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Effect of anthraquinone derivatives on canine and rat intestinal motility

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The effects on gastrointestinal motility of 3 senna preparations containing 18% oxidized Ca-sennosides, 60% Ca-sennosides, or pure sennosides A + B were tested in dogs and rats as measured by electromyography. Oral administration of the oxidized products in the fasted animal increased the activity of the small intestine within 2 h and reduced both caecal and colonic contractions for 24 h. Severe diarrhoea was present 4–6 h after administration and lasted for at least 1 day. Ca-sennosides had a similar, but weaker effect while pure sennosides affected motility only 6–10 h after oral administration. The intracolonic administration of the oxidized products resulted in an immediate reduction of colon motility for 7–8 h and diarrhoea was present within 40 min. Intracolonic Ca-sennosides and sennosides A + B induced only small changes in the intestinal motility, but diarrhoea also appeared. The results confirm that pure sennosides act predominantly on large intestine motility after their degradation by colonic microorganisms. Oxidized products are already effective in the upper gastrointestinal tract. The early action of Ca-sennosides requires further investigation. Side effects after oral senna treatment such as griping or nausea may be caused by motility changes induced by the presence of small amounts of oxidized products in the drug.

The consistency of faeces is the result of the transit rate of the digesta and/or changes in intestinal absorption. The transit rate is normally closely related to variations in the myoelectrical activity of the gut, whereas changes in water and electrolyte absorption are not necessarily caused by changes in motility. Continuous recordings of the electrical activity of the gut wall by chronically implanted electrodes allow an accurate assessment of motor phenomena in the conscious animal (Bueno et al 1975b, 1977; Code & Marlett 1975; Ruckebusch 1970; Ruckebusch 1977; Ruckebusch & Fioramonti 1975; Szurszewski 1969). Similar methods have already been used successfully to establish motility disturbances induced by castor oil, hyperosmotic mannitol, infections or sudden diet changes (Bueno et al 1975a; Christensen & Freeman 1972; Mathias et al 1976, 1977; Ruckebusch & Bueno 1975; Stewart & Bass 1976; Stewart et al 1975).

Senna glycosides (sennosides) which are responsible for the laxative action of senna, seem to pass the stomach and small intestine without being absorbed or attacked by gastric acid or intestinal enzymes. When they reach the large intestine they are broken down by micro-organisms into a pharmacologically active form that influences the motility of the colon as measured by visual observation or the balloon technique (Breimer & Baars 1976; Hardcastle & Wilkins 1970; Okada 1940; Schmid 1952; Schmidt 1960; Straub & Triendl 1934; van Os 1976). As their effect on other parts of the gut has had less attention, although side effects that may originate from the upper gastrointestinal tract like griping or nausea are well-known (Glatzel 1972; Godding 1976; Richter 1966), we have examined three senna preparations for their effects on the whole gastrointestinal motility in conscious dogs and rats using the electromyographic method.

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METHODS

Animals

Six mongrel dogs (14–22 kg) and 15 Wistar rats (300–350 g) of either sex were housed individually in modified metabolism cages, the rats on a 12:12 light-dark rhythm, and prepared with pairs of Ni-Cr electrodes (diameter 120 μm, length 100 cm in dogs; diameter 80 μm, length 50 cm in rats) chronically implanted into the gut wall (Bueno et al 1975b; Ruckebusch & Fioramonti 1975).

10–12 pairs of electrodes were positioned at regular intervals from the antrum to the colon in dogs and 6–7 pairs in rats. The last electrode was placed on the distal colon in dogs and on the proximal colon (3 cm distal of the Valvula ileocaecalis) in rats. The free ends of the electrodes were brought subcutaneously to the back of the neck. One dog was fitted with a cannula (external diameter 15 mm) in the proximal colon to allow intracolonic administra-

tion of the drugs. Transit studies were performed in 180 fasted female Wistar rats (180–270 g), 5 per cage, on a 12:12 light-dark rhythm at 24 ± 1 °C.

