Evaluation of the Effects of Sennosides on Uterine Motility in the Pregnant Ewe

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Abstract. The effects of sennosides on uterine motility were evaluated by electromyography in healthy adult ewes between day 70 and 120 of pregnancy to assess possible disturbances of the physiological pattern of contractility and eventual risks in pregnancy maintenance. At this stage of pregnancy, the ovine genital tract presented motility episodes of 6–8 min duration occurring at approximately hourly intervals. A dose-range study (10–160 mg/kg intracolonicallly) in 2 ewes showed that diarrhea was systematically obtained with doses > 20 mg/kg and was connected with a marked depression of both ileum and spiral colon motility. A standard dose of 60 mg/kg administered intracolonicallly 1–3 times at 7- to 10-day intervals to 12 ewes was used in the uterus studies. The experiments showed that sennosides did not stimulate uterine motility in the pregnant ewe, but slightly depressed it in some ewes. Cervix motility was never influenced. Intolerance of the drug was observed in half of the animals resulting mainly in anorexia or weakness and confirming a specific toxicity of senna in ruminants which is not known from other species. These effects were not related to uterine motility and pregnancy maintenance was normal in all ewes.

Introduction

Constipation is a trouble of gastrointestinal transit with a high prevalence during pregnancy [1]. The etiological factors involved are multiple: dietary changes, sedentary life, pressure exerted on the bowel by the enlarging uterus and variations in hormone levels. Although fiber-rich diets or appropriate physical exercise could be able, to some extent, to prevent the occurrence of

constipation, recourse to medication is often necessary.

Antraquinones have an ancient history as laxatives. There exists general agreement concerning their gross mechanism of action (colon specificity of anthranoid glycosides like sennosides), and possible gastrointestinal side effects (nausea, griping, etc.). Some toxicological aspects related to pregnancy, however, remain controversial and impede the general use of anthraquinone-containing

preparations by pregnant women. Literature references concerning such risks during pregnancy are rather scarce and, if any, never comprehend a scientific study. For example, it was reported that anthraquinones could have an abortive effect at high dosage in problematic pregnancies by increasing uterine muscle contractility [2]. This statement was mainly based on two references [3, 4] which in fact failed to yield supporting evidence for the declared abortive or uterine-stimulating effect of anthraquinones, especially aloe. More recently, similar statements were repeated in review articles without any reference to support them [5–7]. In spite of this lack of scientific basis, it is usual for all anthraquinones to state a risk in taking the drug during pregnancy or lactation (e.g. the official monographs of the BGA (FRG) for aloe and senna, or in France, monographs of senna-containing preparations in the *Dictionnaire Vidal*). In contrast, pharmacology textbooks like Goodman & Gilman do not mention any undesirable effect of senna during pregnancy and occasionally indicated that aloe 'has an undeserved reputation as an abortifacient' [8]. In the USA, the FDA classification for senna in regard to pregnancy mentions no risk for the fetus in animal species but sufficient investigations in women do not exist. Finally, several British authors subscribe to the assumption that senna can be safely utilized by pregnant women [1, 9, 10].

Based on our own experience on the effect of sennosides in dogs and rats [11, 12], it was clear that the laxative effect of sennosides in these species was accompanied by an inhibition of colonic motility, and, to a lesser extent, of the small intestine. That diarrhea is often linked to inhibition rather than to activation of intestinal motility is now generally assumed [13]. Such a result disagrees

with the idea that sennosides enhance not only gastrointestinal motility but also uterine motility, probably by activation of hypogastric nerves [4]. Nevertheless, the hypothesis that anthraquinones may influence uterine contractility is not unreasonable. Indeed, it has been shown that they induce the release of prostaglandins into the colon, mainly PGE [14–16] which generally exerts an activatory influence on the myometrium [17]. On the other hand, an increase of cAMP levels, a mechanism known to mediate uterine tocolysis, has been described in cultures of ruminant luteal cells treated with PGE *in vitro* [18] or following laxative administration in rats *in vivo* [14, 15].

