

Effect of Olsalazine Sodium on Migrating Motor Complexes in the Upper Small Bowel of Human Volunteers

Märta Ryde and Sven Gustavsson

*Department of Human Pharmacology, Pharmacia AB and Department of Surgery,
Uppsala University Hospital, Uppsala, Sweden*

ABSTRACT

The effect of a peroral dose of olsalazine sodium on the migrating motor complexes (MMC) in the upper small bowel was studied by manometry in nine healthy volunteers during fasting. Recordings were obtained from the duodenum and/or the upper jejunum for 4.0 - 7.5 h.

During total baseline observation periods of 30 h, fourteen MMCs could be identified compared to ten complexes during post dose registrations of 25 h. This gives an average mean interval for baseline pre dose complexes of 2.2 h, and for post dose complexes 2.5 h. If excluding the two subjects, who had the longest interval until the first MMC before dosing and did not present any MMC after dosing, the corresponding figures are 1.9 h and 1.9 h, respectively.

Although our material is small with respect to the large individual variation in the recordings the results indicate that MMC does occur after an olsalazine sodium dose which is twice the dose normally recommended. Besides we can conclude that there is no apparent interference with the time for MMC occurrence in the upper small bowel in fasting humans.

INTRODUCTION

In recent studies (1, 2, 6, 9), 5-aminosalicylic acid (5-ASA) has been shown to be the main therapeutic compound of sulfasalazine (SASP) in the treatment of ulcerative colitis. In order to avoid some of the side effects encountered during SASP therapy, which emerge from the sulphapyridine component, an azo-compound of two 5-ASA molecules was synthesized. This

compound, olsalazine sodium (WHO pINN) [disodium 3,3'-azo-bis-(6-hydroxy-benzoate), disodium 5,5'-azo-di-salicylate, ADS] is now under evaluation in clinical studies. It has been shown to have a therapeutic effect in patients suffering acute attacks (7, 13), as well as a prophylactic effect against relapses in patients in remission (12). As for SASP the azo-bridge in ADS is split by bacteria in the caecum and the liberated 5-ASA is then further metabolized to N-acetyl-5-aminosalicylic acid (ac-5-ASA) (10).

In clinical trials and in early human studies with ADS, occasional episodes of diarrhoea have been reported, in some cases already a few hours after the first dose. One of the hypotheses to explain the diarrhoea was disturbance in the migrating motility complexes (MMC) of the small bowel. Experiments with fasted rats showed that ADS but not SASP, changed the distribution pattern of a transit marker in the small bowel which could be interpreted as an indirect evidence for a disturbancy of the MMC in rats (5).

The aim of the present study was to explore the effect of ADS on interdigestive MMC in the upper small bowel of human volunteers.

MATERIAL AND METHODS

Material

Drug: 250mg ADS was filled into hard gelatine capsules no. 1.

Placebo: Starch coloured with riboflavine and Indigotin laque colour was dispensed in hard gelatine capsules no. 1.

Subjects: Nine healthy male volunteers (aged 27-45 years) participated in the study. They were all healthy according to medical history, physical examination and laboratory investigation and were not on any medical treatment. They signed an informed consent and the study was approved by the Ethics Review committé at the Medical Faculty at Uppsala University

Methods

Analytical method: blood was collected into heparinized tubes which were kept in an ice bath for half an hour and then centrifuged at 3000 rpm at +4° C. The plasma samples were assayed for content of ADS with liquid chromatography and spectrophotometric

detection after acidic extraction. For determination of 5-ASA and ac-5-ASA derivatisation with proprionic anhydride preceded the acidic extraction and liquid chromatography with fluorescence detection.

Recording equipment: Small bowel manometry was used to study the effect of ADS on the MMCs in the upper small bowel. A standard triple lumen catheter for pulmonary artery pressure registration (Pulmoball, Vygon, 125 cm), with one opening located at the tip, and one 30 cm proximally of the tip, was introduced via the nose of the participating volunteers. The third lumen of the catheter led to a balloon close to the tip of the catheter. By inflation of the balloon, the tip of the catheter passed at least to the horizontal part of the duodenum as checked by fluoroscopy. A continuous perfusion of sodium chloride through both lumens was started. The pressures from these two lumens were recorded via two external transducers (Statham-Gould, Statham Instruments Inc.) The transducers were connected to a polygraph (Pharmacia AB) and the intraluminal pressure was continuously recorded for 4.0-7.5 h. The set-up was calibrated at room temperature.