Electromyographic studies

Recordings of the electrical activity were obtained from 1 to 4 weeks after surgery by connecting the free ends of the electrodes to an e.e.g. machine. Direct recording was at a paper speed of 0·7 or 1·2 mm s^{-1} and at a time constant of 0·1 s. Spiking activity was also registered in an 'integrated' form after elimination of the slow waves by a high-pass filter, summed and plotted using a potentiometric recorder at a paper speed of 5 cm h^{-1} (Latour 1973). In dogs, records were visually evaluated. In rats, the number of migrating myoelectric complexes as well as the number of contraction periods per hour were counted for the antrum, the caecum and the colon. Statistical significance was assessed using the Student's *t*-test.

Test substances were given in hard gelatin capsules to dogs either 1 h before feeding or after fasting for 16 h. Controls were on the same dog but without drug. Intracolonic administration of an aqueous suspension was also assessed in the dog with a colonic canula. Measurements from dogs were made continuously. In rats, single periods, each of 24–30 h were used. After the rats had fasted for 16 h, a control measurement of 4–6 h was made, then the test substance as an aqueous suspension was administered by gastric tube and recordings made for 20–24 h. No experiment was repeated in the same animal before the normal motility pattern was re-established and diarrhoea had disappeared.

Drugs

These were: Dried purified senna extract containing 60% Ca-sennosides A + B according to the Bornträger reaction (Sandoz, Basel, Switzerland). Quality control* (h.p.l.c.) revealed a content of 48% sennosides A + B, 2–3% rhein, the remainder being unidentified as no reference substances were available.

Dried purified senna extract containing 18% Ca-sennosides A + B (Bombay Oil Company, India). This drug was completely oxidized* in an aqueous $FeCl_3$-solution for 5 h at 130 °C. No intact Ca-sennosides were present (t.l.c.), but rhein was found and there were some other spots which could not be identified because of the lack of reference substances.

* Performed by the chemical department of Madaus & Co. (Cologne, G.F.R.).

Sennosides A + B (1:1, Roth, Karlsruhe, G.F.R.) mol. wt 862·72. Doses of test compounds were 20–30 mg kg^{-1} orally and 10 mg kg^{-1} for intracolonic administration in the dog and 120 mg kg^{-1} in the rat. Doses and number of experiments are summarized in Table 1.

Table 1. Doses and number of experiments

	Fasted dog (oral)	Fed dog (oral)	Fasted dog (colonic)	Fasted rat (oral)
Dose of drug (mg kg^{-1})	20–30	20–30	10	120
	(No. of experiments)			
Senna extract 60% A + B	8	4	2	10
Senna extract 18% A + B oxidized	10	4	2	11
Sennosides A + B	4		2	4

Transit studies

Drugs (Ca-sennosides or oxidized Ca-sennosides) were administered by gastric tube in doses of 90, 120 or 250 mg kg^{-1} in 5 ml 1% tragacanth solution at different times (0, 30, 60, 120 or 240 min) before administration of a coloured marker (carmine 1% dissolved in 1·5% tragacanth solution, 10 ml kg^{-1} oral). Controls received vehicle. Ten rats were used for each group. Carbachol chloride (Merck, Darmstadt; 4 ml = 1 mg kg^{-1} s.c.) was given at the same time as the carmine marker. This dose has been previously shown not to obscure significant effects of drugs on transit time, while inducing a regular flow of ingesta thus facilitating measurement of the coloured part of the intestine. 20 min later the animals were killed and the gastrointestinal tract was removed, gently stretched on filter paper and the length of the small intestine as well as the length of the coloured part measured and expressed as percent of the length of the whole small intestine.