Based on these contradictory opinions and hypotheses, we endeavored to provide a clear picture of sennoside's effects on the pregnant uterus. The choice of the ewe as animal model could appear somewhat unexpected due to huge species differences in gastrointestinal physiology between sheep as a ruminant and the human. Nevertheless, the ovine pregnant uterus presents a characteristic pattern of contractility throughout pregnancy which is well known [19, 20] so that any disturbances induced by drugs can be easily detected. Therefore, the effects of sennosides on the contractility of the uterus and cervix of the ewe were investigated using an electromyographic technique *in vivo* to evaluate the risk of inducing abortion with laxative doses of sennosides.

Materials and Methods

Animals and Surgery

Healthy adult pregnant multiparous ewes, 8 Lacune and 6 Romanov presenting no history of reproductive pathological diseases, were included in the present study. Two Lacune ewes were used in a dose-

finding study, 6 Lacaune ewes were assigned to a first study group, while the 6 Romanov ewes were assigned to a second series of experiments following the same protocol as that designed for the first group.

Surgery was done between the 49th and the 65th day of pregnancy according to a procedure described elsewhere [21]. Electrodes were positioned on the pregnant horn(s) and on the cervix. For the dose-finding study, electrodes were also positioned on the distal ileum and on the spiral colon. In addition, in all the ewes a medical Silastic® catheter (4 mm external diameter) was inserted into the lumen of the proximal colon to allow intracolonic sennoside administration, as an oral administration of sennosides in ruminants would lead to a premature activation of the drug by the microbial flora of the forestomachs.

Records

After surgery, the ewes were placed in individual cages. They were fed hay, oats and concentrates consistent with good farming practice and tap water ad libitum. Throughout the course of the experiments, the ewes received no therapeutic treatment. Recording procedures are described elsewhere [21]. EMGs were integrated and displayed 24 h/day on recorders. In both study groups, EMGs were quantified automatically in 5-min epochs using a microcomputer.

Drugs

Purified senna extracts, containing more than 90% of sennosides A and B, were used (Lot No. 46330; Dr. Madaus GmbH & Co., Cologne, FRG). For administration, sennosides were suspended in 20 ml distilled water (35 °C) and gently introduced into the colon through the catheter. Following the injection, the catheter was rinsed twice (10 ml each).

Design of the Study

Pilot studies were performed in 2 pregnant ewes between 87 and 129 days of gestation in order to ascertain the laxative efficacy of sennosides in this species and to determine the adequate dose to be used. Sennosides were administered intracolonic in regularly increasing doses from 10 to 160 mg/kg, separated from each other by at least 4 days. Uterocervical and ileocolonic EMGs were recorded throughout these pilot experiments. Laxative effects were determined by gross estimation of stool consistency. Effects on intestinal motility were described in terms of changes in both the MMC pattern (ileum)

and basal activity (spiral colon) according to the literature [22]. Effects on uterocervical motility were described in terms of changes in the pregnancy activity pattern [20].

The final experimental study was performed in the two groups of 6 ewes between 75 and 125 days of pregnancy. It consisted of the quantitative evaluation of the effects of an appropriate laxative dose of sennosides (as determined in the pilot study) on the motility of the pregnant genital tract after single intracolonic administrations at 6- to 10-day intervals. Effects on uterocervical activity were quantified using computer values (arbitrary units). *Magnitude* of activity episodes (i.e. amplitude $\times$ duration) was determined using the corresponding area under the activity-time curves. *Frequency of occurrence* was assessed by inspection of charts. Means $\pm$ SD were calculated for both parameters for the 24 h preceding injection (control) and two periods of 24 h after injection, and expressed in percent of the control values. Statistical differences were assessed by Wilcoxon's matched test.

Results

Preliminary Study

Intracolonic administration of sennoside doses higher than 20 mg/kg systematically resulted in laxative effects after a lag time of at least 5 h. Return to normal stool consistency was observed between 20 and 44 h postinjection. Inhibition of the basal activity of the spiral colon and also a disruption of the MMC pattern of the ileum were registered parallel to the diarrheic process (fig. 1). Intestinal motility disturbances started 2–3 h postinjection and lasted for a highly variable time (from 4 to 24 h) hardly related to the dose. The cyclic occurrence of contractile episodes on both the cervix and pregnant uterine horn remained unaffected in one of both ewes (fig. 1), while in the second a slowing down of the frequency of occurrence of activity episodes was noted on the uterus for doses of 40 and 80 mg/kg.

