Effects of cholinceptor and 5-hydroxytryptamine₃ receptor antagonism on erythromycin-induced canine intestinal motility disruption and emesis

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1 Erythromycin administration is associated with gastrointestinal problems, disturbed gastrointestinal motility and emesis. This study in the dog investigates the underlying mechanisms.

2 Intestinal myoelectrical activity and the occurrence and latency of emesis were recorded in eight conscious dogs. All drugs were administered intravenously.

3 Erythromycin (7 mg kg⁻¹) increased contractions of the proximal small intestine, and caused emesis in all fasted dogs and in 5 dogs after food. Atropine (50 mg kg⁻¹ min⁻¹) and hexamethonium (10 mg kg⁻¹ h⁻¹) partially inhibited the GI motility effects but did not significantly reduce emesis.

4 Metoclopramide at a high dose (2 mg kg⁻¹ h⁻¹) reduced the incidence of emesis in the presence of increased intestinal motility, but a low dose (150 µg kg⁻¹ h⁻¹) was ineffective.

5 A 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist, MDL 72222 (1 mg kg⁻¹), reduced emesis when given alone and combined with metoclopramide (low dose). The 5-HT₄ receptor agonist BRL24924 (Renzapride, 1 mg kg⁻¹) had no effect on emesis either alone in combination with metoclopramide.

6 In conclusion, erythromycin-induced GI motility disturbances and emesis are not causally related. Whereas the increase in intestinal smooth muscle activity is possibly cholinergically mediated, emesis occurs at least in part via a 5-hydroxytryptaminergic mechanism, but does not involve the dopamine system.

Keywords: Erythromycin; gastrointestinal motility; 5-hydroxytryptamine; Renzapride; MDL72222; cholinergic; atropine; hexamethonium; emesis; metoclopramide

Introduction

Investigation of the effects of erythromycin on the gastrointestinal (GI) tract began less than a decade ago. These studies were prompted by numerous reports associating cramping, nausea, vomiting and diarrhoea with erythromycin treatment, which in some cases were severe enough to discontinue treatment (Shoemaker & Yow, 1954; Mather *et al.*, 1981; Downey & Chaput de Saintonge, 1986; Hovi *et al.*, 1987; Shanks *et al.*, 1989). Erythromycin was found to have a disruptive effect on gastrointestinal motor patterns (Pilot *et al.*, 1984; Itoh *et al.*, 1984), even when administered at very low, subtherapeutic doses (Tomomasa *et al.*, 1986; Otterson & Sarna, 1990). At therapeutic doses erythromycin interrupts and disrupts the migrating motor complex (MMC) pattern which occurs naturally during fasting, induces increased gastric and upper intestinal motor activity and causes emesis after both oral and intravenous administration (Qin *et al.*, 1985; 1986; Zara *et al.*, 1991). In the past two years, use has been made of these motor GI effects by giving erythromycin to patients with gastroparesis in order accelerate gastric emptying (Janssens *et al.*, 1990).

In spite of these beneficial effects, patients on erythromycin still report adverse GI effects. The aims of the present study in the dog were to investigate the possible pathways by which these alterations in gastrointestinal function occur, and whether there was a causal relationship between GI motility disturbances and emesis.

Methods

Eight dogs of either sex were used in the experiments. Under halothane/nitrous oxide anaesthesia, twelve silver electrodes

were implanted on the serosal surface of the small intestine, four on the duodenum and eight on the jejunum and ileum. The electrode leads were exteriorized laterally (Qin, 1989). After operation, two weeks were allowed for recovery before beginning experiments.

Before each recording the dogs were fasted for 18 h. The experiments were performed in either the pre or post prandial state when the dog was fed a tin of 390 g 'PAL' dog's meat (Pedigree Petfoods Ltd) 10 min before the recording began. During the recording the dog stood on a table, supported by a canvas sling. Intestinal myoelectrical signals were recorded on two cassette tapes by use of two four-channel Medilog MR-10 recorders (Oxford Medical Systems), and replayed on a 4-channel PB-2 Replay Unit (Oxford Medical Systems). During replay the data were sent to an Apple II micro-computer via an interface, and saved as a sequential text file for further analysis (Barnett *et al.*, 1989).

Experimental protocol

Erythromycin After 3 hours of basal recording erythromycin lactobionate (Erythrocin, Abbott Laboratories Ltd) at the dose of 7 mg kg⁻¹ was infused intravenously for 30 min. The recording was continued for a further 3 h after the end of the infusion.