RESULTS

Dogs

Controls showed migrating myoelectric complexes in the small intestine every 90–120 min from 10 to 24 h after the daily meal. These consisted of two phases, one of irregular spiking activity followed by a phase of regular spiking activity, in which all slow waves were superposed by action potentials (Fig. 1). At the same time, an increased electrical activity in the

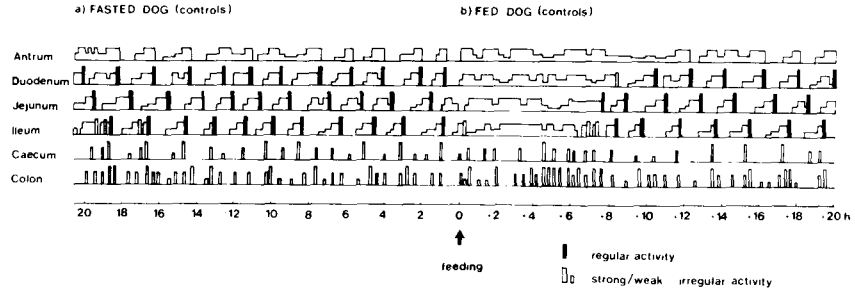

FIG. 1. Diagrammatic representation of the electrical activity in different parts of dog gastrointestinal tract before and after feeding.

antrum was recorded, whereas in both the caecum and colon contraction periods partly related to the arrival of a myoelectric complex in the ileum, occurred. After food, the motility of all parts of the intestine increased due to suppression of the quiescence periods.

After oral administration of Ca-sennosides to the fasted dog the myoelectric complexes in the small intestine disappeared for 13–20 h. Caecal and colonic contraction frequencies were significantly depressed for about 24 h (Fig. 2) and severe diarrhoea occurred within 4–6 h. Administration of the drug 1 h before feeding did not alter the normal postprandial pattern of the motility of the upper gastrointestinal tract (Fig. 2), but caecal and colonic motilities were depressed or, at least, the normal increase in colonic activity in response to feeding failed to appear. The diarrhoea was similar to that seen in the fasted dog.

The sennoside oxidation product by mouth also caused the myoelectric complexes of the jejunoileum in the fasted dog to disappear within 2 h for 12–14 h. Concomitantly, caecal and colonic motilities were significantly reduced for more than 24 h and diarrhoea occurred within 6 h for at least 1 day, whether the dog was fasted or fed (Fig. 3).

Pure sennosides did not affect the intestinal motility until 6 h after oral administration (Fig. 4). In 3 out of 4 experiments, antral and small intestinal motility were disorganized and the reduced contraction frequency in the caecum and colon 6–10 h after treatment became normal about 10 h later. There was a moderate laxative effect after 8–16 h. In the 4th experiment, there were no changes in motility and no diarrhoea. In contrast, the sennoside oxidation products placed in the colon immediately reduced its motility for 3–8 h and diarrhoea occurred 40 min later and lasted for some hours (Fig. 5). With the exception of the ileum, which tended to be disorganized with prolonged irregular actiivty and reduced regular activity, upper gastrointestinal motility was unaffected. Colon motility was mildly affected by intracolonic Ca-sennosides. Diarrhoea occurred some hours later and lasted for about 1 day. Pure sennosides by the same route produced severe diarrhoea within 30 min, which lasted several days. There were no striking changes in the electrical activity.

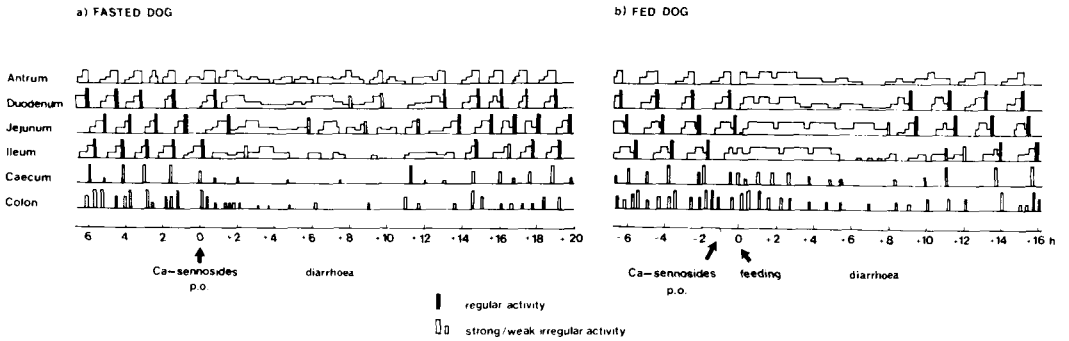

FIG. 2. Motor effect of orally administered Ca-sennosides in a fasted (a) or fed dog (b).

