Effect of high dose aminosalicylic acid on gastroduodenal mucosa

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DJ LEDDIN, DA MALATJALIAN, D PALEY. Effect of high dose aminosalicylic acid on gastroduodenal mucosa. *Can J Gastroenterol* 1993;7(3):319-321. Oral administration of a solution of aminosalicylic acid (5-ASA) (60 g/100 mL) at a dosage of 80 mg/kg/day to dogs did not cause erosions or ulceration in the proximal gut. There was no biochemical or histological evidence of nephrotoxicity although high peak serum concentrations of the drug were obtained. High doses of 5-ASA may be used in the proximal intestine without gastroduodenal damage.

Key Words: 5-ASA, Dog, Duodenum, Stomach, Ulceration

Effet d'une dose élevée d'acide aminosalicylique sur la muqueuse gastroduodénale

RÉSUMÉ: L'administration orale d'une solution d'acide aminosalicylique (5-AAS) (60 g/100 mL) à une posologie de 80 g/kg/j à des chiens n'a pas causé d'érosions ni d'ulcérations au niveau de l'intestin proximal. Il n'y a pas eu de signe biochimique ni histologique de néphrotoxicité, bien que des concentrations sériques de pointe élevées du médicament aient été obtenues. Des doses élevées de 5-AAS peuvent être utilisées au niveau de l'intestin proximal sans atteinte gastroduodénale.

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AMINOSALICYLIC ACID (5-ASA) IS structurally similar to acetylsalicylic acid, a drug which injures the gastroduodenal mucosa (1). The purpose of this study was to investigate whether oral administration of a suspension of 5-ASA (4 g/60 mL) also causes gastroduodenal injury, and to determine if this formulation affects renal and hematological function. The kinetics of absorption were also studied.

METHODS

Twelve conditioned (six control and six experimental) parasite-free, female ex-breeder, Beagle dogs were studied. Baseline hematological, bone marrow, biochemistry and urine parameters were obtained in all animals. Urinary specific gravity, osmolality, protein and pH were measured after an overnight fast. The urine was examined microscopically for the presence of casts. Blood and urine studies were performed twice

TABLE 1
Results of the urinary parameters

	Pre-treatment		End of study	
	Control	Aminosalicylic acid	Control	Aminosalicylic acid
Urea (mmol/L)	4.7±0.3	5.5±0.5	5.1±0.7	6.6±1.0
Creatinine (µmol/L)	64.2±3.1	70.2±3.2	65.8±2.1	75.2±4.9
Osmolality (mosmol/kg)	1562±349	1861±200	1579±246	1593±339
Specific gravity	1.027±0.00	1.032±0.00	1.037±0.01	1.034±0.00
Protein (g/L)	0.15±0.05	0.22±0.16	0.19±0.07	0.42±0.12
pH	6.4±0.4	6.33±0.56	6.4±0.51	6.4±0.25

The mean ± standard error of the mean urea, creatinine, urine osmolality, urinary specific gravity, urinary protein and urinary pH pretreatment and at the end of the study

Figure 1 Aminosalicylic acid (5-ASA) levels in µg/mL of serum (mean ± standard error of the mean) pre and post administration of 5-ASA

weekly during the study and marrow aspirate repeated at the study's end.

5-ASA was administered orally, twice daily for 15 days, by syringe at a dose of 40 mg/kg. Controls received the same volume of saline but no active drug. After eight days, blood for 5-ASA levels was taken prior to the morning dose and at 1, 2, 3, 4, 6 and 9 h post dose. The serum was separated, frozen at 20°C and shipped on dry ice for analysis of 5-ASA and N-acetyl 5-ASA levels.

At termination of the study all animals underwent a complete autopsy by an experienced pathologist following sacrifice with barbiturate. The pathologist was unaware of whether

the animal was a control or 5-ASA-treated. Gross abnormalities were recorded. Samples were taken of bone marrow as well as all internal organs for light microscopy. Microscopic abnormalities were scored as: 1, mild; 2, moderate; 3, severe.

Statistical analysis: The hematological, biochemical and renal parameters were analyzed by Profile Analysis using SAS. The nonparametric data were analyzed by Mann-Whitney testing.

