)	9 (7)	.047

GI-symptom severity score, and GI-related discontinuations. Most patients reported one or more GI side effects while taking erythromycin. Table 2 and Figure 1 detail the GI outcomes by treatment group. The distribution of daily GI-symptom severity scores is in Figure 2.

The mean GI-symptom severity score was higher for subjects who discontinued therapy because of GI side effects (2.30) than for the rest of the treatment groups (0.498) ($P = .001$). Subjects who self-administered medications for GI symptoms had a higher mean GI-symptom severity score (1.393) than those who did not (0.602) ($P = .007$).

According to a stepwise logistic regression, age, weight, education level, diagnosis, number of medications for chronic conditions, and form of erythromycin taken did not determine which subjects had any GI side effects. Subjects taking a greater number of medications for chronic conditions, however, were more likely to subsequently discontinue the erythromycin ($P = .040$).

The ethylsuccinate group was more likely to have a moderate or severe side effect according to the logistic regression ($P = .034$). Further analysis of each moderate to severe GI side effect, however, revealed that nausea was the only side effect that occurred significantly more often in the subjects taking ethylsuccinate (25%) compared with subjects in the particles-in-tablet group (5%) ($P < .001$) (Figure 3). Most of these subjects reported having this level of nausea for 1 day. There were no significant differences in the incidence of moderate to severe abdominal pain, diarrhea, or vomiting.

Seven percent of the ethylsuccinate group and 2% of the particles-in-tablet group ($P = .047$) telephoned the physician regarding their GI side effects. Eight of these

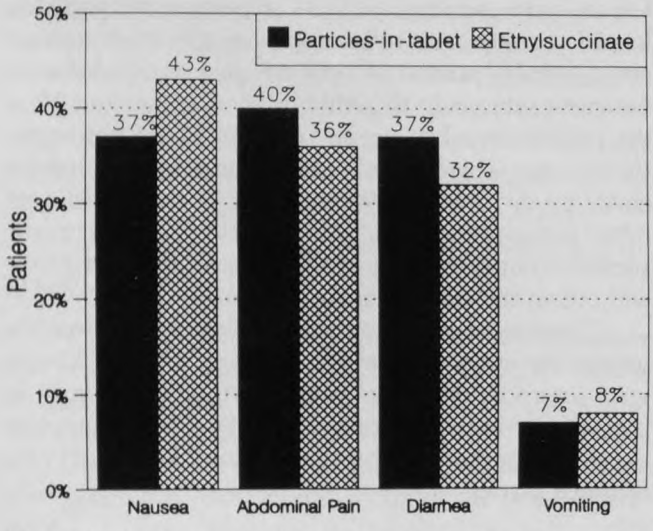

Figure 1. Incidence of all gastrointestinal side effects (mild, moderate, or severe) reported by patients taking erythromycin (either particles-in-tablet form or ethylsuccinate). Statistical comparison revealed no significant differences between the two groups of patients.

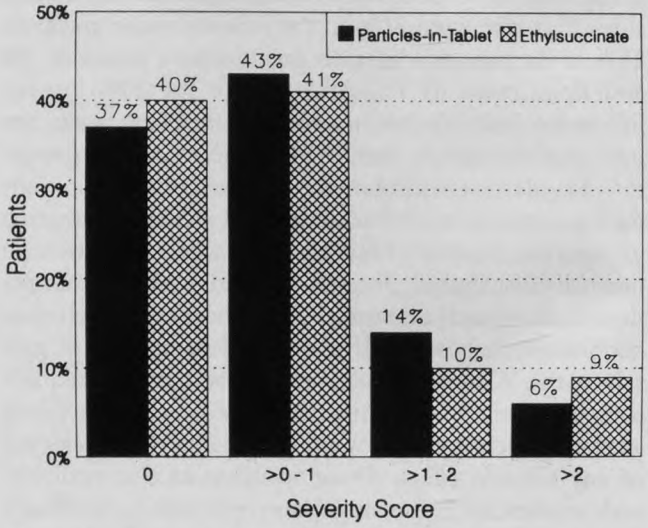

Figure 2. Average daily gastrointestinal-symptom severity score reported by patients taking either the particles-in-tablet or the ethylsuccinate form of erythromycin. Statistical comparison revealed no significant differences.