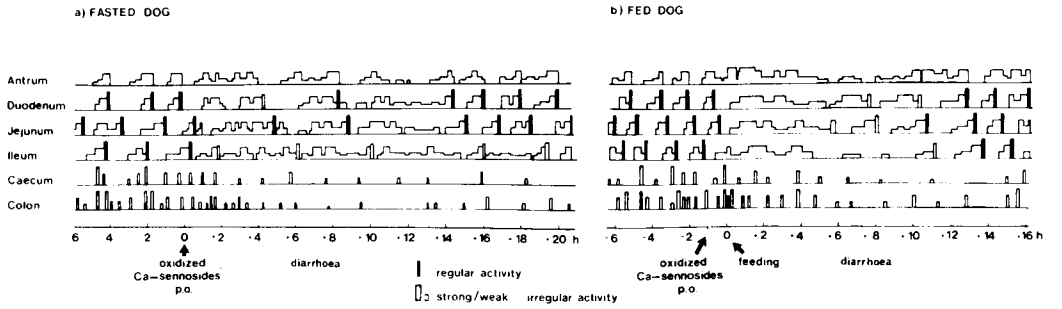

FIG. 3. Effect of orally administered oxidized sennosides in a fasted (a) or fed dog (b).

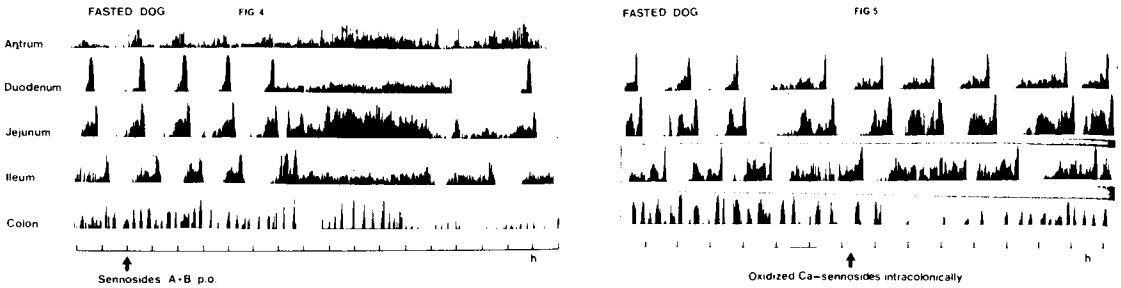

FIG. 4. Electrical activity summed at 20 s intervals of different parts of dog gastrointestinal tract after oral administration of pure sennosides.

FIG. 5. Electrical activity summed at 20 s intervals of different parts of dog gastrointestinal tract after colonic administration of oxidized Ca-sennosides.

Rats

Myoelectric complexes in the small intestine of untreated rats appeared every 15–25 min (see Ruckebusch & Fioramonti 1975). The caecum showed short and distinct contraction periods interrupted by periods of quiescence. These contractions were continued in the colon and interspersed with periods of high level of spiking activity. As in the dog, continuous irregular spiking activity occurred after feeding. Oral administration of sennoside oxidation products and Ca-sennosides resulted in a distinct diarrhoea in only 50% of the rats. Pure sennosides caused a laxative effect in only 1 out of 4 experiments.

Sennoside oxidation products significantly inhibited the number of myoelectric complexes in the duodenum, jejunum and ileum within 2 h and up to 20 h after administration (Fig. 6). Minimal values were reached progressively from duodenum to ileum. Antral activity remained unaffected, but caecal and colonic motility also dropped. Normal values were not obtained until after 20 h. Ca-sennosides had a similar, but milder effect on small intestinal motility. Colonic and caecal activities, however, were severely reduced with almost no sign of recovery after 20 h. Pure sennosides showed no early effect on gastrointestinal motility in the 3 experiments in which no diarrhoea was evident. One experiment which resulted in a laxative effect, caused a slight reduction of the number of the myoelectric complexes in the small intestine and a pronounced depression of caeco-colonic motility.

The two senna extracts exerted no effect on small intestinal transit time. Neither different doses of the drugs nor different times of pretreatment resulted in significant changes in the coloured length of the small intestine compared with the control.

