Effects of oral laxatives on colonic motor complexes in dogs

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SUMMARY The effect of oral laxatives on the organisation of colonic motor complexes was investigated in four conscious dogs. Six strain gauge transducers were implanted on the colon of each dog. After a control period of two to three hours, dogs were orally dosed with 1, 2, or 4 ml/kg of castor oil, or 0.5 g/kg magnesium citrate. Oral olive oil, 4 ml/kg, was used as control. The recording was continued for another 10 hours or until defecation occurred. Each dog showed spontaneous cyclic bursts of contractions (contractile states) at all recording sites during the control period. Contractile states migrating orad or caudad over at least half the length of the colon were called colonic migrating motor complexes (CMMC). Castor oil and magnesium citrate significantly increased the period of colonic motor complexes, but olive oil had no significant effect. None of the above substances changed the percentage of orad migrating motor complexes, as compared with the control values. Periods in which colonic motor activity was completely absent for at least 60 min over at least three consecutive recording sites occurred more frequently after all of the substances. The occurrence of these periods of inhibition, however, was not a consistent feature and there seemed to be no relationship between the occurrence of inhibitory periods and defecation during the recording period. The dogs defecated within 10 hours after administration of magnesium citrate, 1, 2, and 4 ml/kg of castor oil in 12.5, 25, 37.5, and 88.8% of experiments respectively, but never with olive oil. Defecation was generally accompanied by giant migrating contractions in the colon. We conclude that oral laxatives, magnesium citrate and castor oil have a profound effect on colonic motor complexes and colonic motor activity. The period of CMMC is significantly prolonged after their oral administration because of an increased number of non-migrating motor complexes or periods of inhibition of motor activity.

Laxatives, purchased over the counter or by prescription, are frequently used to relieve constipation or to prepare the colon for endoscopic or radiological examination. The laxatives soften the stool and hasten its passage through the colon or the gastrointestinal tract depending upon whether they are administered through the rectum or taken orally. A number of laxatives are known to change the epithelial transport in the small intestine and the colon from net absorption to net secretion which may

be one of the major factors in softening of the stool. A net secretion, however, by itself may not be enough to speed up gastrointestinal transit for an early defecation. Changes in motor activity are likely to accompany this phenomenon, but such changes are not completely understood at this time, particularly in the colon.

Atchison *et al*^{1,2} reported that orally administered laxatives such as castor oil, magnesium sulphate and phenolphthalein produced a unique pattern of electrical response activity (ERA) in the small intestine where groups of three to four electrical response activity bursts migrated caudad. These

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laxatives also disrupted the migrating motor complexes in the small intestine for two to three days. Mathias *et al*³ reported that ricinoleic acid produced caudad migrating bursts of response activity in ligated ileal segments of anaesthetised rabbits.

The effects of castor oil and sodium ricinoleate on the cat colon have previously been studied *in vitro* and *in vivo*.^{4,5} It was reported that the laxatives produce an uncoupling of electrical control activity (ECA) and that such uncoupling of electrical control activity may lead to disorganised contractions.

Sarna *et al*⁶ recently described migrating and non-migrating motor complexes in the dog colon. Each recording site in the colon shows a periodic burst of contractions followed by a quiescent state. The bursts of contractions that migrated orad or caudad over at least half the length of the colon were called colonic migrating motor complexes. All other occurrences of these contractile states were called colonic non-migrating motor complexes. The colonic motor complexes are not disrupted by a meal but their period is prolonged.⁷ It was proposed that these motor complexes in the colon move contents back and forth with a net slow distal propulsion.^{6,8}

Our objective in this study was to determine the effect of orally administered laxatives on colonic

motor complexes in the conscious dog. The laxatives used were magnesium citrate, an inorganic laxative, and castor oil, an organic laxative. Both of these laxatives are known to alter epithelial fluid transport.⁹⁻¹² Magnesium citrate acts primarily through its osmotic action and castor oil by altering the fluid transport and motor activity.¹³ Olive oil was given as a control for castor oil to monitor possible changes in colonic motor activity caused by fat ingestion. In comparable doses olive oil is not a secretagogue.¹¹ An abstract of this work has been published elsewhere.¹⁴

Methods

ANIMALS

The experiments were done on four healthy conscious dogs of either sex weighing 20–25 kg. Under general sodium pentobarbital anaesthesia a midventral laparotomy was carried out to gain access to the abdominal cavity. The total accessible length of the colon was determined immediately after the administration of 100 µg/kg atropine to minimise shortening of the colon caused by handling. The prospective recording sites were marked with sutures. A set of six strain gauge transducers was implanted on the colon at the marked sites. The most