Fig. 1. Effects of a laxative dose of sennosides on the motility (integrated EMG) of the ileum and spiral colon (a), and on pregnant uterus and the cervix (b). Note intestinal depression and absence of effects on the genital tract.

First Study Group

For the final study, a standard dose of 60 mg/kg was selected. At this dose, a laxative effect was obtained within 4–8 h postinjection which never lasted for more than 16–20 h. A total of nine administrations were performed in this group. Each ewe received at least one injection. Most of the ewes had to be eliminated from further studies on the basis of evident pathological disorders (weakness, anorexia, hyperketonemia) which occurred within the 6–10 days left between

experiments. Figure 2a presents an example of activity-time curves obtained by plotting computer values gathered from the uterus and the cervix during 24 h predrug and 48 h postdrug. Although inconsistent motility changes were observed in single experiments in response to sennoside administration, statistical evaluation of all experiments showed that neither magnitude nor frequency of occurrence of activity episodes in the uterus or cervix were significantly different from control periods ($p > 0.05$).

Fig. 2. Computer plot of pregnant uterus and cervix contractility (arbitrary units). **a** Absence of evident disturbances of both activity patterns in one ewe (first study group). **b** Marked drop of uterus motility of another ewe (second study group).

Second Study Group

In this series again, some ewes had to be eliminated from further injections of sennosides because of pathological troubles similar to those observed in the first study group and a total of eleven experiments was performed. The motility pattern of the cervix 24 or 48 h after sennosides was within the physiological range and significant changes of either frequency or magnitude (fig. 3) of contractile episodes were never observed. Conversely, for the uterus some individual

experiments showed a significant decrease ($p < 0.05$) in frequency or in magnitude of contractile episodes (fig. 2b, 3).

Development of Pregnancy

Either at the completion of the experiments (7 of 14 ewes) or before, due to the outbreak of pathological troubles (7 of 14 ewes), ewes were placed indoors, under surveillance, in the laboratory sheep fold. Two of the ewes (one per group) which presented hindlimb paralysis were sacrificed at 83 and

Fig. 3. Magnitude of genital tract activity episodes for the eleven experiments of the second study group. Different labels indicate different ewes. Values are means from 11–40 activity episodes/24 h and are expressed in percent of controls: * $p < 0.05$.

91 days of pregnancy, respectively. Both exhibited normally developed twin fetuses and their uterus and placentas were normal. One of them showed traces of inflammation on the proximal colon wall between 20 and 40 cm aborally to the catheter. The second presented no signs of mucosal erosion or any evident intestinal pathology. The other 5 ewes with pathological signs responded positively to treatment, mainly corticoid therapy, and apparently recovered. Pregnancies progressed normally and healthy active lambs were born.

Discussion

The present study clearly indicated that adequate doses of sennosides given intracolonic to pregnant ewes exerted laxative effects which were connected with a marked depression of both ileum and spiral colon motility. In contrast, sennosides did not

stimulate the ovine pregnant uterus and cervix. The only observed effect, although inconsistently recorded in some individual experiments, was a slight depression of either magnitude or frequency of uterine contractile episodes for 24–48 h postinjection. That this inhibitory effect was without consequences on pregnancy maintenance is evident by the fact that the ewes which presented the most marked depressions had pregnancies which progressed normally until term. Absence of embryo-lethal or teratogenic effects of sennosides has also been confirmed in rats and rabbits [23]. Nevertheless, in our study, half of the ewes presented pathological troubles consecutively to sennoside administration. Intoxication by various senna species in natural conditions has been reported for ruminants, clinical signs include unspecific symptoms like anorexia or weakness but also posterior paralysis [24]. This description agreed with the clinical signs observed in the present study in the affected

ewes which were probably independent of the reproductive state. This should lead to the conclusion that the ovine species is not appropriate for investigations with sennosides, because of the specific toxicity of senna in ruminants. Problems comparable to those encountered in the present study have never been reported for other animal species or human beings.