Study design: The volunteers fasted for about 8 h before the study, and water, but no food, was allowed until the study was finished. After the catheter position was obtained, the volunteer was lying comfortable in a supine position and a baseline registration was started. A MMC complex was identified as an intense spiking activity which apparently differed from the preceding motility pattern and was of about 5 min persistence. After registration of at least one baseline complex showing a normal rest activity, an oral dose of 2 g (5.78 mmol) ADS (8 capsules á 0.25 g) was given with 100-150 ml of water, and the registration was continued for another couple of hours. To each of four subjects, 8 placebo capsules were given at least 1 h before the dose, with the same amount of water, in order to document any effect of an intake of only capsules plus water.

Blood samples were drawn at time 0, 0.5, 1 and 2 h after the dose to confirm an adequate absorption of the drug.

RESULTS

In all volunteers at least one pre dose MMC complex could be

identified. The maximal spiking height was estimated to 60-130 mm Hg at the distal location.

That the complexes really migrated distally was verified in four of our volunteers, with registration both at the proximal and distal opening, giving a migration velocity of 6.5 cm - 15 cm/min. The registrations in the other five subjects were considered to represent classical MMC activity though the registration was made only through one channel since the appearance of the registrations were identical with those for the subjects who actually showed migration.

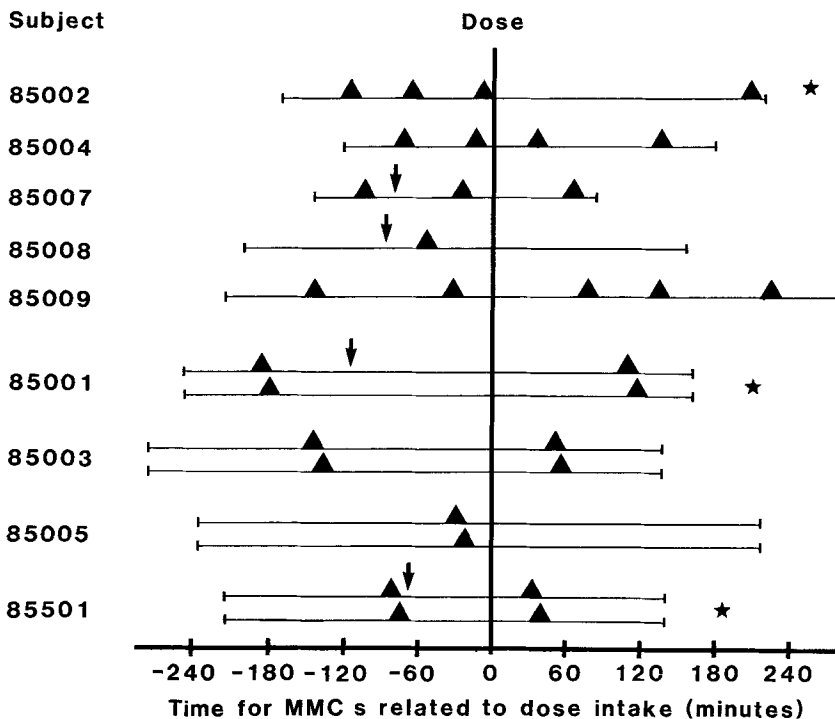


Fig. 1. Individual time for appearance of MMCs (▲) and placebo (▼) intake related to a 2 g ADS dose in nine healthy male volunteers. In those individuals where a clear migration of the MMCs is seen a double line is drawn (—▲). The start and the end of the resp. lines indicate the extension of each individual study. The subjects who reported incidences of diarrhoea are marked with *.

No obvious effects on the MMCs were seen in the nine subjects after the 2 g oral ADS dose or, in four of the subjects, after eight placebo capsules taken with the same amount of liquid as

the dose (Fig. 1). A statistical evaluation was not found feasible due to the large individual variation in relation to the number of subjects tested.

During total pre dose observation periods of 30.5 h, in the nine volunteers, 14 MMCs could be identified, and during the post dosage registrations of 25 h, ten complexes were recognized (Fig. 1). This gives an average mean interval of 2.2 h for baseline complexes, and 2.5 h for post dose complexes. With regard to all nine participants only those with the longest registration time > 140 min, from introduction of the catheter to the first MMC, did not show up with any MMC post dose, all other subjects had at least one MMC post dose. It could be expected that the mere intake of eight capsules could interfere with the MMC but the data on the effect of placebo capsules in four of our subjects does not indicate this. Excluding the two subjects, who had the longest (>140 min) pre dose MMC interval, (85005 and 85008, see Fig. 1), and who did not present any post dose MMC during another 3-4 h, the corresponding figures were 1.9 h and 1.9 h, respectively.

In all but two subjects the peak plasma concentration of ADS was reached within 1 h (Table 1) which is in accordance with findings in earlier studies. 5-ASA was not found in any plasma sample and ac-5-ASA was found already 2 h after dosage in four out of nine volunteers.

Table 1. Individual and mean plasma concentrations of Olsalazine sodium (ADS) and N-acetyl-5-aminosalicylic acid (ac-5-ASA) after a 2 g (5.78 mmol) single oral dose in nine healthy male volunteers.

