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► To cite this version:

Jean Fioramonti, G. Staumont, Rafael Garcia Villar, Lionel Bueno. Effect of sennosides on colon motility in dogs. Pharmacology, 1988, 36 no. 1, pp.23-30. hal-02724170

HAL Id: hal-02724170

<https://hal.inrae.fr/hal-02724170>

Submitted on 2 Jun 2020

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Effect of Sennosides on Colon Motility in Dogs

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Key Words. Laxatives · Sennosides · Colon · Motility · Dog

Abstract. Oral administration of sennosides (20–30 mg/kg) to fasted dogs has been shown to induce a strong and long-lasting inhibition of myoelectric colon activity which was evident after a delay of 6–10 h corresponding to oro-cecal transit and colonic metabolism and was accompanied by abundant diarrhea. When sennosides were given 1 h before a meal, the postprandial increase in colon motility failed to appear. Recent studies with strain gage transducers confirm the inhibition of colonic motility after oral sennosides but, in addition, 3–10 ‘giant contractions’ with a high amplitude appeared during the period of inhibition. Most of these single contractions were propagated over the second half of the colon at a velocity of 0.5–2 cm/min. Elimination of liquid feces was always associated with giant contractions. These giant contractions have also been described with other stimuli (i. v. guanethidine or neostigmine, oral castor oil, intraluminal hypertonic glucose) and are therefore not specific for sennosides.

The dog is an animal species widely used for chronic studies of gastrointestinal and colonic motility. Like all carnivorous species, the dog colon is characterized by a short length, but the digestive phenomena such as fermentations and hydroelectrolytic absorption are comparable to that observed in humans. The main peculiarity of canine colonic motility is a relatively great regularity [1] in comparison with humans [2] or other animal species [3]. The regular occurrence of colonic

contractions in the basal state is very useful in pharmacology. The action of laxatives and more precisely sennosides on canine colonic motility have been investigated by recording myoelectrical activity with intraparietal electrodes [4] or mechanical activity using strain gage transducers sutured to the serosa (unpublished data). In this short review we will present some basic data on myoelectrical and mechanical activity of the dog colon before describing the effects of sennosides.

Colonic Myoelectrical Activity

As for most of the other parts of the digestive tract, colonic myoelectrical activity is characterized by slow waves and bursts of spikes. In the dog colon, slow waves are labile, occur at a frequency of 5–8 cycles/min, do not correspond to contractions and are not associated with spiking activity [5]. Moreover, some slow waves with a frequency of 18/min are artefacts originating from the duodenum [6]. The main characteristic of the colonic electromyogram, originally observed in pigs [7] and then described in several mammalian species [3] including dogs [8] and humans [9] is a duality of spiking activity. The first type of spiking activity consists of short-spike bursts (SSB) lasting for 1.5–3.5 s and occurring most often rhythmically at a rate of 10–11/min. These bursts always appear localized in a colonic segment of a few centimeters in length. The second kind of spiking activity consists of long-spike bursts (LSB) lasting for 10–20 s and appearing either localized or propagated in aboral or oral direction. Such a duality has been described by several authors using different denominations. For example SSBs have been described as ‘discrete electrical responses activity’ by Sarna et al. [10] or as ‘rhythmic spike potentials’ by Schang and Devroede [11].

The significance of these spike bursts in the contractile activity of the colon is different. The LSBs are associated with contractions of large amplitude and are responsible for the mixing and the propulsion of intraluminal content, while the SSBs correspond to contractions of low amplitude and probably reflect a tonic activity of the colonic wall [8].

In the dog colon the LSBs are grouped in periods with a duration of about 5 min on the ascending colon which increases progressively along the colon and reaches 10–15 min at the end of the descending part. These phases of activity recur cyclically at intervals of 20–30 min and are slowly propagated from the ileo-colonic junction to the descending colon. The SSBs occur irregularly without cyclic organization and are preponderant in the distal parts of the colon [8].

Colonic Mechanical Activity

Mechanical activity of the dog colon has been investigated using strain gage transducers sutured to the serosa [1, 12, 13]. Such a technique permitted only the recording of high-amplitude contractions which correspond to the LSBs on the electromyogram [3, 14]. The cyclic phases of contractions, already described for the LSBs [8], were analyzed in detail for their propagation [14] or for their nycthemeral fluctuations [1]. The main change in the dog colonic motility is associated with the meal intake. In all dogs the frequency of the phases of contractile activity was increased and the motility index nearly doubled during a 8- to 10-hour period beginning 2–3 h after the meal. Such an increase in colonic motility is associated with the arrival of digesta into the colon since it did not appear when the intestinal content was drained out through a cannula cephalad to the ileo-colonic junction. In some dogs a supplementary phase of contractions appeared just after the meal which probably corresponds to the gastro-colonic reflex [15], followed in some instances by a period of inhibition, the origin of which remains unknown.