Atropine, hexamethonium and metoclopramide The following protocol was used to study the effects of atropine, hexamethonium and metoclopramide on GI motility, and to investigate whether these compounds have an effect on the erythromycin-induced motility and emesis. After a basal period of 3 h, one of these three drugs was infused intravenously for one hour, following which there was a recovery period of 3 h. Erythromycin was infused (7 mg kg⁻¹) during the last 30 min of each drug infusion.

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MDL 72222 and BRL 24924 These experiments were conducted primarily to investigate the effect of the two compounds on erythromycin-induced emesis. Because the emetic response was more pronounced when the animals were fasted, this series of experiments was performed on fasted dogs only. Half of the dose (5 ml) of the compound under study was injected intravenously after a 3 h basal period. Thirty minutes later an infusion of erythromycin (7 mg kg^{-1}) was started and at the same time the remaining 5 ml of the compound under investigation was injected. The infusion of erythromycin lasted for 30 min. In order to investigate the possibility of potentiation these experiments were repeated in the presence of metoclopramide at a low dose of $150 \mu\text{g kg}^{-1} \text{ h}^{-1}$ infused for 1 h starting at the time of the first injection of MDL2222 or BRL24924.

Drugs and dosages

All drugs were given by the i.v. route. Erythromycin lactobionate ($7 \text{ mg kg}^{-1} 30 \text{ min}^{-1}$; Abbott Laboratories), was dissolved in 10 ml water, and the volume of infusion was increased to 50 ml with 0.9% saline. Atropine sulphate ($50 \text{ mg kg}^{-1} \text{ min}^{-1}$) was obtained in ampoule form from Antigen Ltd., and 0.9% saline was added to obtain the infusion volume. Hexamethonium ($10 \text{ mg kg}^{-1} \text{ h}^{-1}$, Sigma Chemical Co., Poole, Dorset) was dissolved in 0.9% saline. Metoclopramide (low dose: $150 \mu\text{g kg}^{-1} \text{ h}^{-1}$, high dose: $2 \text{ mg kg}^{-1} \text{ h}^{-1}$) was obtained in ampoule form from Smith-Kline Beecham, and the infusion volume was obtained by adding 0.9% saline. MDL 72222 (1 mg kg^{-1}), a gift from Merrel Dow, and BRL 24924 (1 mg kg^{-1}), a gift from Smith-Kline Beecham, were dissolved into 10 ml of 0.9% saline.

Data analysis

Electromyographic signals from the intestine were filtered so that only the fast potentials (spikes) were retained. The spikes were changed into TTL compatible pulses which were counted by an Apple microcomputer (Barnett *et al.*, 1989). Because of the cyclical nature of the preprandial motor patterns, comparison of spike numbers before and after treatment were done only in postprandial studies when spike activity is more uniform. In postprandial experiments, therefore, three periods were chosen for comparison. The first period (control) consisted of the 30 min before any drug was given, and the other two (Periods 2 and 3) were the two thirty minute periods of the hour of drug infusion. Erythromycin was always given during the second of these two periods (Period 3). The number of spikes in each period was summed and the values obtained in Periods 2 and 3 were compared to the control values of Period 1, by use of Wilcoxon's signed rank test for statistical analysis. Data are shown as median and interquartile values.

Results

Motility

Erythromycin Erythromycin lactobionate given intravenously interrupted the basal pre- and post-prandial motility patterns which were replaced by increased irregular spike activity in the duodenum and jejunum (Figure 1). The effects of erythromycin were more pronounced and prolonged in the duodenum than in the jejunum. When the infusion of erythromycin was stopped the irregular spike activity gradually decreased but continued to the end of the experiment with no evidence of a return to a basal pattern in either proximal or distal regions of the small intestine. In fed dogs, compared with the control period, the number of spikes during the infusion of erythromycin was significantly increased at the duodenum and jejunum, but not in the ileum (Table 1). Ileal

Figure 1 Effects of erythromycin ($7 \text{ mg kg}^{-1} 30 \text{ min}^{-1}$) on pre (A) and post (B) prandial intestinal electrical activity recorded by electrodes implanted at 3 different sites ((a) duodenum, (b) jejunum and (c) ileum) of the canine small bowel. The number of spikes occurring in each minute of recording has been normalised, with the first 10 min showing calibration of $120 \text{ pulses min}^{-1}$. The arrows indicate the period of infusion. Note the increase in spikes in the proximal small intestine during and after the infusion of erythromycin in both the fasted and fed states.

activity appeared to be profoundly inhibited during the recovery period in both fed and fasted states.