Missing data were analyzed in two ways. First, any animal with a missing value was deleted from the analysis. Second, the missing data were estimated by BMDP SV statistical estimation.

RESULTS

Clinical status: No adverse effects were observed in any of the control or 5-ASA animals. They ate normally and diarrhea did not occur.

Renal function: The results of the urinary parameters are shown in Table 1. There was no difference between the groups at randomization or during treatment, with the exception of urinary specific gravity which was higher in the control group ($P=0.0004$) when analyzed by BMDP but not by deletion ($P=0.07$). 5-ASA did not increase the number of urinary casts. No epithelial or granular casts were seen.

Hematological function: There was no difference between the groups when analysed for a drug effect on white blood cell count, hemoglobin, platelet count or bone marrow morphology.

Histology: No abnormalities were detected in the esophagus of either control or 5-ASA-treated animals. The proximal stomach, antrum and duodenum were normal grossly. There was no significant difference between control and 5-ASA treated animals when tissue was examined for erosions, ulceration, mononuclear and polymorphonuclear infiltration, glandular hyperplasia or edema.

In the small intestine no gross lesions were observed. There was no significant difference in the villus height, width or crypt depth between the two groups. The number of blebs in the 5-ASA group approached a significant difference from the controls ($P<0.06$) but there was no difference in the number of ruptured blebs or in the total percentage of blebs and ruptured blebs.

No gross abnormalities were seen in the kidneys. On microscopy, hydropic change was seen in some animals in both groups. The sum score was not different (3.0 versus 1.0 [not significant]) by Mann-Whitney analysis.

Kinetics of absorption: The results are shown in Figure 1. Detectable 5-ASA was present in the serum prior to administration of the morning dose although the level was low (0.75 ± 0.35 µg/mL). Absorption peaked in the first hour after administration (maximum level 42.9 ± 3.8 µg/mL) and declined

with time. The levels at 9 h (0.65 ± 0.13 $\mu\text{g/mL}$) were not significantly different from those at 12 h.

Virtually no acetyl 5-ASA was detectable in the serum. At 0 h the level was 0.07 ± 0.03 $\mu\text{g/mL}$ and this peaked 1 h after the 5-ASA peak at 0.16 ± 0.03 $\mu\text{g/mL}$.

DISCUSSION

Crohn's disease may involve the proximal intestine (2). At present there is no formulation of 5-ASA designed to deliver high concentrations of the drug to this area. Intraduodenal infusion of a suspension of 5-ASA (4 g/250 mL) has been used in patients with proximal gut involvement and the results have been sufficiently encouraging to warrant a controlled clinical trial (3).

5-ASA inhibits the cyclo-oxygenase pathway of arachidonic acid metabolism (4). Inhibition of this pathway by nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with the development of gastroduodenal ulceration (5). The results of this study indicate that 5-ASA, in contrast to NSAIDs, does not cause gross or microscopic damage to the canine stomach and duodenum, even when given in high doses.

Inhibition of prostaglandin synthesis is also associated with renal impairment

(6), and 5-ASA has been reported to cause nephrotoxicity (7). Early nephrotoxicity may be manifested by a decrease in urinary concentrating ability. The urinary specific gravity was higher post treatment in the control group but no difference was seen in urinary osmolality, a more sensitive estimate of urinary concentrating ability. No other adverse effects on renal function were detected either biochemically or on microscopy despite high peak serum concentrations of the drug.

5-ASA has also been associated with thrombocytopenia (8). In this study no adverse effects were seen on peripheral blood counts or on bone marrow histology.

The suspension of 5-ASA was rapidly absorbed with peak concentrations at 60 mins. The dog is phylogenetically distinct and, unlike the human, does not acetylate organic compounds (9). Therefore virtually no N-acetyl 5-ASA was detected in the serum of the animals.

CONCLUSIONS

5-ASA, at a dosage of 80 mg/kg/day in a nonenteric coated formulation, does not cause esophageal, gastric or duodenal inflammation in the dog; this supports the contention that high doses of this drug may be used without fear of gastroduodenal damage.

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