DISCUSSION

The normal intestinal myoelectrical activity found for dogs and rats corresponds with previous findings

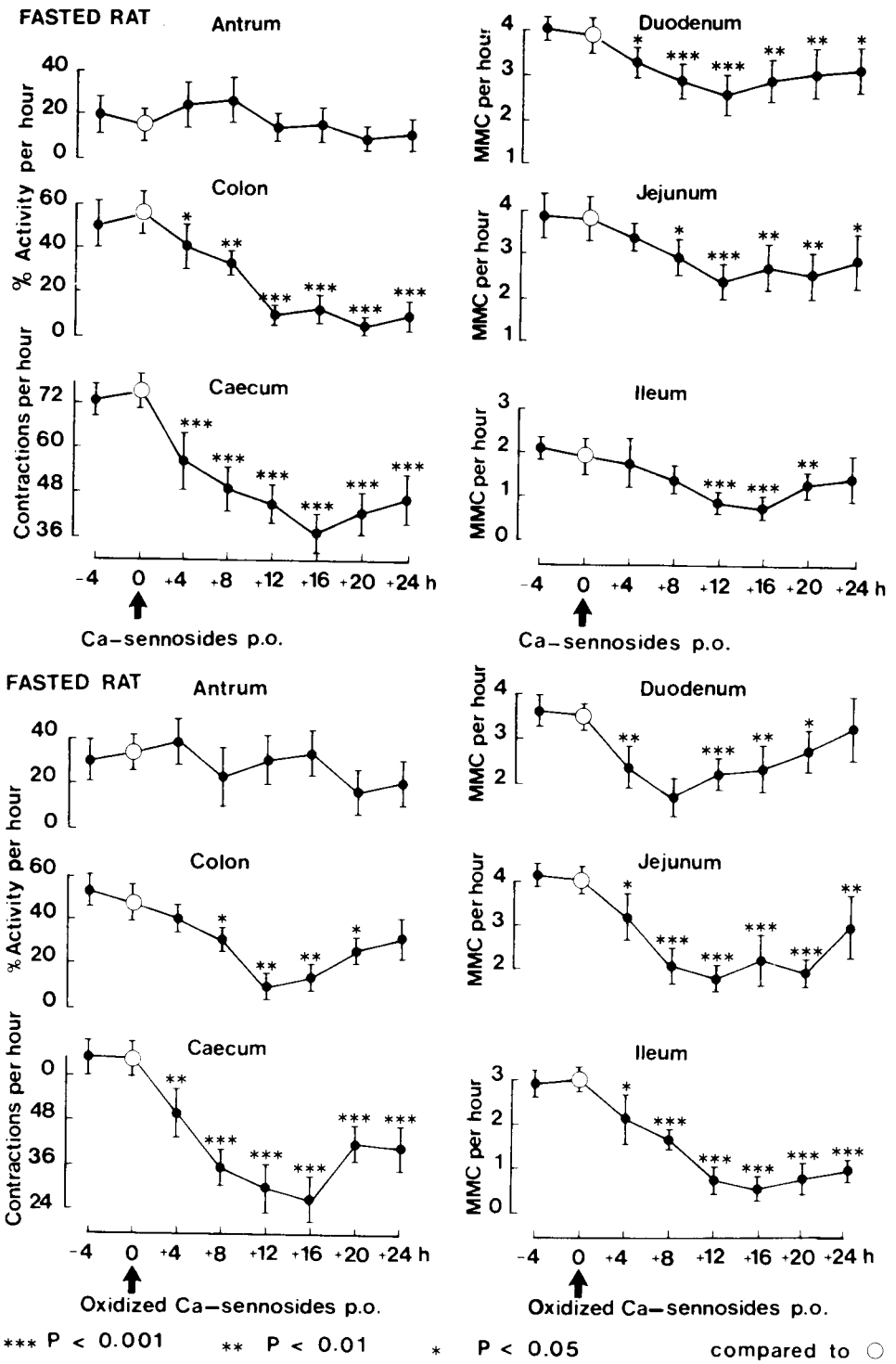

FIG. 6. Electrical activity in different parts of rat gastrointestinal tract after intragastric administration of Ca-sennosides (*top*) or oxidized Ca-sennosides (*bottom*).

