Prospective Comparison of Patient Tolerance to Enteric-Coated vs Nonenteric-Coated Erythromycin

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Erythromycin base and its salts are frequently used in clinical practice. The most frequent side effects of oral erythromycin preparations are gastrointestinal. Various salts and enteric coatings have been developed without adequate comparison in regard to gastrointestinal side effects. The overall incidence of gastrointestinal side effects (abdominal pain and cramps, nausea, vomiting, diarrhea, and gas) of two common erythromycin base formulations, Erythromycin Base Filmtab (Abbott), a nonenteric-coated base tablet, and Eryc (Parke-Davis), a pelletized, encapsulated, enteric-coated base capsule, were compared in 368 adults at two dosage levels (1 g/d and 2 g/d). Minimal differences were found when target symptoms were compared by preparation coating. In contrast, subjects receiving erythromycin at the 2-g/d dosage level reported higher incidence rates for each of the target symptoms, regardless of product coating, than did those patients treated at the 1-g/d dosage level. Enteric coating of erythromycin base offers little protection from the common dose-related gastrointestinal adverse effects of oral erythromycin. **J FAM PRACT 1990; 31:265-270.**

Erythromycin base and its salts are frequently used in clinical practice for the treatment of respiratory, skin, and soft tissue infections and as an alternative drug for penicillin-sensitive organisms in penicillin-allergic patients.[1] The most frequent side effects of oral erythromycin preparations are gastrointestinal and are usually dose related. These side effects include anorexia, nausea, vomiting, abdominal pain, and diarrhea. Patient compliance in the presence of these symptoms may be decreased, or patients may resort to taking the drug with food. The absorption of erythromycin base is markedly decreased when given concomitantly with food and may be no better than total default.[2–4]

In an effort to decrease side effects and increase patient acceptance, various salts of erythromycin (stearate, estolate, ethyl succinate) and enteric coatings have been developed.[5] The differences between these erythromycin salts and preparations with regard to gastrointestinal adverse effects, however, have not been extensively studied. Most of the available side effect data are derived from patient-initiated reports of side effects during efficacy or bioavailability studies.[6–10] A study was designed to compare prospectively the overall incidence of gastrointestinal side effects of two erythromycin formulations: Erythromycin Base Filmtab (Abbott), a base tablet with a nonenteric film coating and Eryc (Parke-Davis), a pelletized, encapsulated, base capsule with an enteric film coating.

METHODS

Consenting patients were interviewed by one of the investigators regarding reasons for therapy, concomitant disease states, and concurrent drug therapy. Patients with a history of unstable peptic ulcer disease or severe renal or hepatic disease or those taking theophylline were excluded. Concomitant use of digitalis glycosides, narcotic analgesics, nonsteroidal antiinflammatory agents or other drugs with a high incidence of gastrointestinal toxicity was noted but did not exclude entrance to the study. Patients

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TABLE 1. COMPARISONS* OF PATIENT GROUPS TAKING ENTERIC-COATED AND NONENTERIC-COATED ERYTHROMYCIN

Demographic Characteristics	Nonenteric-Coated		Enteric-Coated	
	1 g/d	2 g/d	1 g/d	2 g/d
Number of subjects (n)	106	73	98	80
Sex (% male)	44.3	37.0	39.8	48.8
Age, years	38.3†	33.3	34.6	33.6
(±SD)	(±13.1)	(±11.9)	(±10.0)	(±12.1)
Education (% high school graduates)	45.3	60.3	64.3	55.0
Marital status (% married)	42.5	54.8	43.8	38.8
Menstruating (%)	5.7	5.5	5.1	6.3
Prior erythromycin therapy (%)	54.7	53.5	58.1	44.4
Prior erythromycin-induced gastrointestinal side effects (%)	13.2	9.6	1.0	0.0
Number of additional medications	1.2	0.9	0.9	1.3
(±SD)	(±1.5)	(±1.1)	(±1.2)	(±1.4)
Dropouts (% of initial sample)	0	6.4†	3.9	2.4
Administered on empty stomach (%)	59.4	64.3	64.4	70.3
Compliance (% of total dosage)	94	84†	92	82†
(±SD)	(±16)	(±31)	(±19)	(±30)