Fig. 1 Colonic motor complexes in the dog. Each recording site shows bursts of contractions called contractile states followed by periods of quiescence. Solid lines connecting the onset of contractile states indicate caudad migration, broken lines indicate orad migration. Two contractile states migrated over the entire length of the colon and were called colonic migrating motor complexes (CMMC). The remaining contractile states were non-migrating motor complexes.

proximal strain gauge transducer (SG1) was 5 cm distal to the ileocecal junction and the most distal one (SG6) was 5 cm proximal to the peritoneal reflection. The remaining transducers SG2 to SG5, were implanted in between SG1 and SG6 so that the distance between successive gauges was about the same (7–10 cm). The strain gauge transducers were oriented with their longitudinal axis parallel to the circular muscle axis. The lead wires were brought out through a stainless steel cannula in the left abdominal wall as described previously.¹⁵

The dogs were allowed to recover for 10 days after surgery. The animals were fasted for 16 hours before each experiment. On the day of the experiment, at least two hours of control recording was made showing at least two colonic migrating motor complexes as described previously.⁶ A colonic migrating motor complex was defined as that contractile state that migrated orad or caudad over at least four consecutive recording sites – that is, over at least half the length of the colon. A contractile state was defined as a burst of contractions that lasted for at least one minute. Two successive contractile states were separated by a quiescent period of at least two minutes.⁶ One of the following substances was given orally: 1 ml/kg, 2 ml/kg, and 4 ml/kg castor oil (USP, Lannett Co, Philadelphia, PA), 4 ml/kg olive oil (USP, Lannett Co, Philadelphia, PA) or 0.5 g/kg magnesium citrate (McKesson Lab, Dublin, CA). Olive oil, a triglyceride like castor oil but without a cathartic action, was used as a control. Each substance and each concentration was given twice to each dog. Experiments in which dogs expelled part of the laxative by vomiting during the recording session were not counted. Higher doses of the above substances were not used because they frequently caused vomiting. Magnesium citrate and castor oil usually caused diarrhoea overnight or on the following day. The time of onset of diarrhoea was unpredictable. Due to physical limitations, the recordings were continued for only 10 hours after the administration of laxatives or until defecation, whichever came first. A rest period of three to seven days was allowed for the recovery of dogs from the diarrhoeal state. The recordings were made on a Grass polygraph (model 7D) with lower and upper cut off frequencies set at DC and 3 Hz respectively. The signals were recorded simultaneously on a Hewlett Packard model 3968A tape recorder for later condensing of data in time.

In order to distinguish between the effects of instillation of the above substances into the stomach (gastrocolonic response), and the effects caused by the arrival of secretions due to these laxatives and their by-products into the colon, the total recording period was subdivided into test period I and test

Fig. 2 (a) Effects of olive oil and laxatives on the period of colonic migrating motor complexes. Rectangles and bars represent mean $\pm$ SE values. (b) Effects of olive oil and laxatives on the total duration of contractile activity/h during test periods I and II. Open, light, and dark rectangles represent control, test period I and test period II, respectively.

period II. Test period I comprised the first two hours after the administration of a substance and test period II the remaining period. The total duration of contractile activity/hour at all recording sites during these two test periods was determined and compared with the control value.

All the data were analysed visually for the onset and duration of contractile states at each recording site and for the migration characteristics of motor complexes as described previously.⁶ The analysis of variance and Student's t-test were used for statistical analysis. A p value of <0.05 was taken as statistically significant. All values are given as mean $\pm$ SE.

Results

GENERAL EFFECTS OF LAXATIVES

Defecation occurred within the 10 hour recording period after the administration of laxatives in 12.5,

Fig. 3 Effects of magnesium citrate on colonic motor activity. Solid lines show caudad migrating motor complexes. Rest of the contractile states did not show any consistent migration pattern. Magnesium citrate increased the CMMC period mainly by producing more non-migrating motor complexes.

25, 37.5, and 88.8% of experiments with magnesium citrate, 1 ml/kg, and 2 ml/kg and 4 ml/kg castor oil respectively. The earliest defecation occurred five hours after laxative administration. The mean interval between laxative administration and defecation was 7 ± 0.5 SE hours. Olive oil, 4 ml/kg, did not cause defecation within the 10 hour recording period in any of eight experiments and there was no apparent change in stool consistency. Magnesium citrate and castor oil in all doses produced watery stools.