Subject nr	Plasma concentration $\mu\text{mol/l}$ after dose							
	0h	ADS			0h	ac-5-ASA		
		0.5h	1.0h	2.0h		0.5h	1.0h	2.0h
85001 ¹	<0.06	1.6	2.0	1.4	<0.3	<0.3	<0.3	0.4
85002 ²	<0.06	2.3	6.9	5.7	<0.3	<0.3	<0.3	<0.3
85003	<0.06	3.4	3.8	2.6	<0.3	<0.3	<0.3	0.6
85004	<0.06	2.0	4.4	6.1	<0.3	<0.3	<0.3	<0.3
85005	<0.06	2.5	3.0	1.6	<0.3	<0.3	<0.3	<0.3
85007	<0.06	1.0	4.5	-	<0.3	<0.3	<0.3	<0.3
85008	<0.06	3.8	4.4	4.1	<0.3	<0.3	<0.3	0.4
85009 ³	<0.06	2.7	2.9	2.4	<0.3	<0.3	<0.3	0.3
85501 ³	<0.06	1.4	1.9	2.0	<0.3	<0.3	<0.3	<0.3
Mean		2.3	3.8	3.2				
S.D.		0.96	1.55	1.84				

1, 2 and 3 diarrhoea at 2.5 h, 7 h and 3.25 h, resp.

Three subjects, (85001, 85002 and 85501, Table 1), experienced diarrhoea 3-7 h after the 2 g dose which is twice the therapeutically used dose at each dosing event. The diarrhoea was preceded by borborygmi and a feeling of abdominal discomfort. In all three subjects with diarrhoea, at least one MMC was seen after dosing indicating that the MMCs were not influenced by the diarrhoea. No correlation between peak serum concentration of ADS or appearance of ac-5-ASA with diarrhoea was seen.

DISCUSSION

The main finding in the present study was that ADS did not appear to influence the MMC in the upper small bowel since the overall mean pre dose MMC interval was 2.2 h and the post dose interval was 2.5 h.

The fact that in the four subjects where more than one MMC was identified before dose, two subjects showed up with a longer interval between MMCs after dose, one with about the same and one with shorter interval also supports the conclusion that there is no dramatic effect of ADS on MMC frequency in healthy subjects, either increase nor decrease as response to dosing.

We have performed our study using a thin Swan-Gauz type of catheter which has the obvious advantage of being more easily tolerated than conventional manometry tubes. Moreover it must be pointed out that, our results have a bearing only on the motility of the upper small intestinal tract. However studies of MMC in the distal small bowel is less suitable since only about 10% of the MMCs in humans pass all the way down to the caecum (11).

It has been proposed by Thompson et al. (14) that there are no similar distinct activities in the small bowel beside the migrating complexes, which makes us confident that all registrations were MMC complexes though the migration pattern was only identified in four of our subjects.

The mean intervals of about 2 h between the predose MMCs found in this study are of the same order as those reported by for instance Vantrappen et al. (15) and Thompson (14) in healthy volunteers. The max spiking height of the MMCs - range 60-130 mm Hg - in our study, was also similar to the amplitudes

reported by for instance Thompson (14) and Erckenbrecht et al. (3). The migration velocity - 6.5 - 15 cm/min - found by us is in accordance with the findings (7.7 cm/min) of Vantrappen et al. (15).

A correlation between peak plasma concentration of ADS and appearance of ac-5-ASA in plasma and the episodes of diarrhoea can not be recognized from the results in this study. However the mean plasma peak concentration of ADS is almost the same as that found after a 1 g dose in our own laboratory and by van Hogezaand et al (8). The low mean peak concentration of ADS and the appearance of ac-5-ASA in plasma already at 2 h in 4 of 9 subjects (Table 1) might indicate an accelerated transit of the drug through the small intestine as a consequence of the simultaneous, continuous infusion of saline.

The results of this study show that oral administration of ADS obviously did not affect the MMCs in the upper small intestine in man. Thus, the changes in bowel habits sometimes seen in clinical studies with ADS and in three of our volunteers, does not seem to be referred to disturbances in the initiation of interdigestive MMCs.

In a study in rats (5) ADS was found to change the distribution in the small intestine of a transit marker which was taken as an indication of disturbancy of the MMC. This is not supported by the results in this study which might either be explained by species variation or, more probably, by the fact that the method used in the animal study was an indirect method. The results found in rats could as well be a result of an increased volume of the content in the small intestine. This is in accordance with the increase in ion and water secretion seen in the ileum in animal studies (4) with ADS.

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Address for reprints:

Märta Ryde
Department of Human Pharmacology
Pharmacia AB
751 82 Uppsala