

MACROLIDES AS PROKINETIC AGENTS

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INTRODUCTION

It is now firmly established that in the fasting state low doses of erythromycin induce phase 3 of the migrating motor complex, while higher doses only stimulate the stomach and may inhibit the small intestine (Sarna et al., 1991; Tack et al., 1992).

Derivatives of erythromycin were soon discovered with enhanced motility effects, and decreased antibiotic potency

(Omura et al., 1987; Itoh and Omura, 1987). It was proposed to give the name motilides to all macrolides with a) a direct contractile effect *in vitro* on rabbit duodenal segments; b) the capacity to induce, *in vivo*, phase 3 activity in dogs. Besides these two effects, these compounds have many other properties in common with the peptide motilin.

GASTRIC EMPTYING AND GASTROPARESIS (Table 1)

Interest in the therapeutic potential of motilides has been largely stimulated by the original report by Janssens et al., (1990) that erythromycin markedly accelerates gastric emptying in patients with diabetic gastroparesis. This report has been confirmed by several groups (Richards et al., 1990; Wadhwa et al., 1991; Boiron et al., 1993) and erythromycin has also been successfully used in other conditions accompanied by gastroparesis such as postvagotomy (Mozwecz et al., 1990; Hill et al., 1993; Hocking et al., 1993), systemic sclerosis (Dull et al., 1990), cancer therapy (Maliakkal et al., 1991) and anorexia nervosa (Stacher et al., 1993).

The motor patterns responsible for the effect of erythromycin on gastric emptying have been studied in volun-

teers. Erythromycin induces powerful peristaltic contractions in the antrum (Sarna et al., 1991), improves antroduodenal coordination and induces phase 3-like patterns superimposed on the fed motility (Annese et al., 1992). Erythromycin also seems to affect the proximal stomach (Edelbroek et al., 1993). Erythromycin abolishes the lag phase (Mantides et al., 1993), and the emptying rate of solids and liquids are the same (Janssens et al., 1990). This may be due to the induction of phase 3 patterns, and suggests that erythromycin accelerates gastric emptying at the expense of grinding and sieving. Indeed in dogs erythromycin causes rapid gastric emptying of untrituated solids (Lin et al., 1994).

Table 1: Effects of motilides on gastric emptying in gastroparesis

Subjects	Dose ¹	Time ²	Drug ³	Effect	Reference
diabetics	200 mg i.v., 20 min	pp	EM	accelerates emptying of liquids and solids	Janssens, 1990
diabetics	250 mg p.o.	meal, -20 min,tid	EM	accelerates emptying of liquids and solids (less pronounced)	Janssens, 1990
diabetics,idiopathic	6 mg/kg i.v.	pp	EM	accelerates gastric emptying	Richards, 1990
diabetics	100 mg i.p.	meal, -30 min,tid	EM	normalizes gastric emptying, suppresses vomiting	Wadhwa, 1991
diabetics	100-500 mg i.v.	meal, +6 hrs	EM	normalizes gastric emptying	Boiron, 1993
diabetics	250, 1000 mg p.o.	meal, -30 min	EM	accelerates gastric emptying	Desautels, 1995
postvagotomy	250 mg p.o.	pp, tid	EM	normalizes gastric emptying	Mozwecz, 1990
postvagotomy	250 mg p.o.	tid	EM	improved rate of gastric emptying	Hill, 1993
postvagotomy	100 mg i.v.	qid	EM	tachygastria improved	Hocking, 1993
systemic sclerosis	250 mg p.o.	pp, tid	EM	improves gastric emptying	Dull, 1990
cancer therapy	250 mg i.v.	pp	EM	improves gastric emptying, symptoms	Maliakkal, 1991
anorexia nervosa	200 mg i.v.	pp	EM	accelerates gastric emptying	Stacher, 1993

¹: all doses are given in mg, and were administered over the time period indicated (i.v.: intravenously; p.o.: orally).