*Mean numbers
†$P \leq .05$

were randomly assigned to one of two treatment groups at the 250-mg or 500-mg dosage level, as prescribed by their personal physician. The drug regimens for the four treatment groups were (1) erythromycin base in a nonenteric-coated tablet, Erythromycin Base Filmtab (Abbott), 250 mg four times daily on an empty stomach; (2) erythromycin base in a nonenteric-coated tablet, Erythromycin Base Filmtab (Abbott), two 250-mg tablets (500 mg) four times daily on an empty stomach; (3) erythromycin base in an enteric-coated capsule, Eryc (Parke-Davis), 250 mg four times daily on an empty stomach; and (4) erythromycin base in an enteric-coated capsule, Eryc, two capsules (500 mg) four times daily on an empty stomach. Prescriptions provided a 7- to 14-day supply of therapy with instructions to take the medication 30 to 60 minutes before meals. Drugs were provided in unit of use containers.

Patient tolerance and compliance information was obtained from two sources: a telephone interview and a combined compliance log and side-effect diary. The telephone interview was conducted on day 3 and day 7 of therapy using an unobtrusive but structured format. Questions regarding gastrointestinal side effects were mixed with questions regarding symptoms not associated with erythromycin use. These "distractor" questions usually pertained to the underlying infectious process and included such symptoms as nasal congestion, cough, and drowsiness. Subjects were asked to score the severity of each symptom as none, mild, moderate, or severe. Subjects were also asked to indicate their degree of compliance to the four times daily regimen and timing of medication administration (ie, on an empty stomach).

The combined compliance log and side-effect diary allowed patients to track target symptoms and chart medication administration on a daily basis. A self-addressed, stamped envelope was provided so that the diary and unused medications could be returned for validation and pill count.

Differences in frequency of occurrence of individual gastrointestinal side effects between the two different erythromycin preparations and the two different dosage levels (1 g/d vs 2 g/d) were explored by chi-square analysis using CRUNCH, a statistical software package for personal computers.[11]

RESULTS

Group Descriptions

Three-hundred sixty-eight patients with a mean age of 35 years gave informed consent and were enrolled into the study. Data were analyzed for 357 subjects. Eleven (3%) subjects dropped from the study for the following reasons: poor compliance (4), enrolled inappropriately (2), change in antibiotic therapy (1), voluntary drop—patient recovery (1), and voluntary drop—unknown reason (3). There was no difference in the number of dropouts from the enteric-coated and nonenteric-coated groups (enteric-coated 6 [6.3%] vs nonenteric-coated 5 [6.4%]). There was, however, an increased dropout rate in the 2-g/d, nonenteric-coated product group as compared with the 1-g/d nonenteric-coated group (6.4% vs 0%; $P \leq .01$).

Demographic and compliance characteristics in the enteric-coated and nonenteric-coated product groups were

TABLE 2. COMPARISON OF REPORTED SYMPTOMS (MILD OR GREATER) (%), BY PREPARATION COATING

	Day 3		Day 7	
	Nonenteric-Coated	Enteric-Coated	Nonenteric-Coated	Enteric-Coated
Erythromycin, 1 g/d				
Telephone interview	(n = 204)		(n = 204)	
Abdominal pain	12.3	18.4	13.2	20.4
Abdominal cramps	7.6	11.2	15.1	20.4
Nausea	15.1	17.4	9.4	17.4
Vomiting	0	0	3.8	6.1
Diarrhea	9.4	14.3	17.0	15.3
Gas	26.4	30.6	24.5	23.5
Side-effect diary	(n = 166)		(n = 158)	
Abdominal pain	14.3	32.1*	12.2	15.8
Nausea, vomiting	14.3	22.0	3.7	14.3*
Diarrhea	12.9	18.5	8.5	4.0
Erythromycin, 2 g/d				
Telephone interview	(n = 153)		(n = 153)	
Abdominal pain	45.2*	27.5	31.5	43.8
Abdominal cramps	34.3	32.5	34.3	42.5
Nausea	39.7	33.8	37.0	37.5
Vomiting	9.6	20.0	24.7	30.0
Diarrhea	32.9	28.7	39.7	41.3
Gas	46.6	38.8	45.2	50.0
Side-effect diary	(n = 115)		(n = 102)	
Abdominal pain	48.3	48.2	13.5	30.0
Nausea, vomiting	38.3	29.1	17.3	13.7
Diarrhea	32.1	32.1	17.3	16.0

*$P \leq .05$

compared at the two different dosage levels, supporting valid randomization (Table 1). There was a slightly older mean age in the 1-g/d nonenteric-coated group than in the 2-g/d group.