Atropine Although atropine inhibited both the basal pre- and post-prandial motility pattern when given on its own during the first 30 min of infusion (Period 2, Table 1), its effect on erythromycin-induced spike activity depended on whether the animals were fed or fasted (Figure 2). Postprandially, atropine did not abolish the increase in spike activity caused by erythromycin. Thus, in the presence of atropine the number of spikes during the infusion of erythromycin was significantly increased in the duodenum when compared with the control period (Table 1, Figure 2). In eight fasted dogs the only effect seen with erythromycin in the presence of atropine was an increase in spike activity in the duodenum during the 30 min of infusion (Period 3). In the jejunum and ileum during the erythromycin infusion, and at the 3 electrode sites during the recovery period erythromycin was unable to overcome the smooth muscle inhibition consistent with the presence of atropine (Figure 2).

Hexamethonium Unlike atropine, hexamethonium decreased the effects of erythromycin on the proximal intestine in both the fasted and fed states (Figure 3). Postprandially, during the first 30 min of hexamethonium infusion (Period 2, Table 1) spike activity was significantly depressed. The number of spikes increased during the administration of erythromycin (Period 3, Table 1), although they were not significantly different from control values.

Table 1 Postprandial spike activity before and after erythromycin–alone and in combination with drugs in the small intestine of the fed dog

Drugs	n	Electrode site	Median spike number (interquartile)		
			Period 1 (control)	Period 2	Period 3
Erythromycin 7 mg kg ⁻¹	8	Duodenum	565 (416–763)	–	2022 (1275–3213)**
		Jejunum	241 (204–663)	–	763 (288–1670)*
		Ileum	628 (357–1027)	–	739 (544–1146)
Atropine 50 mg kg ⁻¹ min ⁻¹	8	Duodenum	216 (105–272)	64 (54–81)*	642 (411–1078)*
		Jejunum	162 (46–373)	120 (30–280)	195 (68–320)
		Ileum	266 (164–409)	156 (52–189)**	146 (62–275)
Hexamethonium 10 mg kg ⁻¹ 1h ⁻¹	8	Duodenum	223 (100–377)	111 (24–213)**	217 (150–565)
		Jejunum	514 (287–653)	202 (140–295)**	103 (45–222)**
		Ileum	265 (184–369)	97 (66–264)**	144 (64–377)
Metoclopramide 150 µg kg ⁻¹	8	Duodenum	390 (271–432)	306 (197–498)	1527 (870–1858)**
		Jejunum	264 (218–543)	233 (183–698)	683 (350–1083)*
		Ileum	478 (268–607)	565 (355–705)	481 (246–613)
Metoclopramide 2 mg kg ⁻¹	8	Duodenum	408 (309–492)	467 (333–561)	1216 (716–1755)*
		Jejunum	490 (226–541)	410 (307–680)	654 (295–828)
		Ileum	439 (261–562)	622 (187–795)	532 (280–859)

The 3 periods of 30 min each are consecutive. Period 1: immediately before administration of any drug. Period 2: atropine, hexamethonium and metoclopramide were administered alone. Period 3: the above drugs were given in conjunction with erythromycin. The number of spikes in Periods 2 and 3 were compared to the number in the control period. Values are given as median and interquartile range from *n* studies. **P* < 0.05, ***P* < 0.01, Wilcoxon matched pairs test.

Figure 2 Effect of atropine (50 mg kg⁻¹ min⁻¹) on erythromycin (7 mg kg⁻¹ 30 min⁻¹)-induced spike activity in the duodenum (a), jejunum (b) and ileum (c) in the pre (A) and post (B) prandial states. The dashed lines indicate the atropine infusion and the arrows the erythromycin infusion. The number of spikes occurring in each minute of recording has been normalised, with the first 10 min showing calibration of 120 pulses min⁻¹. For statistical analysis, in each 'fed' trace, the number of spikes was counted during 3 consecutive 30 min periods, before and including the dashed lines.

Figure 3 Effect of hexamethonium (10 mg kg⁻¹ h⁻¹) on erythromycin (7 mg kg⁻¹ 30 min⁻¹)-induced spike activity in the duodenum (a), jejunum (b) and ileum (c) in the pre (A) and post (B) prandial states. The dashed lines indicate the period of hexamethonium and the arrows the erythromycin infusion. The number of spikes occurring in each minute of recording has been normalised, with the first 10 min showing calibration of 120 pulses min⁻¹. For statistical analysis, in each 'fed' trace, the number of spikes was counted during 3 consecutive 30 min periods, before and including the dashed lines.