²: pp= postprandial; qid= four times daily; tid= three times daily.

³: EM= erythromycin

LES PRESSURE AND OESOPHAGEAL BODY MOTILITY; REFLUX DISEASE (Table 2)

Four groups reported that erythromycin increases LES pressure in man (*Chaussade et al.*, 1994; *Janssens et al.*, 1990; *Dalton et al.*, 1990; *Pennathur et al.*, 1993; *Pennathur et al.*, 1994).

Erythromycin has less effect on the oesophageal body. In two studies with volunteers (*Chaussade et al.*, 1994; *Pennathur et al.*, 1993), and in three studies with patients with reflux disease (*Champion et al.*, 1994; *Pennathur et al.*, 1994; *Harrison et al.*, 1991), only one found an effect on the amplitude of peristaltic contractions (*Harrison et al.*, 1991). The duration of peristaltic contractions showed a tendency to increase in two of these studies (*Chaussade et al.*, 1994; *Pennathur et al.*, 1994), while a decrease in the propagation velocity was noted by *Champion et al.*, (1994)

and *Chaussade et al.*, (1994).

These effects suggest that erythromycin could find application in the treatment of gastro-oesophageal reflux, but so far two studies did not find a favourable effect on reflux parameters (*Champion et al.*, 1994; *Harrison et al.*, 1991). However, in a small study with human volunteers the gastro-oesophageal reflux caused by white wine was reversed by infusing 3.5 mg/kg EM-A before ingestion (*Pfeiffer et al.*, 1991), and the same group found that in patients with reflux disease erythromycin at 3 mg/kg given i.v. 10 min before lunch, shortened reflux duration (*Pehl et al.*, 1994)

Although motilides appear to have properties useful in the treatment of reflux disease, it is obvious that more data are needed to evaluate their potential.

SMALL BOWEL MOTILITY AND SMALL INTESTINAL PSEUDO-OBSTRUCTION

In chronic idiopathic pseudo-obstruction erythromycin is able to induce phase 3 activity (*Miller et al.*, 1990; *Di Lorenzo et al.*, 1991). Improvement of clinical symptoms has also been reported (*Berger et al.*, 1990; *Chami et al.*, 1991).

In children with the presumptive diagnosis of chronic intestinal pseudo-obstruction, erythromycin facilitates the postpyloric passage of tubes during duodenal intubation for antroduodenal manometry. The authors assume that propagating antral contractions sweep the tube through the open pyloric channel into the duodenum (*Di Lorenzo et*

al., 1990). Accordingly, erythromycin also facilitates the migration of an enteral feeding tube (*Keshavarzian and Isaac*, 1993).

Preliminary studies have also looked for an application of motilides in the treatment of postoperative ileus. In cholecystectomy patients erythromycin did not affect the appearance of flatus or bowel movements (*Bonacini et al.*, 1993), but with EM-523 a dose-dependent decrease of the time until the start of bowel sounds was observed in a similar patient population (*Hanyu et al.*, 1991)

Table 2: Effects of motilides on the human oesophagus

Subjects	Dose ¹	Time ²	Drug ³	Effect	Study ⁴
volunteers	150 mg i.v., 20 min	fasting	EM	increases LES pressure and duration of peristaltic contractions	Chaussade et al., 1991
volunteers	3.5 mg/kg i.v.	phase 3, +5 min	EM	increases LES pressure	Janssens et al., 1990
volunteers	500 mg p.o.	pp	EM	increases LES pressure	Dalton et al., 1990
patients with reflux	250 mg p.o.	qid	EM	tendency to reduce long reflux episodes	Champion et al., 1991
patients with reflux	250 mg p.o.	tid	EM	no effect on reflux	Harrison et al., 1991
volunteers	3.5 mg/kg i.v.	pp	EM	suppresses reflux caused by white wine	Pfeiffer et al., 1991
volunteers	0.5-2.0 mg i.v., 15 min		EM-523	induces esophageal MMC	Itoh et al., 1991
patients with systemic sclerosis	150 mg i.v., 30 min		EM	increases LES pressure, and fundic contractions	Chaussade et al., 1991
volunteers	500 mg i.v., 30 min		EM	increases LES pressure	Pennathur et al., 1993
patients with reflux	500 mg i.v., 30 min		EM	increases LES pressure, prolongs duration of contractions in esophagus	Pennathur et al., 1994
patients with reflux	3 mg/kg i.v.	lunch, -10 min	EM	shortens reflux duration	Pehl et al., 1994