Compliance, based on telephone interview, compliance log, and pill count, was not different between the enteric-coated and nonenteric-coated groups, but a significant difference was evident when the 1-g/d and 2-g/d dosage was compared. Compliance exceeded 90% in the 1-g/d group and was about 10% lower (82% to 84%) in the 2-g/d group ($P \leq .05$). Despite printed and verbal instructions to subjects to ingest study erythromycin on an empty stomach, 30 to 60 minutes before eating and at bedtime, 30% to 40% did not comply with these instructions. There were no differences, however, between groups in the incidence of noncompliance as a result of these medication administration timing errors.

Patient Tolerance to Erythromycin

Side Effects Comparison by Tablet Coating. When the number of patients reporting specific target symptoms (abdominal pain and cramps, nausea, vomiting, diarrhea, and gas) was compared by preparation coating at the 1-g/d dosage level, minimal differences were found (Table 2). During the telephone interview after 3 and 7 days of therapy, there were no significant differences in adverse effects rated mild or greater in severity between the nonenteric-coated and the enteric-coated product. Subjects returning compliance log and side-effect diaries reported more abdominal pain during the first 3 days (32.1% vs 14.3%) and more nausea and vomiting during days 4 through 7 (14.3% vs 3.7%) in the enteric-coated product groups.

Although a difference favoring the 2-g/d enteric-coated preparation could be demonstrated for abdominal pain on day 3 (42.2% vs 27.5%), side effects were prominent with both preparations. Side-effect diary data did not support this difference, and twice as much vomiting was associated with the enteric-coated preparation (20% vs 9.6%) at the same time and dosage. Subjects receiving 2 g/d in the enteric-coated product group reported more abdominal pain later in the treatment course on their side-effect diaries than did subjects in the nonenteric-coated product group (30% vs 13.5%).

Side Effect Comparison by Dosage Level. In contrast to comparisons done by product coating, substantial differences were found when the number of patients reporting specific target symptoms was compared by daily dosage (Figure 1). The enteric coating of erythromycin base offered little protection from dose-related gastrointestinal side effects. During the telephone interview after 3 days of

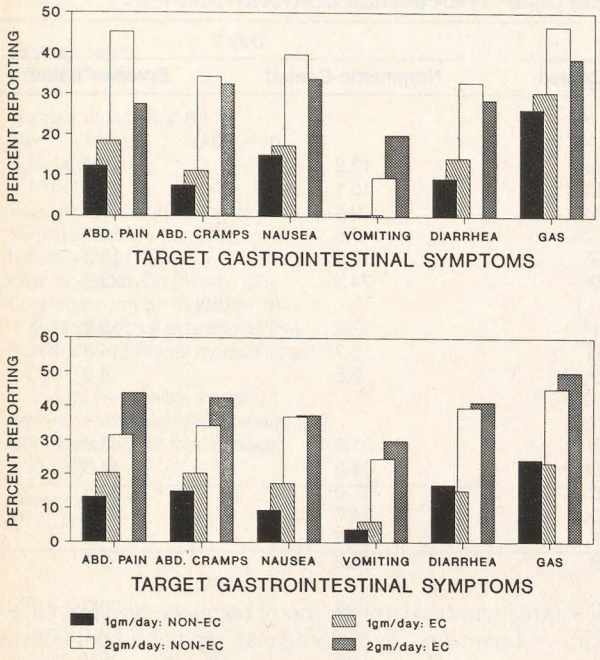

Figure 1. Erythromycin-induced gastrointestinal adverse effect comparisons by dosage level and preparation on day 3 (top graph) and day 7 (bottom graph). (1 g/d = 250 mg four times daily; 2 g/d = 500 mg four times daily; NON-EC—nonenteric-coated product; EC—enteric-coated product.)

therapy, subjects receiving erythromycin at the 2-g/d dosage level reported higher incidence rates for each of the target symptoms, regardless of product coating, than did those patients treated at the 1-g/d dosage level (Table 3). In all but two cases these differences were statistically significant. The exceptions, where differences did not reach statistical significance, were abdominal pain and gas in the enteric-coated group. After 7 days of therapy, these differences persisted.

Analysis of returned compliance logs and side-effect diaries gave results that corresponded to telephone interviews during the first 3 days for patients on the nonenteric-coated product. Differences for patients on the enteric-coated product showed similar trends but were not statistically significant during the first 3 days. Through days 4 through 7 the difference in the incidence of nausea and vomiting for the nonenteric-coated product and the difference in the incidence of diarrhea for the group receiving enteric-coated product reached statistical significance.