(Bueno et al 1975b, 1977; Ruckebusch & Fioramonti 1975).

Oral administration of Ca-sennosides or their oxidized products induced a sudden reduction or even a disappearance of the migrating myoelectric complexes, accompanied by a tendency towards a continuous irregular spiking activity in the small intestine and a pronounced reduction of colonic activity. Pure sennosides showed a 6–8 h delay before an effect was noticeable which may correspond to the transit time necessary to reach the large intestine. This supports the presumed mechanism of senna action in that sennosides have to be transformed by colonic microorganisms before becoming active. Their action on motility, however, was not restricted to the colon, the upper gastrointestinal tract was also affected, though to a lesser extent than with the other preparations. If the action of senna is based on a stimulation of the colonic myenteric neurons as was proposed by Okada (1940) and Smith (1968), the local effect may be spread by neural pathways and the degree of spread may be related to the concentration of active derivatives in the colon.

The sudden changes in motility of the small intestine after oral administration of oxidized Ca-sennosides was not surprising as it is unreasonable to expect that they would specifically influence colon motor activity. The near simultaneous reaction of the large intestine is evidence for reflex mechanisms which differ from those after eating in that colonic motility was not stimulated, but depressed. In rats, the gastrointestinal myoelectric activity reacts very sensitively to oxidized Ca-sennosides, because motility disturbance were recorded even when no diarrhoea was apparent.

Surprisingly, Ca-sennosides administered orally had a similar effect on upper gastrointestinal motility as their oxidized products, in a time too short to allow their degradation in the large intestine. At present, the most likely explanation is that the action on motility may be induced not by the Ca-sennosides themselves, but by contaminating compounds such as rhein and other Bornträger-positive substances (see Methods). This would mean that intestinal motility is a very sensitive indicator of the content of oxidized derivatives in senna drugs. An explanation in terms of the Ca-sennosides being less stable in acid pH of the stomach than non-salt sennosides seems unlikely. Intracolonic administration of oxidized Ca-sennosides induced an almost immediate effect on both colonic motility and stool production. Ileal motility was also affected. The effect of intracolonic Ca-sennosides and sennosides A + B on colonic motility was less pronounced, although diarrhoea occurred but the experiments with pure sennosides A + B were not enough for definite conclusions to be drawn.

The relationship between changes in gastrointestinal motility and the induction of diarrhoea is not fully resolved. However, diarrhoea is normally accompanied by colonic hypomotility as is constipation by colonic hypermotility (Waller et al 1972; Wangel & Deller 1965). This is explained by the loss of the normal segmenting contractions and therefore a smaller resistance to flow (Connell 1962). The reduced number of contractions in the colon after all three senna preparations indicates that a fast passage of the digesta through the colon may contribute to diarrhoeal conditions. In the rat, the flow rate in the small intestine was not increased. This was confirmed by preliminary experiments in the dog. Schmid (1952), using coloured food, also found that small intestinal transit time was hardly influenced by senna administered orally, but that time of passage along the colon was significantly reduced. In man, gastric emptying and small intestinal transit did not differ in constipation and diarrhoea, whereas time of passage along the colon was significantly faster in patients suffering from diarrhoea (Waller 1975). Oxidized senna placed via the colon stimulated the peristaltic response in a manner similar to other laxatives, e.g. bisacodyl and oxyphenisatin (Hardcastle & Mann 1968; Hardcastle & Wilkins 1970; Ritchie 1972).

The normal myoelectrical activity of the gut is often affected during diarrhoea (Stewart et al 1975; Stewart & Bass 1976; Mathias et al 1977; Vantrappen et al 1977). The extent to which motility is influenced, seems to depend on the type of infection or on the drug used to induce diarrhoea. With senna, motility changes certainly play an important role in the laxative effect. Oxidized derivatives induce diarrhoea in a faster and more severe way than the sennosides themselves and may be responsible for undesired side effects.

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