Recently a peculiar kind of contractions, called 'giant migrating contractions' have been described in the dog colon [16]. These single contractions last less than 1 min with an amplitude 2–3 times higher than that of the strongest contractions in the normal colonic motor profile. Most of them are propagated over the second half of the colon at a velocity of 0.5–2 cm/min. These contractions have been rarely observed spontaneously. Our experience indicates that defecation is always associated with the giant contractions but not all of them correspond to a defecation. They can be induced experimentally by several stimuli such as intravenous guanethidine or neostigmine, oral castor oil, intraluminal glucose, but rarely by rectal distension [16].

Action of Sennosides

Sennosides, in contrast to most other laxatives, have a specific colonic site of action since they are activated only by metabolism of colonic microorganisms. For this reason a specific action on colonic motility may be postulated. Experiments performed in humans indicate a stimulatory action of sennosides and other laxatives on colonic motility. In 1970, Hardcastle and Wilkins [17] introduced through a colostomy sennosides previously incubated with feces or *Escherichia coli* and, using manometry, immediately observed powerful peristaltic colonic contractions. This effect did not appear with nonincubated sennosides but was produced by rhein anthrone, a main metabolite of sennosides. Similarly, in 1972, Ritchie [18] observed mass peristalsis, using cinefluorography, after intracolonic administration of another laxative compound, oxyphenisatin.

In contrast to these results obtained in humans, the only published data concerning the action of sennosides on colonic motility in dogs, obtained by electromyography, indicate an inhibition of colonic contractile activity [4]. The duration and the latency of the effects after oral administration of senna extract depended upon the degree of purification. Administration of 20–30 mg/kg of dried purified senna extract containing 48% sennosides A + B in fasted dogs significantly depressed the frequency of the phases of spiking activity for about 24 h. Such an effect appeared very shortly (less than 1 h) after oral administration, the inhibition of colonic activity was nearly total for 10–12 h and severe diarrhea always occurred within 4–6 h (fig. 1). In contrast, pure sennosides administered orally at the same dosage inhibited colonic activity after a longer delay (6–10 h), during a shorter period (10 h) and had a moderate laxative effect 8–16 h after oral administration. Dried purified senna extract, containing 18% sennosides A + B completely oxidized in an aqueous FeCl_3 solution for 5 h at 130 °C administered orally at the same dosage, significantly reduced colonic spiking activity after a delay of 2 h and for more than 24 h. Such an effect was accompanied by diarrhea within 6 h and for at least 1 day.

Myoelectrical activity of the stomach and the small intestine was also monitored in this study. Disruption of the cyclic gastrointestinal activity appeared after oral administration of the three senna preparations. However, the less pronounced effects were observed with pure sennosides which altered antral and small intestinal motility after a delay of 6 h and for 6–10 h. In contrast, oral administration of the 48% sennoside preparation or of the sennoside oxidation product in-

Fig. 1. Electrical activity in different parts of the gastrointestinal tract in dogs receiving an oral dose of 20 mg/kg sennosides. Each rectangle represents a phase of myoelectrical spiking activity. A = Antrum, D = duodenum, J = jejunum, C = cecum, Col = colon [ref. 4].

Fig. 2. Mechanical activity of the colon recorded with strain gage transducers in a dog receiving oral sennosides at two dosages. Note the inhibition of the basal colonic motility and the giant contractions associated with defecation.

duced disturbances of gastrointestinal motility for 12–20 h and after a short delay (2 h).

Inhibition of colonic motility also appeared after intracolonic administration of each of the three preparations of sennosides at a dose of 10 mg/kg. The most pronounced inhibition appeared for 3–8 h immediately after administration of oxidized sennosides. Pure or 48% sennosides mildly affected colonic motility.

Recently, unpublished data obtained in our laboratory by recording mechanical activity of the dog colon through strain gage transducers sutured to the serosa have confirmed the sennoside-induced colonic inhibition. Moreover, during the period of inhibi-

tion which began 3–5 h after oral sennosides, 3–10 giant contractions appeared (fig. 2), similar to those previously described by Karaus and Sarna [16]. These contractions lasted less than 1 min; for this reason they probably did not appear clearly on the colonic electromyograms and were not described in the work of Garcia-Villar et al. [4]. Emission of liquid feces was always associated with giant contractions but not all of these contractions corresponded to a defecation.

The minimum dose of oral sennosides which induced the above described disturbances of colonic motility and diarrhea varied between 5 and 25 mg/kg in the seven

mongrel dogs used. This minimum dose was generally lower for heavy dogs (20–30 kg) than for dogs of 8–10 kg in body weight, which indicates that a dose expressed per animal would be more convenient than a dose expressed per kilogram of body weight. As indicated in figure 2, the duration of the colonic inhibition seems to be dose-related within the same animal. In the dog used in figure 2, the effects lasted for 3 h after a dose of 5 mg/kg and more than 10 h after a dose of 30 mg/kg.