DISCUSSION

In this study the frequency of gastrointestinal side effects was compared for varying doses of nonenteric-coated and enteric-coated erythromycin preparations. No significant differences were found in the frequency of side effects occurring at comparable dosages of the nonenteric-coated and enteric-coated erythromycin preparations studied. There was, however, a significant difference in the occurrence of side effects as a function of the dosage level of erythromycin, irrespective of preparation ($P \leq .01$). Erythromycin base prescribed at a dosage of 500 mg, 4 times daily (2 g/d), was accompanied by gastrointestinal side effects (abdominal pain and cramps, diarrhea, nausea, and vomiting) nearly one third of the time.

The dropout rate was low overall. There were significantly more dropouts in the nonenteric-coated 2-g/d vs the nonenteric-coated 1-g/d dosage regimen (6.4% vs 0%; $P \leq .01$), but there was no difference in dropouts between the enteric-coated and nonenteric-coated groups. If the underlying reason for the "poor compliance" and "unknown reason" dropouts was assumed to be severe gastrointestinal side effects, the differential dropout rate mitigates against detection of significant differences in the frequency of adverse effects. Yet differences were nevertheless observed, and if patients had remained enrolled, the observed differences would have been even more dramatic.

These results are similar to those of the work of others. Carter et al[12] demonstrated that, in an open, nonrandomized, post-treatment questionnaire study, erythromycin 1 g/d was frequently associated with gastrointestinal disturbances and that an enteric-coated tablet was associated with more severe adverse effects and required discontinuation more frequently. Bleeker[9] found a 50% higher incidence of gastrointestinal side effects with an enteric-coated erythromycin base capsule compared with erythromycin stearate tablets in a randomized study in 40 patients with acne. Bowie et al[8] were forced to alter protocol early in their efficacy study because of an unacceptable frequency of side effects associated with erythromycin base at 2 g/d.

One enteric-coated preparation has been shown to produce serum concentrations greater than those resulting from erythromycin stearate capsules.[13] Advertisements for various formulations of oral erythromycins stress these differences in serum concentrations. Claims and counterclaims are difficult to evaluate, partly because similar studies conducted by different investigators have, in some instances, yielded opposite results.[14] In general, however, all of the different preparations are usually absorbed well enough to reach serum concentrations higher than those needed to inhibit susceptible pathogens.

TABLE 3. COMPARISON OF REPORTED SYMPTOMS (MILD OR GREATER) (%), BY DOSAGE LEVEL

	Day 3		Day 7	
	1 g/d	2 g/d	1 g/d	2 g/d
Nonenteric Coating				
Telephone interview				
Abdominal pain	12.3	45.2*	13.2	31.5*
Abdominal cramps	7.6	34.3*	15.1	34.3*
Nausea	15.1	39.7*	9.4	37.0*
Vomiting	0	9.6*	3.8	24.7*
Diarrhea	9.4	32.9*	17.0	39.7*
Gas	26.4	46.6*	24.5	45.2*
Side-effect diary				
Abdominal pain	14.3	48.3*	12.2	13.5
Nausea, vomiting	14.3	39.3*	3.7	17.3†
Diarrhea	12.9	32.2*	8.5	7.3
Enteric Coating				
Telephone interview				
Abdominal pain	18.4	27.5	20.4	43.8*
Abdominal cramps	11.2	32.5*	20.4	42.5*
Nausea	17.4	33.8*	17.4	37.5*
Vomiting	0	20.0*	6.1	30.0*
Diarrhea	14.3	28.7*	15.3	41.3*
Gas	30.6	38.8	23.5	50.0*
Side-effect diary				
Abdominal pain	32.1	48.2	15.8	30.0
Nausea, vomiting	22.0	29.1	14.3	13.7
Diarrhea	18.5	32.1	4.0	16.0†

*$P \leq .01$
†$P \leq .05$

The main difficulty with oral erythromycin is not bioavailability, but gastrointestinal intolerance.[14] Gastrointestinal adverse effects are common with oral erythromycin formulations and are dose related. Incidence figures range from 7% to 73%.[6–10,12,15] Most of the available side effect data are derived from patient-initiated reports of side effects during efficacy or bioavailability studies.[6–10] Inadequate data are available in adults to indicate that any erythromycin salt or any one brand of erythromycin causes less gastrointestinal toxicity than any other. This prospective study further substantiates earlier, less rigorous reports.

