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Case report

Effects of erythromycin in chronic idiopathic intestinal pseudo-obstruction

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Abstract: The prokinetic effects of erythromycin, a macrolide antibiotic, on the gastrointestinal tract as a motilin receptor agonist and its potential value for the treatment of gastrointestinal motility disorders have recently attracted interest. The effects of erythromycin on the clinical symptoms and gastrointestinal motility of patients with chronic idiopathic pseudo-obstruction have not been investigated extersively. We presented a case of chronic idiopathic intestinal pseudo-obstruction, in a 67-year-old man in whom oral erythromycin (900 mg/day) dramatically improved postprandial abdominal distention, nausea, and vomiting. Other agents with prokinetic effects on intestinal motility, i.e., cisapride, domperidone, metoclopramide, and trimebutine maleate did not have a favorable effect. Gastric emptying, measured by the sulfamethizole method; and intestinal transit, evaluated using radio-opaque markers, were markedly improved by treatment with erythromycin. Our experience suggests that the prokinetic effects of erythromycin may be of therapeutic value in chronic idiopathic intestinal pseudo-obstruction.

Key words: chronic idiopathic intestinal pseudo-obstruction, erythromycin, gastric emptying, intestinal transit

Introduction

Chronic idiopathic intestinal pseudo-obstruction (CIIP) is an uncommon syndrome characterized by impaired gut motility that may affect all parts of gastrointestinal tract.[1] There are recurrent symptoms of intestinal obstruction without mechanical occlusion due to any apparent underlying disease. Various drugs have been used, unsuccessfully, in the treatment of pseudo-obstruction. Prokinetic drugs, such as cisapride, erythromycin, and erythromycin analogues improve gastric emptying in patients with gastrointestinal motility disorders, including gastroparesis and intestinal pseudo-obstruction.[2–5] Improvements in gastrointestinal motility (i.e., in gastric emptying and intestinal transit) and improvements in clinical symptoms after treatment with erythromycin have rarely been reported in patients with CIIP.[5]

We present a case of CIIP, in a 67-year-old man in whom oral erythromycin markedly improved both gastric emptying, measured by the sulfamethizole method,[6,7] and intestinal transit, evaluated using radio-opaque markers.[8] Cisapride, domperidone, metoclopramide, and trimebutine maleate had no favorable effects.

Case report

A 67-year old man was admitted to our hospital on 28 July 1995 with a 4-month history of recurrent postprandial nausea, vomiting, abdominal distention, and a weight loss of more than 9 kg. There were no urinary symptoms, and no other family members were affected. On examination the man (weight 43 kg; height 153 cm) showed no apparent distress. Blood pressure was 112/80 mmHg in the upright and supine positions and pulse rate was 84/min. His skin was slightly dry, and no lymphadenopathy was noted. No abnormalities were found on the face, neck, or chest. Bowel sounds were normal, and hepatic dullness on percussion was unclear. The abdomen was distended; no tenderness or palpable masses were noted. Results of rectal examination for tumors and blood were negative. Motor and sensory nervous function was normal. Autonomic symptoms,

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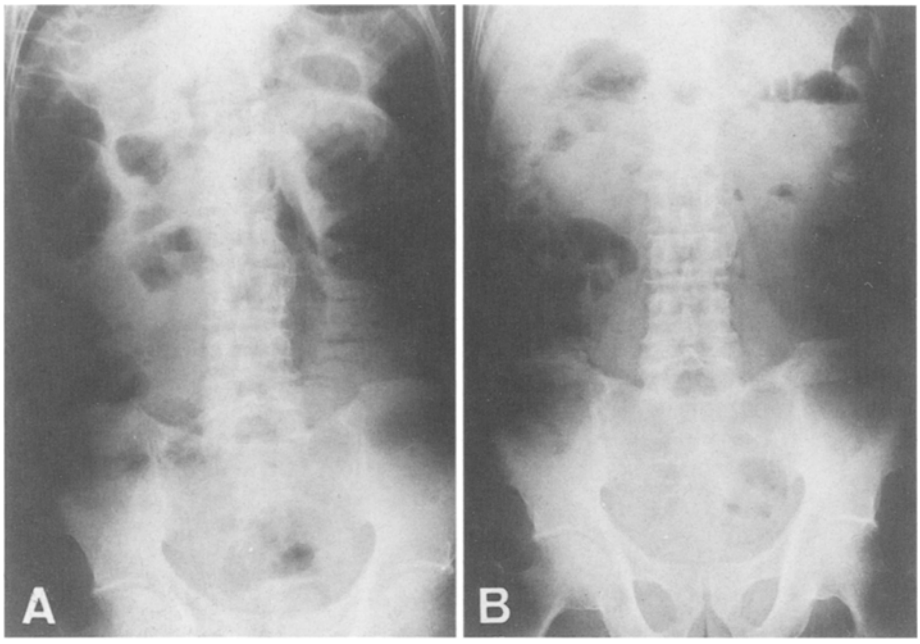