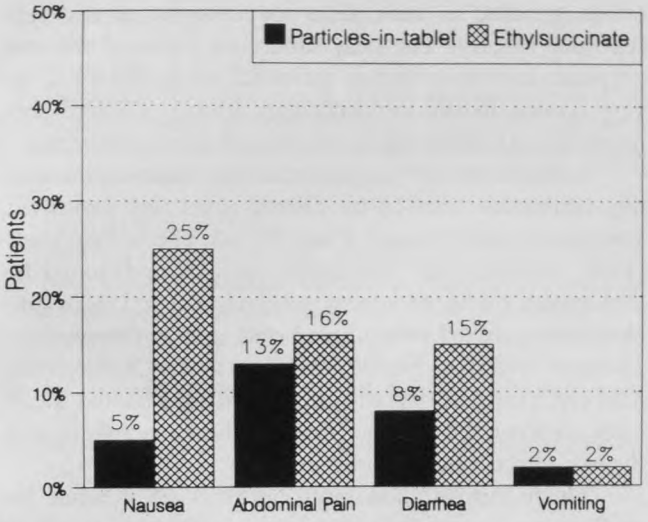

Figure 3. Incidence of moderate and severe gastrointestinal side effects reported by patients taking either the particles-in-tablet or the ethylsuccinate form of erythromycin. Statistical comparison revealed a significant difference ($P < .001$) only in the reported incidence of nausea between the two groups of patients.

11 calls (73%) were from ethylsuccinate subjects who experienced moderate to severe nausea.

Efficacy

Self-reported efficacy was equal between the treatment groups ($P = .294$). For subjects taking the particles-in-tablet form, the efficacy rates were 39% completely cleared up, 48% improved, and 12% not improved. For those taking the ethylsuccinate form, the efficacy rates were 49% completely cleared up, 39% improved, and 12% not improved.

Compliance

There was no difference in compliance. The ethylsuccinate group took 89% of the prescribed erythromycin, and the particles-in-tablet group took 88% ($P = .851$). Seventy-eight percent of the particles-in-tablet subjects and 77% of the ethylsuccinate subjects ($P = .875$) took all medication.

Discussion

This study was designed to investigate the incidence and severity of four gastrointestinal side effects associated with taking erythromycin in particles-in-tablet form compared with the ethylsuccinate form. Overall, there was no significant difference in the incidence or severity of GI side effects. Sixty-three percent of subjects taking the particles-in-tablet form reported GI side effects compared with 60% who were taking the ethylsuccinate form ($P = .343$). Mean and median GI symptom severity scores were also the same.

Although the ethylsuccinate group reported a higher incidence of moderate and severe nausea (25% as compared with 5%; $P < .001$), compliance and discontinuation rates were identical. This indicates that the nausea reported by subjects taking ethylsuccinate did not cause them to reduce or stop their medication any more frequently than subjects taking the particles-in-tablet form. This may be due to the short duration of the symptom. Efficacy rates were also the same. This means that, despite GI side effects, subjects in both groups perceived themselves equally improved or cured of their primary illness.

Ethylsuccinate subjects (primarily those with moderate to severe nausea) called the physician about GI side effects more frequently than particles-in-tablet patients. However, the overall numbers are small, representing less than 5% of all subjects enrolled in this study. At this rate, the actual difference in volume of GI-related patient calls in a practice setting would be negligible. We therefore conclude that this result, although statistically significant, is of little clinical importance.

This study was blinded for the observers only. After careful consideration, we selected this as the most practical and realistic design. Blinding subjects to the erythromycin brand would have required manufacturing special tablets or using matching placebos in addition to the active drug. This would require taking a tablet seven times a day. By using the actual dosage forms, we were able to evaluate compliance with both dosing schedules.

Subjects who had previously taken erythromycin may have remembered the brand name or recognized the tablets after opening their study packets. This may have negatively biased subjects who had previous adverse effects with either brand of erythromycin, particularly ethylsuccinate, which has been on the market longer. In this case, our study would have favored the particles-in-tablet formulation. Because we did not identify subjects who had previous nonallergic adverse reactions to the two brands of erythromycin, we cannot confirm or refute the possibility of recognition bias.

This study shows a relatively high incidence of subject-reported GI side effects, although within the range reported in a previous study.[5] This could be due to the data-collection instrument. The diary contained daily entries specifically asking for the presence of four GI symptoms. Although we included four non-GI symptoms in the diary as distractors, this method may have been more sensitive than open-ended questioning or telephone surveys.