EFFECTS OF LAXATIVES ON COLONIC MIGRATING MOTOR COMPLEXES

All dogs showed spontaneous colonic migrating and non-migrating motor complexes as shown in Figure 1. Each recording site showed alternating contractile and quiescent states. The solid lines connecting the onsets of contractile states at adjacent sites show caudad migration while the broken lines show orad migration of colonic motor complexes. The tracing in Figure 1 shows two colonic migrating motor complexes and two colonic non-migrating motor complexes. The time lag between two successive

Fig. 4 Effects of 1 ml/kg castor oil on colonic motor activity. Colonic migrating motor complexes are indicated by solid lines. Castor oil decreased the number of CMMC by producing long periods of inhibition of motor activity. Amplitude of contractions after castor oil was smaller than of those during the control period.

CMMC was called the period of colonic migrating motor complexes. The contractile states in a colonic non-migrating motor complex do not migrate at all or do not migrate consistently in the orad or the caudad direction over at least half the length of the colon. Two consecutive colonic migrating motor complexes may thus be separated by a quiescent state or by one or more non-migrating motor complexes.

Magnesium citrate significantly increased the CMMC period from 48 ± 4 SE min to 117 ± 12 SE min (Fig. 2a). The increase in CMMC period caused by magnesium citrate was largely because of the occurrence of non-migrating motor complexes in the colon (Fig. 3). Magnesium citrate had no significant effect on the total duration of contractile activity/hour during the first two hours after its administration (test period I), but it significantly increased it during the remaining period (test period II) as shown in Fig. 2b.

Castor oil, 1, 2, and 4 ml/kg, significantly increased the CMMC period from 48 ± 4 SE to 112 ± 26 , 131 ± 24 and 211 ± 63 SE min respectively. The increase in the CMMC period after castor oil was largely because of an increase in the duration of quiescent states as shown in Figure 4. In some experiments, however, the increase was also because of an increased incidence of non-migrating motor complexes. All doses of castor oil significantly decreased the total duration of contractile activity/hour during test period II (Fig. 2b). Only 4 ml/kg castor oil signifi-

Fig. 5 Effects of olive oil on colonic motor activity. Solid lines show the caudad migrating motor complexes, and broken lines the orad migrating motor complexes. Rest of the contractile states did not migrate over more than half the length of the colon. Olive oil had no significant effect on the period of colonic migrating motor complexes.

cantly decreased the duration of total contractile activity/hour during test period I. Visual observation indicated that the amplitude of colonic contractions was smaller after castor oil than that during the control recording period.

Olive oil had no significant effect on the CMMC period or the total duration of contractile activity/hour during test periods I and II (Figs 2 and 5).

None of the substances at any dose changed the percentage of orad migrating motor complexes in comparison with control values. The percentages were 16 ± 4 SE and 17 ± 8 SE before and after all three doses of castor oil, 16 ± 8 SE and 17 ± 4 SE before and after magnesium citrate, and 6 ± 6 SE and 8 ± 3 SE before and after olive oil.

REGIONAL EFFECTS OF LAXATIVES ON COLONIC MOTOR ACTIVITY

The effects of oral laxatives on the period of contractile states in the proximal (SG1, SG2), middle (SG3, SG4) and distal colon (SG5, SG6) were evaluated separately. Magnesium citrate and olive oil both increased the period of contractile states during test period II in the proximal and the middle colon (Fig. 6). In contrast, castor oil (1 and 2 ml/kg) significantly increased the period of contractile states in the distal colon only. The increase after 4 ml/kg did

Fig. 6 Effects of olive oil, magnesium citrate and castor oil on the period of cyclic motor activity in the proximal, middle and distal colon. The first 10 strain gauge transducers comprised the proximal colon, next two the middle colon, and the last two the distal colon.

not reach the level of significance. There was no consistent effect at other doses and in other parts of the colon.