Fig. 1A,B. Plain abdominal X-ray films of the patient **A** on admission and **B** after treatment with erythromycin (900 mg/day). Dilatation in the left upper quadrant of the small intestine and multiple gas shadows in the small intestine observed on admission (**A**) were markedly decreased by treatment with erythromycin (**B**)

i.e., postural hypotension, abnormal sweating, and impotence, were not found.

Plain abdominal X-ray film showed marked dilatation in the left upper quadrant of the small intestine and multiple gas shadows in the small intestine (Fig. 1A). Small intestinography with Gastrografin (Schering, Germany) showed marked dilatation of the duodenum and the proximal jejunum (Fig. 2). Upper gastrointestinal endoscopy showed reflux esophagitis and retention of fluid and food in the duodenum and the proximal jejunum. No abnormalities were found in mucosal specimens of the proximal duodenum and jejunum. There were no findings suggestive of neoplasm, villous atrophy, or amyloidosis (Congo-red stain). Results of colonoscopic examination were normal, showing no stenosis in the gastrointestinal tract. Bacterial culture of duodenal fluid showed overgrowth of *Escherichia coli*, *Clostridium butyricum*, and *Bacteroides*. Esophageal manometric study showed lower esophageal sphincter pressure to be 15 mmHg. Renogram showed no disorder.

Laboratory data are summarized in Table 1. Blood analysis showed anemia and a low serum albumin level. The results of testing urinary secretion of indican were compatible with bacterial overgrowth. Laboratory tests did not detect any disorder known to cause intestinal pseudo-obstruction.

Oral administration of cisapride (20 mg/day given for 4 days), metoclopramide (30 mg/day for 3 days), domperidone (60 mg/day for 4 days), and trimebutine maleate (600 mg/day for 4 days) had no favorable effect and all agents caused frequent intense abdominal pain. In contrast, oral erythromycin (900 mg/day) dramatically alleviated the postprandial abdominal distention and eliminated the nausea and vomiting. On plain abdominal X-ray film, the dilatation in the left upper quadrant of the small intestine and the multiple gas shadows in the small intestine were markedly decreased (Fig. 1B). On upper gastrointestinal endoscopic examination, retention of food and fluid in the proximal duodenum was minimal. Urinary indican test was positive before and after 2 weeks of treatment with erythromycin (900 mg/day).

On the 4th day of treatment with erythromycin (900 mg/day), gastric emptying, evaluated using the sulfamethizole method,[6,7] was markedly improved, shown by the values for the area under the corrected serum sulfamethizole concentration-time curves up to 120 min. The values before and after treatment were 1.22 and 8.89 μg·h/ml, respectively (Fig. 3).

Intestinal transit, evaluated using 20 radio-opaque markers,[8] was improved by treatment with erythromycin (900 mg/day). Intestinal transit was evaluated before and from the 6th day of erythromycin treatment. Before treatment, half of the markers remained in either the stomach or the duodenum and the rest were in the proximal jejunum 24 h after ingestion. After 48 h, all markers were in the proximal jejunum; after 72 h, 16 markers had reached the colon. On treatment with erythromycin, after 6 h, 19 markers were in the middle jejunum and 1 was in the proximal jejunum. After 24 h, 12 markers were in the ileum and the remainder were in the middle jejunum. After 48 h, 2 markers were in the ileum, and 18 markers had already passed into the colon.

During the 1st 2 weeks' treatment with erythromycin (900 mg/day); the patient sometimes complained of ab-