Metoclopramide Neither the low ($150 \mu\text{g kg}^{-1} \text{h}^{-1}$) nor the high dose ($2 \text{ mg kg}^{-1} \text{h}^{-1}$) of metoclopramide had an effect on motility during the first 30 min of infusion (Period 2). The control MMC pattern of the fasted state was not disturbed (Figure 4), and the number of postprandial spikes was the same as control (Table 1). When erythromycin was infused (Period 3), the spike number in the proximal intestine was significantly increased (Figure 4, Table 1), although the higher dose of metoclopramide appeared to reduce the erythromycin-induced effect on spike activity.

Emesis

Erythromycin After the infusion of erythromycin, all 8 dogs vomited when fasted, and five out of eight when fed (Table 2). One fed dog which did not vomit showed signs of nausea and retching, and this animal was categorised as having no emetic episodes. Table 2 illustrates the effects of the five drugs given in conjunction with erythromycin to investigate the emetic mechanism, showing the number of subjects with a positive emetic response as well as the latency of onset of the response. Atropine and hexamethonium tended to reduce the number of animals with emesis, although this was not statistically significant ($P > 0.05$). Metoclopramide at a low dose and BRL24924 (either alone or in combination with low dose metoclopramide) were even less effective than the cholinergic drugs in decreasing the incidence of emesis. Only metoclopramide at a high dose and the 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist MDL72222 significantly reduced the emesis caused by erythromycin. The combination of MDL72222 and a low dose of metoclo-

pramide did not further decrease the erythromycin-induced emesis.

Discussion

The present study shows that erythromycin interrupted pre and postprandial motility patterns, increased intestinal spike activity and caused emesis in the canine small intestine. The dose of erythromycin used in the present study lies within the therapeutic range used clinically in intravenous therapy.

The involvement of a cholinergic mechanism at both the pre- and postganglionic levels in the erythromycin-induced increase in motility is suggested by the partial inhibition of this activity by atropine and hexamethonium. The higher density of cholinergic nerves in the proximal small intestine (Schulze-Derieu, 1981) could also explain why the motor effects of erythromycin were more pronounced on the proximal small intestine than the distal. However, the differential effect may implicate another receptor system in the light of recent findings that erythromycin competes with the intestinal peptide motilin in binding duodenal receptors (Kondo *et al.*, 1988; Peeters *et al.*, 1989) and that the number and sensitivity of these receptor sites are higher in the proximal small bowel (Matsumoto *et al.*, 1986; Bormans *et al.*, 1988; Peeters *et al.*, 1988).

The possibility that the large increase in contractile activity seen in the presence of erythromycin was responsible for the high incidence of emesis was investigated with the use of motor-inhibiting cholinergic antagonists and of known anti-emetics. Could the two effects of erythromycin be dissociated? Although the increase in intestinal motility was greatly decreased by atropine and hexamethonium, the incidence of induced emesis was only slightly reduced by the two cholinergic agents. Metoclopramide, on the other hand, when given at a high dose, significantly decreased the incidence of emesis elicited by erythromycin but did not prevent the significant increase in intestinal motility. This dissociation of effects suggests that the disruption of GI motility and the emesis observed with erythromycin are not causally related.

All animals had at least one emetic episode when erythromycin was administered pre-prandially, but if erythromycin was infused when the post-prandial pattern was well established in the intestine, fewer animals had emetic episodes, and food delayed the onset of emesis. It is possible that the digestive hormones released by the meal act on receptors located either in the area postrema or the vomiting centre to reduce the emetic effect, or that the segmental peristaltic movements which propel the meal down the bowel counteract a possible reverse peristalsis.

Only metoclopramide at a high dose and MDL72222 significantly reduced erythromycin-induced emesis. Studies with patients receiving cytotoxic drugs have shown that the antiemetic effects of metoclopramide are dose-dependent. Only at a high dose (2 mg kg^{-1} every 2 h to 10 mg kg^{-1} over 24 h i.v.) does metoclopramide reduce emesis caused by cisplatin (Gralla *et al.*, 1981). A lower dose of metoclopramide (10 to 30 mg i.v.), which antagonizes emesis induced by apomorphine, and is therefore thought to occur through dopamine antagonism, is ineffective against cisplatin-induced emesis. The efficacy of metoclopramide at high doses was confirmed by the present study in the dog while a low dose was without effect, thus suggesting a mechanism other than on dopamine receptors.