PERIODS OF TOTAL INHIBITION OF COLONIC MOTOR ACTIVITY BY LAXATIVES

Periods in which motor activity was completely absent for at least 60 minutes over at least three consecutive recording sites were called periods of total inhibition of motor activity (Fig. 4). Such periods of total inhibition of motor activity were observed in only three of 40 experiments (7.5%) during the control period. In contrast, periods of total inhibition occurred in 50, 25, 37.5, 50, and 75% of experiments after olive oil, magnesium citrate, 1 ml/kg, 2 ml/kg and 4 ml/kg castor oil respectively (Table). The total duration of inhibitory periods as a percentage of the total recording period was the shortest after magnesium citrate and the longest after 4 ml/kg castor oil (Table). The first incidence of total inhibition of motor activity with magnesium citrate occurred soon after its administration while that with castor oil and olive oil took 40 minutes to several hours (Table).

There seemed to be no relationship between the

Table Periods of total inhibition of motor activities before and after test substances

	Control	Olive oil 4 ml/kg	Magn citr 50 mg/kg	Castor oil 1 ml/kg	Castor oil 2 ml/kg	Castor oil 4 ml/kg
Occurrence of PI* (% of experiments)	7.5	50	25	37.5	50	75
Percentage time of PI* (out of total recording time)	2.9	10.6	5.5	12.8	11.7	26.1
Mean duration of PI* [range] (min)	65 [62–69]	129 [71–202]	127 [60–195]	131 [62–185]	116 [78–149]	115 [68–257]
Mean time lag between laxative administration and first occurrence of PI* [range] (min)	—	219 [72–353]	7 [0–14]	173 [160–190]	196 [55–455]	73 [40–100]

*PI: Periods of total inhibition of motor activity at three or more consecutive recording sites.

occurrence of total inhibitory periods and the occurrence of defecation within the 10 hour recording period. Defecation within the recording period occurred in 40% of experiments in which total inhibitory periods were present and in 41% of experiments in which they were not present.

MOTOR ACTIVITY DURING DEFECTION AFTER LAXATIVES

When defecation occurred during the recording period after laxatives it was generally associated with giant migrating contractions (GMC) as we have described previously.¹⁶ We observed a total of 14 defecations during the 10 hour recording period after administration of the laxatives. In one case, a GMC migrated over the entire colon. Ten defecations were accompanied by giant migrating contractions that migrated over part of the colon as shown in Figure 7.

Their mean migration distance was 26.9 ± 4.3 SE cm. During two defecations only single giant contractions occurred at the most distal recording site and in one case giant contractions occurred almost simultaneously at different recording sites at the time of defecation. The mean amplitude ratio of the giant contractions and the maximal amplitude of contractions during the contractile states in the control period at the same recording sites was 2.8 ± 0.2 SE.

Discussion

Several laxatives are known to alter epithelial fluid transport resulting in net fluid accumulation.^{9,10} Net fluid accumulation may result from decreased absorption or increased secretion or both. Ricinoleic acid, the active component of castor oil and magnesium sulphate, both increase secretion in the small

Fig. 7 Colonic motor activity during defecation after castor oil: (A) a migrating motor complex during the control period. (B) the last 60 min of recording before defecation. Expanded recording at the time of defecation (c) shows a giant migrating contraction migrating over the proximal, middle and part of the distal colon.

intestine of man.^{14,15} It was, therefore, proposed that the early bowel movement of soft faecal material after these laxatives or frequent bowel movements during the diarrhoeal state may primarily be because of changes in epithelial transport.^{9,10} The possible role of motor activity in this phenomenon was questioned.

Our findings suggest that laxatives may have profound concurrent effects on colonic motor activity. It is not known, however, if the changes in motor activity are caused by an increased fluid load entering the colon from the small intestine or by a direct action of active components of laxatives on the colon. The epithelial transport and motor functions of the gastrointestinal tract are closely related, a change in one may induce a change in the other. For this reason, it may be difficult to separate motor effects that are secondary to secretion from those that are due to direct effects of active components of laxatives. It seems that both motor as well as epithelial transport changes may be important in the action of laxatives.

Both castor oil and magnesium citrate significantly increased the period of colonic migrating motor complexes, but this effect was achieved in different ways. The increase in the period of colonic migrating motor complexes after castor oil was largely because of prolonged periods of quiescence and hence a decrease in the total duration of contractile activity of the colon. The increase in CMMC period after magnesium citrate, on the other hand, was largely caused by an increase in the number of non-migrating motor complexes and thus an increase in the total duration of contractile activity. In contrast, olive oil had no significant effect on the period of colonic migrating motor complexes.