There were no differences in the incidence of noncompliance resulting from medication administration timing errors between groups. Thirty percent to 40% of subjects took erythromycin with food despite verbal instructions to the contrary. The prevalence of this noncompliance may have added negative bias against the enteric-coated product groups. Studies have documented unaltered bioavailability of enteric-coated pellets of erythromycin base in the presence of food and markedly decreased absorption of nonenteric-coated erythromycin base.[2–4,16,17] Erythromycin stimulates smooth muscle and gastrointestinal motility, and gastrointestinal reactions have been reported even with intravenous administration of erythromycin.[18] The decreased rate of compliance seen in the 2-g/d dosage groups (Table 1) may be related to the increased serum level and subsequent higher incidence of gastrointestinal side effects.

Erythromycin is an extremely useful antibiotic. Prevalent gastrointestinal toxicity associated with its use, however, often limits its utility. From these data, obtained from an unobtrusive telephone questionnaire on days 3 and 7 of therapy and a combined compliance log and side-effect diary completed by the patient daily, there appears to be little advantage to prescribing an enteric-coated erythromycin base preparation, particularly if it is more expensive. Clinicians should be aware of the high incidence of gastrointestinal side effects associated with erythromycin (especially at 2 g/d) and should provide prescriptions that allow the clinician the option of decreasing the dose (ie, prescribe 250 mg tablets or capsules, "take two . . . ") should gastrointestinal adverse effects occur.

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References

1. Carter BL, Helling DK, Jones ME, et al: Multicenter study of family physician prescribing. J Fam Pract 1984; 19:497–501
2. Fraser DG: Selection of an oral erythromycin product. Am J Hosp Pharm 1980; 37:1199–1205
3. Boggiano BG, Gleeson M: Gastric acid inactivation of erythromycin stearate in solid dosage forms. J Pharm Sci 1976; 65:497–502
4. Welling PG, Huang H, Hewett PF, Lyons LL: Bioavailability of erythromycin stearate: Influence of food and fluid volume. J Pharm Sci 1978; 67:764–766
5. Meade RH: Drug therapy reviews: Antimicrobial spectrum, pharmacology, and therapeutic use of erythromycin and its derivatives. Am J Hosp Pharm 1979; 36:1185–1189
6. Brown ST, Pedersen AHB, Holmes KK: Comparison of erythromycin base and estolate in gonococcal urethritis. JAMA 1977; 238:1371–1373
7. Shanson DC, Tidbury P, McNabb WR, Tadayon M: The pharmacokinetics and tolerance of oral erythromycin stearate compared with erythromycin ethylsuccinate: Implications for preventing endocarditis. J Antimicrob Chemother 1984; 14:157–163
8. Bowie WR, Manzon LM, Borrie-Hume CJ, et al: Efficacy of treatment regimens for lower urogenital *Chlamydia trachomatis* infection in women. Am J Obstet Gynecol 1982; 142:125–128
9. Bleeker J: Tolerance and efficacy of erythromycin stearate tablets versus enteric-coated base capsules in the treatment of patients with acne vulgaris. J Intern Med Res 1983; 11:38–41
10. Kuder HV: Propionyl erythromycin. A review of 20,525 case reports for side effect data. Clin Pharmacol Ther 1960; 1:604–609
11. Crunch Interactive Statistical Package. Oakland, Calif, CRUNCH Software, 1987
12. Carter BL, Woodhead JC, Cole KJ, Milavetz G: Gastrointestinal side effects with erythromycin preparations. Drug Intell Clin Pharm 1987; 21:734–738
13. McDonald PJ, Mather LE, Story MJ: Studies on absorption of a newly developed enteric-coated erythromycin base. J Clin Pharmacol 1977; 17:601–606
14. Oral erythromycins. Med Lett 1985; 27:1–3
15. Griffith RS, Black HR: Erythromycin. Med Clin North Am 1970; 54:1199–1215
16. Rutland J, Berend N, Marlin GE: The influence of food on the bioavailability of new formulations of erythromycin stearate and base. Br J Clin Pharm 1979; 8:343–347
17. Randinitis EJ, Sedman AJ, Welling PG, Kinkel AW: Effect of a high-fat meal on the bioavailability of a polymer-coated erythromycin particle tablet formulation. J Clin Pharmacol 1989; 29:79–84
18. Putzi R, Blaser J, Luthy R, et al: Side-effects due to the intravenous infusion of erythromycin lactobionate. Infection 1983; 11:161–163