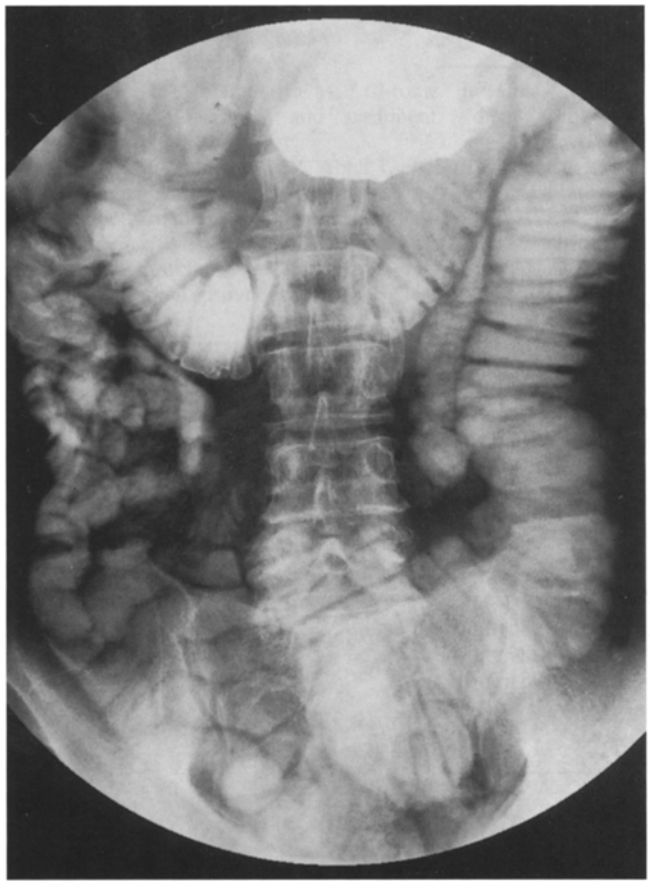

Fig. 2. Gastro–small intestinography with gastrografin (Shering, Germany) on admission. There was marked dilatation, with no mechanical occlusion, in the duodenum and proximal jejunum

dominal pain the dosage of erythromycin was decreased to 400 mg/day. Postprandial abdominal distention and nausea then recurred. The addition of orally administered trimebutine maleate (400 mg/day) to erythromycin (400 mg/day) alleviated these symptoms, as well as the abdominal pain. The effects of combination treatment were not as favorable as those of erythromycin (900 mg/day) alone, and trimebutine maleate (400 mg/day) alone had no favorable effects. The combination treatment of erythromycin (400 mg/day) and trimebutine maleate (400 mg/day) was continued for 12 weeks and no side effects were noted.

Discussion

In this 67-year-old man with CIIP, erythromycin markedly alleviated symptoms overall and improved gastric emptying and intestinal transit. Erythromycin has prokinetic effects as a motilin agonist, binding to motilin receptors.[9] There is a high density of motilin receptors in the gastroduodenal area and the proximal jejunum.[10] In this patient, marked dilatation of the duodenum and proximal jejunum was shown on small intestinography; these findings appear to explain the favorable effects of erythromycin.

Tack et al.[11] reported that intravenous erythromycin (200 mg) induced phase-III-like migratory myoelectric complex activity in the stomach in patients with diabetic gastroparesis, the effects lasting for about 16 min. Sarna et al.[12] found that intravenous erythromycin (500 mg) stimulated motor activity in the stomach; the effects lasted for about 60 min. The effects of erythromycin on motor activity in the stomach were transient, since the plasma half-life of erythromycin is about 30 min.[12] We chose to use erythromycin 900 mg/day (300 mg three times/day, orally) as the initial treatment, taking into account both the transient effect of erythromycin on motor activity and the delayed gastric emptying, which may lead to delayed absorption, as erythromycin is thought to be emptied from the stomach and absorbed from the small intestine. High doses of intravenous erythromycin reportedly have no significant effects on small intestinal motor activity.[11,12] On the other hand, phase-III-like migratory myoelectric complex activity induced by a low-dose of intravenous erythromycin reportedly migrates to the jejunum.[11] In our patient, high doses of oral erythromycin improved both intestinal transit and gastric emptying. The discrepancy between our findings and the results reported by Tack et al.[11] and Sarna et al.[12], may have arisen from differences in the route of administration of erythromycin and from the delayed gastric emptying in our patient (resulting in delayed absorption).

Since erythromycin is an antibiotic, these effects may have contributed to the symptomatic improvement. However, urinary indican was positive before and after 2 weeks of treatment with erythromycin, indicating that erythromycin did not eradicate the bacterial overgrowth in the intestine. These findings suggest that the antibiotic effects of erythromycin were not solely responsible for the alleviation of symptoms.