Lower doses of ricinoleic acid, the active ingredient of castor oil, stimulate and higher doses inhibit colonic motor activity *in vitro*.¹⁷ We did not find such a biphasic effect with oral doses of castor oil ranging from 1–4 ml/kg. Higher oral doses of castor oil could not be used due to their emetic effects. In our study the periods of total inhibition of motor activity increased at higher doses of castor oil. These differences may be because of several reasons: (1) In *in vitro* environment, the ricinoleic acid was directly in contact with the enteric plexuses and the smooth muscle. In our preparation, the ricinoleic acid may primarily be in contact with the mucosa. It is not known if the ricinoleic acid is taken up by the mucosal surface to contact the plexuses. (2) Other factors such as net fluid accumulation in the lumen, entero-enteric reflexes and intact extrinsic neural innervation may also contribute to overall *in vivo* effects while these factors are absent in *in vitro* environment. (3) The effective doses of ricinoleic acid to which the colon

was exposed in our study may be different from those used in *in vitro* experiments.

The orad migration of colonic motor complexes, though less frequent than their caudad migration, is a unique feature of colonic motor activity. Phase III activity in the small intestine has not been reported to migrate orad. None of the laxatives changed the percentage of orad migrating motor complexes. Thus the direction of migration of motor complexes may not play a role in diarrhoea.

Several investigators reported previously that the colon is hypomotile during the diarrhoeal state.^{18,19} We also found an increased incidence of prolonged periods of motor quiescence after castor oil and magnesium citrate. But the occurrence of these increased periods of quiescence was unpredictable and it was not always related to the occurrence of early defecation. It is possible that the occurrence of the prolonged periods of motor quiescence may depend upon the amount of faecal material present in the colon at the time of the experiment. On some days the dogs may have defecated before the experiments and on other days they may not have. On the other hand, when colonic motor activity was recorded from patients with diarrhoea, they usually had diarrhoea for several days and their colon may be more or less empty of faecal material.

The motor response of the colon to oral laxatives seems to be different from that of the small intestine. Atchison *et al*^{1,2} reported that bursts of electrical response activity and hence contractions were more organised in the jejunum after laxatives and they propagated caudad. Similarly, Mathias *et al*^{3,20} and Burns *et al*²¹ reported organised caudad migration of response activity in response to ricinoleic acid, cholera toxin and *Escherichia coli*. The colon seems to respond to laxatives by increasing the duration of quiescent states or by producing more disorganised contractile activity. This finding is in agreement with that of Christensen *et al*⁴ *in vitro* and of Wienbeck⁵ *in vivo* that the electrical control activity is phase-unlocked for a greater percentage of time in the cat colon after treatment with castor oil or ricinoleic acid.

Olive oil had no apparent effect on stool consistency and did not cause defecation during the recording period in our study. The main fatty acid in the triglyceride olive oil, is known to induce water and electrolyte secretion in the small intestine and to inhibit absorption in the colon.^{14,22} It has, however, also been reported that oleic acid is better absorbed in the small intestine than ricinoleic acid.¹¹ It is, therefore, possible that very low concentrations of oleic acid reached the colon and, therefore, the colon was able to absorb the additional fluid secretion of small intestine. Other investigators have also

reported that large doses of olive oil do not cause diarrhoea whereas identical doses of castor oil do.⁵

The final act of defecation after laxatives was not related to the presence or absence of colonic motor complexes or to increased or decreased colonic motor activity but to the occurrence of giant migrating contractions. Hardcastle and Mann also reported that laxatives like bisacodyl, oxyphenisatin, and sennoside administered directly into the colon, produced giant migrating contractions that were associated with rapid propulsion of colonic contents.^{23,24} We reported recently that these giant migrating contractions are associated with spontaneous and pharmacologically induced defecation.¹⁶ The mechanisms that trigger giant migrating contractions and early defecation several hours after the oral administration of castor oil or magnesium citrate are not known yet. Is it because of the arrival of a certain volume of faecal material in the colon, a direct stimulatory effect of active components of laxatives when they reach a certain concentration in the intraluminal contents or plasma, or is it because of a calculated response or reflex of the colon after it realises that it cannot handle the increased fluid load and it must be expelled? Further work needs to be done to elucidate the mechanism of early defecation caused by laxatives.

In conclusion, oral laxatives that are known to induce net fluid accumulation also have profound effects on colonic migrating motor complexes and colonic motor activity. The physiological effect of oral laxatives – that is, early defecation of soft stools, may be because of changes in both epithelial transport and gastrointestinal motor function.

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