The effects of oral sennosides were reproduced by intracolonic administration but the delay in their appearance was shorter (0.5–1.5 h).

Discussion and Conclusions

The data reported above indicate that in dogs oral administration of sennosides induces, after a delay corresponding to orocecal transit and colonic metabolism, a long-lasting inhibition of the basal colonic motor profile and the appearance of high-amplitude contractions mainly associated with defecation.

The action of oral sennosides on gastric and small intestinal motility cannot be easily explained. The disturbances observed after pure sennoside administration may indicate that some unidentified metabolite [5] acts after colonic absorption and systemic passage. The fact that the most important disturbances of the upper bowel were observed with the 48% sennoside preparation suggests an action of impurities as already underlined for the acute toxicity and the laxative effect of sennosides in mice [19].

The question arises whether the effects described herein are specific for sennosides

and therefore experiments with other laxative compounds, using the same techniques, must be done. A second question is whether the disturbances of colonic motility are due to an action of sennosides or are a consequence of fluid secretion. A recent study shows that an increase of fluid volume in the colon induced by a duodenal infusion of hypertonic mannitol solution in dogs was associated with an increased colonic motility [20]. Similarly, diarrhea induced by overfeeding in dogs corresponded also to a stimulation of colonic motility [8]. These two data indirectly favour a direct action of sennosides on colonic motility which is not a consequence of fluid accumulation.

It seems that one of the main mechanisms of the laxative action of sennosides involves prostaglandins because sennoside administration stimulated the output of prostaglandin E_2 into the colonic lumen and the sennoside-induced fluid secretion is blocked by indometacin [21]. Since PGE_2 has been found to inhibit colonic motility both in vivo [22] and in vitro [23], a prostaglandin-mediated mechanism may be postulated to explain the action of sennosides on colonic motility.

The laxative action of rhein, a stable metabolite of sennosides, has been found to be antagonized by morphine [24]. This effect does not indicate a mechanism of action but corresponds to the well-known antidiarrheal properties of opiates.

A recent study [25] shows that sennosides and other laxatives induce the release of histamine and serotonin by the rat intestine. These data indicate that the involvement of histaminergic and serotonergic pathways may be postulated in the action of sennosides in colonic motility.