We refined the subject diary as a result of our pilot study; however, it was not possible to conclusively test its validity or reliability. Nevertheless, our results clearly demonstrate the internal validity of the diary and the severity scores. Subjects who stopped because of GI side effects had significantly higher GI-symptom severity scores than the rest of the subjects in the treatment groups. Also, subjects who self-administered medications for GI symptoms had significantly higher GI-symptom severity scores than those who did not.

The compliance rate for both groups was higher than in general practice[14] but similar to another randomized clinical trial with erythromycin.[8] Despite the different dosing schedules, 77% of the ethylsuccinate group and 78% of the particles-in-tablet group reported taking all their medications. These high compliance rates may have resulted from our methods. We asked physicians to enroll patients who were likely to be compliant with completion of the diary. Also, we used pill counts, which tend to overestimate compliance compared with rates obtained using electronic surveillance devices.[15]

More subjects in the ethylsuccinate group did not return diaries, although this was not statistically significant (19 as compared with 10, $P = .074$). Even assuming that all such subjects from both groups discontinued medication because of GI side effects, the difference in discontinuation rates due to GI side effects would still not be statistically significant.

Among subjects who returned diaries, there were more women in the particles-in-tablet group (69% as compared with 57%; $P = .040$). When studied using logistic regression analysis, sex did not account for any differences in the incidence of GI side effects.

Subjects were instructed to take their erythromycin with meals. This instruction was given for several reasons. First, previous studies have obtained conflicting results for erythromycin blood levels when the medication was taken while fasting or postprandially.[16] Second, the study by Ellsworth et al[8] comparing enteric-coated with nonenteric-coated erythromycin was criticized for instructing subjects to take the medication on an empty stomach.[17] Third, patient information for both preparations states that the medications can be administered without regard to meals.[18] Finally, an informal survey of pharmacists and primary care practitioners in our area revealed that the common clinical practice was to administer erythromycin with food. Therefore, the instructions to subjects in this study followed generally accepted practice.

After decades of use, erythromycin, an extremely useful antibiotic, continues to cause considerable GI side effects. This study shows little clinical advantage for the particles-in-tablet form, a newer, more expensive preparation. Gastrointestinal side effects were comparable between groups, as were rates for compliance and self-reported efficacy. The only difference between the two preparations was a higher incidence of moderate to severe nausea in the ethylsuccinate group. Despite this, there was no difference in GI-related discontinuations.

A recent review[7] suggests that investigational macrolide antibiotics with 16-membered rings (eg, josamycin, spiramycin) may produce fewer GI side effects than traditional 14-membered macrolides such as erythromycin.[7] Preliminary studies show that the newly released macrolides clarithromycin, a 14-membered ring, and azithromycin, a 15-membered ring, may also produce fewer GI side effects than erythromycin.[19] Well-controlled studies should specifically compare the GI side effects of these macrolides with the side effects of erythromycin.

Thirty-four million prescriptions are written for erythromycin annually, according to a 1984 estimate.[3] At this rate, up to $430 million could be saved annually by prescribing erythromycin ethylsuccinate instead of erythromycin particles-in-tablets. Although the particles-in-tablet form could be considered as an alternative for patients who specifically complain of moderate to severe nausea, there appears to be no advantage for patients complaining of abdominal pain, diarrhea, or vomiting. In this era of cost constraints, it behooves all practitioners to avoid prescribing more expensive medications unless proven advantages exist.

Acknowledgments

Supported by a grant from the Charlotte-Mecklenburg Health Services Foundation.

Our sincere thanks to the nursing, pharmacy, and clerical staffs and the physician subinvestigators affiliated with the following practices who made this multicenter study possible: *Arboretum Urgent Care*: R.W. Watkins, A.F. Titus; *Carmel Family Physicians*: T. Barringer, R. Almquist, R.E. Arnold, J.B. Walthall, B. Gesing, L.M. Teigland, D. Honeycutt; *Davidson Clinic*: S. Carperos, R. Beamon, W.G. Katibah, S.K. Mange; *Metrolina Family Physicians, Nalle Clinic*: G. Hall, J. Huff. We also acknowledge the support of the residents and fellow faculty members at the *Family Practice Center, Carolinas Medical Center*: D. Menscer, M.N. Hall, J.L. Sigmon; and staff members Cheryl Pulliam for graphics and Rebecca Warren for data entry.

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