It has recently been suggested that the anti-emetic effect of a high dose of metoclopramide is related to its action on 5-hydroxytryptamine (5-HT) receptors rather than to the dopamine antagonism obtained with lower doses (Miner & Sanger, 1986). Subsequently specific 5-HT₃ receptor antagonists were shown to be potent anti-emetics both experimentally and clinically (Fozard, 1987; Sanger, 1990). In the present study we used MDL 72222, which reduces emesis caused by cisplatin in ferrets (Miner & Sanger, 1986). Similar

Figure 4 Effect of high dose metoclopramide (2 mg kg^{-1}) on erythromycin (7 mg kg^{-1} 30 min^{-1})-induced spike activity in the duodenum (a), jejunum (b) and ileum (c) in the pre (A) and post (B) prandial states. The dashed lines indicate the metoclopramide infusion and the arrows the erythromycin infusion. The number of spikes occurring in each minute of recording has been normalised, with the first 10 min showing calibration of $120 \text{ pulses min}^{-1}$. For statistical analysis, in each 'fed' trace, the number of spikes was counted during 3 consecutive 30 min periods, before and including the dashed lines.

Table 2 Emetic response to erythromycin and to drugs modulating the response in the fasted and fed dog

Drug		n (total)	n (emesis)	n Onset latency (min) [0–10 11–20 >20]		
Erythromycin alone	Fasted Fed	8 8	8 5	5 1	3 2	– 2
Atropine	Fasted Fed	8 8	5 5	3 –	1 4	1 1
Hexamethonium	Fasted Fed	8 8	5 3	3 –	2 2	– 1
Metoclopramide (Low dose)	Fasted Fed	8 8	7 5	5 –	2 5	– –
Metoclopramide (High dose)	Fasted Fed	8 8	3* 3	1 2	2 1	– –
MDL72222	Fasted	8	4*	3	–	1
MDL + low dose metoclopramide	Fasted	8	4*	2	2	–
BRL24924	Fasted	8	7	6	1	–
BRL + low dose metoclopramide	Fasted	8	6	3	2	1

Erythromycin (7 mg kg⁻¹) was given either alone or in combination with all the drugs listed in the first column. For each treatment the number (*n*) of animals with emesis was compared with the number when erythromycin was given alone where **P* < 0.05, Fisher's exact test, and onset of latency is also shown.

results on emesis were obtained with another purported 5-HT₃ receptor antagonist, BRL 24924 (Renzapride), also in ferrets (Andrews *et al.*, 1986). The anti-emetic effect of these compounds was confirmed in the dog (Fitzpatrick *et al.*, 1990; Gullickson *et al.*, 1991) and man (Cunningham *et al.*, 1987).

In the present study the actions of MDL 72222 and BRL 24924 on erythromycin-induced emesis were studied because of their reported anti-emetic potential. Because emesis occurred more readily in the fasted than in the fed state, the two compounds were only studied in fasted dogs. They were used either on their own to test the 5-hydroxytryptaminergic component of any anti-emetic action, or in combination with a low dose of metoclopramide to investigate whether the emetic mechanism involved at least in part a dopamine pathway. MDL 72222 and other 5-HT₃ receptor antagonists have previously been shown to have no significant effect on pre and post prandial intestinal motility patterns (Davidson *et al.*, 1990). In the present study, only MDL 72222 was effective against the emesis caused by erythromycin, both alone and in combination with low-dose metoclopramide, confirming the anti-emetic efficacy of 5-HT₃ receptor antagonists and indicating that a 5-hydroxytryptaminergic mechanism is involved in the emesis provoked by erythromycin. BRL 24924 did not reduce emesis triggered by erythromycin even when combined with a low dose of metoclopramide.

Following the definition of a new class of 5-HT receptors (Dumuis *et al.* 1988), it is now suggested that substituted

benzamides like BRL24924 act on 5-HT₄ receptors, rather than on 5-HT₃ receptors as was first reported. The main action of these drugs is said to be 'prokinetic', they accelerate gastric emptying, increase antro-duodenal coordination, and are mild anti-emetics. It is thus possible that the anti-emetic effect of 5-HT₄ receptor agonists may be secondary to enhanced peristaltic coordination due to the activation of the 5-HT₄ peripheral receptor on the gastrointestinal tract (Craig & Clarke, 1989; 1991). It is not surprising that BRL24924 was not effective in preventing or decreasing emesis caused by erythromycin in the present study. Erythromycin has recently been shown to enhance gastric emptying by increasing antro-duodenal coordination (Janssens *et al.*, 1990; Ottersson & Sarna, 1990), and any compound that would decrease emesis by accelerating gastric emptying and coordinating peristalsis would be ineffective against erythromycin-induced emesis.

In summary, at clinically therapeutic doses, erythromycin causes large increases in small intestinal motility as well as emesis in the dog, these two effects occurring independently. The increase in contractile activity appears to be partly under cholinergic control, whereas emesis appears to occur via the activation of 5-HT₃ receptors without evidence for a dopamine pathway involvement.

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