References

- 1 Fioramonti, J.; Buéno, L.: Diurnal changes in colonic motor profile in conscious dogs. *Dig. Dis. Sci.* 28: 257-264 (1983).
- 2 Frexinos, J.; Buéno, L.; Fioramonti, J.: Diurnal changes in myoelectric spiking activity of the human colon. *Gastroenterology* 88: 1104-1110 (1985).
- 3 Fioramonti, J.: Etude comparée des fonctions motrices du gros intestin; Dr. Sci. thesis Toulouse (1981).
- 4 Garcia-Villar, R.; Leng-Peschlow, E.; Ruckebusch, Y.: Effect of anthraquinone derivatives on canine and rat intestinal motility. *J. Pharm. Pharmacol.* 32: 323-329 (1980).
- 5 Buéno, L.; Garcia-Villar, R.; Ruckebusch, Y.: Activité électrique du côlon chez le chien éveillé. *C.r. Séanc. Acad. Sci. Ser. D* 285: 1463-1466 (1977).
- 6 Fioramonti, J.; Buéno, L.; Sarna, S.K.; Ruckebusch, Y.: Origin of high slow wave frequency in the dog colon. *Reprod. Nutr. Dev.* 20: 983-990 (1980).
- 7 Fioramonti, J.; Buéno, L.: Motor activity in the large intestine of the pig related to dietary fibre and retention time. *Br. J. Nutr.* 43: 155-162 (1980).
- 8 Fioramonti, J.; Garcia-Villar, R.; Buéno, L.; Ruckebusch, Y.: Colonic myoelectrical activity and propulsion in the dog. *Dig. Dis. Sci.* 25: 641-646 (1980).
- 9 Buéno, L.; Fioramonti, J.; Ruckebusch, Y.; Frexinos, J.; Coulom, P.: Evaluation of colonic myoelectrical activity in health and functional disorders. *Gut* 21: 480-485 (1980).
- 10 Sarna, S.K.; Waterfall, W.E.; Bardakjian, B.L.; Lind, J.F.: Types of human colonic electrical activities recorded postoperatively. *Gastroenterology* 81: 61-70 (1981).
- 11 Schang, J.C.; Devroede, G.: Fasting and postprandial myoelectric spiking activity in the human sigmoid colon. *Gastroenterology* 85: 1048-1053 (1983).
- 12 Schuurkes, J.A.J.; Tukker, J.J.: The interdigestive motor complex of the dog. *Archs int. Pharmacodyn. Théor.* 247: 329-334 (1980).
- 13 Sarna, S.K.; Condon, R.; Cowles, V.: Colonic migrating and nonmigrating motor complexes in dogs. *Am. J. Physiol.* 246: G355-G360 (1984).
- 14 Sarna, S.K.: Myoelectric correlates of colonic motor complexes and contractile activity. *Am. J. Physiol.* 250: G213-G220 (1986).
- 15 Tansy, M.F.; Kendall, F.M.: Experimental and clinical aspects of gastrocolic reflexes. *Am. J. dig. Dis.* 18: 521-531 (1973).
- 16 Karaus, M.; Sarna, S.K.: Giant migrating contractions during defecation in the dog colon. *Gastroenterology* 92: 925-933 (1987).
- 17 Hardcastle, J.D.; Wilkins, J.L.: The action of sennosides and related compounds on human colon and rectum. *Gut* 11: 1038-1042 (1970).
- 18 Ritchie, J.: Mass peristalsis in the human colon after contact with oxyphenisatin. *Gut* 13: 211-219 (1972).
- 19 Marvola, M.; Koponen, A.; Hiltunen, R.; Hietala, P.: The effect of raw material purity on the acute toxicity and laxative effect of sennosides. *J. Pharm. Pharmacol.* 33: 108-109 (1981).
- 20 Fioramonti, J.; Droy-Lefaix, M.T.; Buéno, L.: Changes in gastro-intestinal motility induced by cholera toxin and experimental osmotic diarrhoea in dogs: effects of treatment with an argillaceous compound. *Digestion* 36: 230-237 (1987).
- 21 Beubler, E.; Kollar, G.: Stimulation of PGE₂ synthesis and water electrolyte secretion by senna anthraquinones is inhibited by indomethacin. *J. Pharm. Pharmacol.* 37: 248-251 (1985).
- 22 Hunt, R.H.; Dilawari, J.B.; Misiewicz, J.J.: The effect of intravenous prostaglandin F_{2α} and E₂ on the motility of the sigmoid colon. *Gut* 16: 47-49 (1975).
- 23 Sanger, G.J.; Bennett, A.: Regional differences in the response to prostanoids of circular muscle from guinea-pig isolated intestine. *J. Pharm. Pharmacol.* 32: 705-708 (1980).
- 24 Verhaeren, E.H.C.; Geezaerts, V.C.J.; Lemli, J.: The antagonistic effect of morphine on rein-stimulated fluid, electrolyte and glucose movements, in guinea-pig perfused colon. *J. Pharm. Pharmacol.* 39: 39-44 (1987).
- 25 Capasso, F.; Mascolo, N.; Autore, G.; Romano, V.: Laxatives and the production of autacoids by rat colon. *J. Pharm. Pharmacol.* 38: 627-629 (1986).

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Discussion

Sarna: You reported that sennosides inhibit colonic motility. What do you think is the significance of this in inducing diarrhea?

Fioramonti: That the basal motility of the colon is inhibited has been shown with the electromyographic technique and with the strain gage transducers, too. With the latter technique, however, we see, in addition, giant contractions which seem to be responsible for the evacuation of liquid feces.

Sarna: When you infused mannitol in dogs, colon motility was stimulated and the dogs got diarrhea. How do you reconcile these two entirely opposite motor effects associated with the same end result of diarrhea?

Fioramonti: Mannitol has an osmotic effect resulting in the arrival of a large volume in the colon which, obviously, stimulates large intestinal motility. In contrast, the action of sennosides seems not to be only the consequence of an increased fluid secretion, but a true pharmacological action on the smooth muscle cell or on receptors of the myenteric plexus.

Read: Mannitol may have a pharmacological effect, too, as it is fermented to a certain extent and the

fermentation products may well influence motility. I wonder whether you would see the giant migrating contractions and the inhibition of colonic motility when you infuse fairly neutral solutions, for example saline solution, into the colon at a high rate imitating colonic secretion?

Fioramonti: When we infuse mannitol, there is diarrhea after a very short delay of 40 min. I do not think that there is sufficient time for fermentation and an action of the fermentation products. When we infuse a large volume of saline into the colon we do not observe important effects on colonic motility, neither inhibition nor giant contractions.

Wienbeck: With sennosides, does diarrhea start only after the period of motor inhibition and is there an overshooting of activity following this motor inhibition?

Fioramonti: The onset of diarrhea is quite variable depending partly on the continence behaviour of the dog, but normally diarrhea starts within the period of inhibition which, after 30 mg/kg, may last for 10–15 h. There is no rebound of activity.