1: all doses are given in mg, and were administered over the time period indicated (i.v.: intravenously; p.o.: orally).

2: pp= postprandial; qid= four times daily; tid= three times daily.

3: EM= erythromycin; EM-523= the erythromycin analogue developed by Takeda Chemical Company.

4: studies are given in chronological order.

IMPAIRED COLONIC MOTILITY (Table 3)

A few, mostly preliminary studies, have explored the effect of erythromycin on the human colon. The result is basically negative and has been interpreted as due to the absence or low density of motilin receptors.

In other species the situation may be different. In dogs intravenous erythromycin first induced a period of intense colonic motor activity which was followed by a period of inhibition (Zara

et al., 1985). Erythromycin has also a marked effect on the colon of the rabbit, a species in which there is firm evidence for colonic motilin receptors (De-poortere et al., 1991).

Effects on colonic motility may warrant further studies because successful treatment of one patient with reflex ileus, and two with Ogilvie's syndrome has been reported (Armstrong et al., 1991; Bonacini et al., 1991).

GALLBLADDER

Erythromycin stimulates gallbladder contraction in normal volunteers, in post-cholecystolithotomy patients, and in diabetics with autonomic neuropathy (Catnach et al., 1992, 1993; Fiorucci et al., 1992). Low doses of EM-523 (0.5-2.0 mg i.v.) have been shown to be effective as well (Itoh et al., 1991).

Motilides may therefore find application in patients with the risk of gallstone formation, such as those on parenteral nutrition, as a prophylactic to reduce recurrence, or to aid fragment clearance after extracorporeal shock-wave lithotripsy (Catnach et al., 1992).

CONCLUSIONS

It is now well established that erythromycin has profound effects on gastro-intestinal motility. The most convincing data have been obtained in gastroparesis patients when erythromycin was administered intravenously. The efficacy of oral therapy may be less because of the conditions of such patients, and the timing of the administration may be crucial.

Motilides may also be useful in pa-

tients with a risk of gallstone formation, and given the limited number of therapeutic agents able to help patients with pseudo-obstruction, the potential of erythromycin in treating this condition should be further explored. The usefulness in gastro-oesophageal reflux should not be discounted too quickly. Trials in gastritis, small intestinal bacterial overgrowth, postoperative ileus and constipation should be considered.

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Table 3: Effects of motilides on the human Colon

Subjects	Dose ¹	Time ²	Drug ³	Effect	Reference
volunteers	200 mg i.v., 20 min	fasting	EM	induces contractions in the sigmoid region only	Bradette, 1991
patients, constipation	500 mg i.v., 1 hr	fasting	EM	no effect on colonic motility, nausea	Bassotti, 1991
patients, IBS	500 mg i.v., 30 min	fasting	EM	no effect on colonic motility, nausea	Delvaux, 1994
volunteers	6 mg/kg	fasting	EM	no effect on colonic motility, nausea	Yeaton, 1992
volunteers	500mg p.o., or 1.8mg/kg i.v.	fasting	EM	no effect on sigmoid motility or colonic transit	Jameson, 1992

1: all doses are given in mg, and were administrated over the time period indicated (i.v.: intravenously; p.o.: orally).

2: pp= postprandial; qid= four times daily; tid= three times daily.

3: EM= erythromycin

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