The mechanisms by which sennosides could reduce uterine motility deserve attention. The fact that sennosides, given intracolonicly, consistently depressed ileum motility indicated either the presence of a local reflex response of the ileum following stimulation of colonic myenteric plexuses or a local release of an active inhibitory molecule with a systemic mechanism of action. Inhibition of ileum motility following distension of the cecum has been demonstrated [25]; this mechanism mediated by local nervous pathways is in agreement with the early suggestion that the action of senna may be based on a stimulation of colonic myenteric neurons [26]. In addition, local release of PGE under the influence of sennosides [15, 16] may also be responsible for the observed inhibitions of both ileum and colon. Conversely, PGE has been shown to stimulate the pregnant uterus [17]. Therefore, depression of uterine motility as observed in some experiments cannot be connected with a direct action of PGE on the uterus but may result from PGE-induced stimulation of both progesterone secretion by the corpus luteum and adenylate-cyclase activity which elicits corresponding rises in cAMP levels, a mechanism known to mediate uterine tocolysis. A mediation of this effect by a rise in progesterone and cAMP would be in agreement with the fact that, when present, the depressive effect is relatively long-lasting

(24–28 h), restricted to the uterus (the cervix is not inhibited by progesterone, for example during the luteal phase of the ovine estrous cycle [21]) and finally, devoid of direct deleterious effects on pregnancy.

In conclusion, our study in the pregnant ewe gives no supporting evidence that sennosides could exert adverse effects on uterine motility and on pregnancy maintenance.

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Discussion

Ewe: Is it true that this is the first scientific study on the effect of anthraquinones on the uterus?

García-Villar: There are a lot of confusing statements and impressions in the literature, but there are no real hard experimental data on this subject up to now.

Wienbeck: How do you explain the effect of sennosides on the terminal ileum? I think, they are only active after having been metabolized in the colon?

García-Villar: This is right, but there are different possibilities which may enable them to influence other parts of the intestine. The first possibility is that there is a local reflex mechanism. The existence of such mechanisms has been shown, for example, by Fioramonti who could induce ileal inhibition by distension of the proximal colon in sheep.

Sarna: When we infused normal electrolyte solution directly into the colon, we also found that ileal

MMCs were inhibited, probably by reflex mechanisms.

Garcia-Villar: The second explanation is that sennosides may release a secondary messenger in the colon which can act systemically, for example prostaglandins.

Ewe: But why do the prostaglandins not act on the uterus?

Garcia-Villar: We only find an inhibiting effect of the sennosides on the ileum and also, in some experiments, on the uterus. As PGE normally induces uterus contractions, there is only the possibility that prostaglandins are not these mediators or that there is an indirect action of the prostaglandins. It is known that PGE can increase progesterone release from the placenta which has a tocolytic effect. But these are speculations.

Sund: Prostaglandins have a very short half-life of about 30 s in the circulation because they are very efficiently inactivated in the lung. So, I feel, there must be an enormous release of prostaglandins in the intestine to reach the uterus in an effective dose. From a quantitative aspect this seems not very likely.

Garcia-Villar: I totally agree with you. As long as we have no further supporting data, this remains speculation.

Karaus: Are there neuronal connections between the uterus and the large intestine?

Garcia-Villar: I would not exclude reflex mechanisms between these organs, but I have no further information on this.

Beubler: I had the impression at least from some of your slides that there was a greater activity in the uterus of sennoside-treated animals than in controls.

Garcia-Villar: The normal biological variation is between 20 and 30% and this was the variation in sennoside-treated ewes, too. You refer mainly to the irregular activity which, mechanically, has no great importance. There is really no evident stimulation of electrical activity in the uterus after sennosides. I think it is important to note that we measured myoelectric activity in the uterus continuously in these animals covering not only the 24 h of diarrhea but also the time before and at least 48 h afterwards. During this time there is no stimulatory effect of the sennosides on the uterus.