In our patient, gastric emptying, evaluated using the sulfamethizole method,[6,7] was markedly improved by treatment with erythromycin (900 mg/day). Before treatment, the delay in gastric emptying was greater than that seen in any patient we have evaluated by this method. Erythromycin improved the intestinal transit, but, after the treatment, transit was still delayed, compared to that reported in healthy volunteers.[8]

In patients with CIIP, cisapride reportedly increased gastric emptying, but there was no significant difference in overall symptoms between patients treated with cisapride and those given placebo.[2] In our patient, there

Table 1. Laboratory findings on admission

Urinalysis	Unremarkable				
Urinary indican test	(+)				
Fecal occult blood	(−)				
ESR	12 mm/h; 30 mm/2 h				
Blood chemistry					
AST	17 IU/l	T-P	6.5 g/dl	CPK	66 IU/l
ALT	14 IU/l	Alb	2.7 g/dl	Amy	86 IU/l
LDH	203 IU/l	T-Chol	115 mg/dl	Na	138 mEq/l
ALP	141 IU/l	TG	76 mg/dl	K	4.7 mEq/l
r-GTP	19 IU/l	BUN	15 mg/dl	C	100 mEq/l
Ch-E	2358 IU/l	Cr	0.7 mg/dl	FPG	98 mg/dl
T-Bil	0.5 mg/dl	UA	3.7 mg/dl	Hb_{A1c}	5.2%
Hematological findings					
RBC	410 × 10^4/μl	Hb	11.0 g/dl	Ht	40.3%
WBC	6860/μl	Plt	30.8 × 10^4/μl		
Serological findings					
CRP	(−)	Thyroid test	(−)	C-200Ab	(−)
RF	<20 IU/l	Microsome test	(−)	IgG	986 mg/dl
ANA	(−)	CEA	<2.5 ng/ml	IgA	224 mg/dl
TPHA	(−)	HBsAg	(−)	IgM	98 mg/dl
Thyroid function					
TSH	1.54 μU/ml	Free T_3	2.4 pg/ml	Free T_4	1.2 ng/dl

ESR, Erythrocyte sedimentation rate

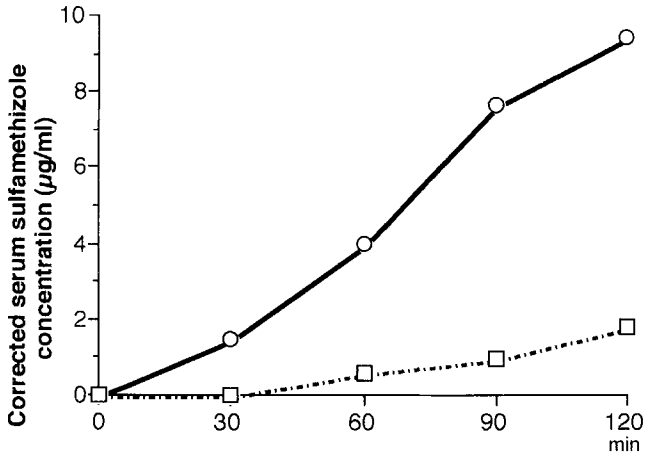

Fig. 3. Corrected serum sulfamethizole levels after ingestion of sulfamethizole before and after treatment with erythromycin (900 mg/day). The values for the area under the corrected serum sulfamethizole concentration-time curves up to 120 min before treatment (*squares*) and after treatment (*circles*) were 1.22 and 8.89 μg·h/ml, respectively. Gastric emptying was dramatically accelerated by the treatment

was no alleviation of the overall symptoms after treatment with cisapride or after treatment with domperidone, metoclopramide, or trimebutine maleate, agents that have prokinetic effects on intestinal motility. Since erythromycin induces phase III migratory myoelectric complex activity,[11,13] its favorable effects in contrast to the lack of effect of the other drugs, suggests that phase III migratory myoelectric complex may have contributed to the alleviation of the overall symptoms in this patient.

The dose of erythromycin was decreased from 900 to 400 mg/day, with the addition of trimebutine maleate (400 mg/day) after 2 weeks of treatment, because the patient experienced occasional pain in the abdomen. Why the addition of trimebutine maleate to erythromycin alleviated the postprandial abdominal distention and nausea to a greater extent than did erythromycin (400 mg/day) alone, was not apparent, particularly since no favorable effects were observed with trimebutine maleate alone. However, reducing the dose of erythromycin to a level much lower than that used for antibiotic treatment may have helped to avoid side effects in this patient during the long-term treatment with erythromycin.

We have presented a case of CIIP in a patient in whom erythromycin had very favorable effects on clinical symptoms, and on gastric emptying and intestinal transit. Our experience suggests that this agent may be of therapeutic value for this syndrome. Long-term clinical trials are necessary to evaluate the definitive role of erythromycin in the treatment of CIIP.

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