Gut, 1989, **30**, 383–386

Effect of bile acid on anorectal function in man

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SUMMARY **The effects of rectal infusions (500 ml) of deoxycholic acid (1 mmol/l, 3 mmol/l) or normal saline on basal anorectal motility and responses to rectal distension were studied in 11 normal volunteers. Deoxycholic acid (1 mmol/l) did not alter anorectal motor patterns under basal conditions but reduced the rectal volumes required to induce a desire to defecate (deoxycholic acid 76 (12) ml *v* saline 123 (12) ml; mean (SEM) $p<0.01$), and to produce anal relaxation (deoxycholic acid 83 (14) ml *v* saline 152 (24) ml; $p<0.05$) and perception of the rectal balloon (deoxycholic acid 56 (10) ml *v* saline 104 (17) ml; $p<0.01$) that were sustained for the period of distension (1 min). Seven of 10 subjects could not tolerate an infusion of 3 mmol/l deoxycholic acid. Between two and 30 minutes after the start of the infusion they experienced an extreme urge to defecate which was associated with large amplitude pressure waves in the rectal channels (amplitude 30 (5) mmHg, duration 0·7 (0·1) min, frequency 1·7 (0·4)/min). Such contractions were never seen during saline infusion. Thus, rectal infusion of deoxycholic acid at physiological concentrations increases the sensitivity of the rectum to distension, and promotes an urgent desire to defecate in normal subjects.**

Impaired absorption of bile acids may be important in the pathogenesis of diarrhoea[1,2] and may also be an aetiological factor in some patients with the irritable bowel syndrome.[1] Colonic bacteria deconjugate and dehydroxylate bile acids,[3] yielding products that stimulate colonic secretion and motor activity. Perfusion of the human colon with solutions containing 3 mmol/l deoxycholic acid (DCA) induced net secretion of salt and water.[4] Although several studies in experimental animals support the enhancement of colonic motility by bile acids,[5–7] there are little data in man. Myoelectric and pressure activity were enhanced by infusion of small volumes (9 ml) of deoxycholic acid into the sigmoid colon of normal volunteers (15 mmol/l DCA) and patients with the irritable bowel syndrome (5 mmol/l DCA).[8] The effective concentrations of bile acid, however, were higher than the concentrations of unbound bile acids that exist in the stool water of normal subjects (1·9 (0·5) mmol/l; mean (SEM)),[9,10] but not in patients with bile acid malabsorption after ileal resection (0·9 to 15·5 mmol/l).[9] Moreover, the pH of the colonic solutions was unphysiological (pH 9·5), pressure activity was measured with a single sensor which gave no insight into whether the increased motor activity was propulsive, and there was no attempt to measure any change in rectal sensitivity. We have studied the effect of infusion of solutions containing physiological concentrations of deoxycholic acid (1 mmol/l and 3 mmol/l) at neutral pH on rectal sensitivity and the pressure activity from multiple sites in the anorectum under basal conditions and after distension of the rectum with a balloon.

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Accepted for publication 1 September 1988.

Methods

SUBJECTS

Studies were carried out on 11 healthy volunteers (18–29 years). Subjects gave written informed consent for the study and the protocol was approved by the Ethical Subcommittee of the Sheffield Area Health Authority in April 1986.

BASAL MOTILITY AND RECTAL DISTENSION

Study design

Eleven subjects (10 men, one woman) attended the unit on up to three occasions, each separated by at least five days. On each occasion the subjects received a rectal infusion of either 500 ml isotonic saline or 500 ml saline containing either 1 or 3 mmol/l deoxycholic acid (DCA) (pH 7, 37°C). Eleven subjects received saline and 1 mmol/l deoxycholic acid and 10 subjects received all three solutions. The order of the studies was randomised and the subjects were unaware of the nature of the infusion. No bowel preparation was used, but the subjects were invited to evacuate the rectum before the study.

With the subjects in the left lateral position, a 7 lumen polyvinyl tube (MUI Scientific, Mississauga, Canada), incorporating an inflatable balloon constructed from 4 cm of distensible latex rubber, was inserted into the rectum with the aid of a sigmoidoscope. The probe was positioned with three side holes in the anal canal (0·5, 1·5, 2·5 cm from the anal verge) and two side holes in the rectum (12, 15 cm from the anal verge), and the rectal balloon was fixed between 6 cm and 10 cm from the anal verge. Each side hole was perfused with water at a rate of 0·2 ml/min using a MUI hydraulic capillary infusion system (MUI Scientific) and pressures were measured with pressure transducers (Druck Ltd, Groby, Leics, UK) situated in each infusion line and connected through amplifiers to an 8 channel chart recorder (Lectromed MT8 PX, Ormed Ltd, Welwyn Garden City, UK). The pressure within the balloon was monitored using a side hole within the balloon linked to a water filled transducer.

Rectal and anal pressures were recorded under basal conditions for 10 minutes and then the infusate was pumped into the rectum at 60 ml/min through a separate narrow (ext diam 1 mm) single lumen polyvinyl tube terminating 4 cm from the anal verge. Subjects were asked to report any sensations that they experienced during or after the infusion. Anorectal pressures were recorded for a further 10 minutes after the infusion. Then the rectal balloon was serially inflated with 10, 20, 30, 40, 50, 75, 100, 150, 200, 250, 300, and 350 ml of air. Each inflation was maintained for one minute, and was separated from the next inflation by at least one minute. At each volume, subjects were asked whether they felt the balloon and, if so, whether they felt the urge to defecate or experienced pain.

ANALYSIS OF THE RECORDS

Basal motility

Steady state anal and rectal pressures and the rate of occurrence of rectal contractions were measured during the 10 minute pre-infusion, the infusion, and 10 min postinfusion recording periods. A rectal contraction was defined as a phasic increase in pressure of 5 mmHg or more lasting at least two seconds. A single contraction was said to occur when the pressure between adjacent peaks fell to less than one third of the peak pressure. Simultaneous increases in pressure involving all channels were regarded as artefacts caused by increases in intra-abdominal pressure and were discounted.

Rectal distension

Distension of the rectum with a balloon induces a brief increase in anal pressure caused by contraction of the external anal sphincter, followed by a more sustained decrease in anal pressure caused by relaxation of the internal anal sphincter.[11] The anal pressure changes are associated with an increase in rectal pressure, followed by a decline to a plateau which is maintained for the duration of the distension.[11] Records of pressure activity during balloon distension were analysed for the lowest distension volume that elicited relaxation in the anal channels, the lowest volume at which anal relaxation was sustained for the duration of the balloon inflation (one minute), and the lowest volume that induced a rectal contraction. The pressure records from the side port in the rectal balloon were analysed for peak pressure and steady state pressure during balloon inflation. Rectal compliance was calculated from the slope of a plot of change in pressure with change in volume.

STATISTICAL ANALYSIS

The statistical significance of differences in the results between infusion of saline and infusion of 1 mmol/l deoxycholic acid was assessed by Student's paired *t* test or χ^2 test.

Results

BASAL MOTILITY

Rectal pressures were always higher after the infusion than before it ($p<0·05$), but there was no statistically significant difference between values after infusions of either 1 mmol/l deoxycholic acid infusions (12·5 (1·7) mmHg) or saline (13·8 (1·7) mmHg). None of the infusions had any effect on basal anal pressures. Deoxycholic acid (1 mmol/l) had no consistent significant effect on anal or rectal contraction rate, although one subject had to abandon the study because of an extreme urge to defecate. Only three of 10 subjects managed to complete the 3 mmol/l deoxycholic acid infusion and in these subjects there was no discernible effect of bile acid on basal motility. The remaining seven

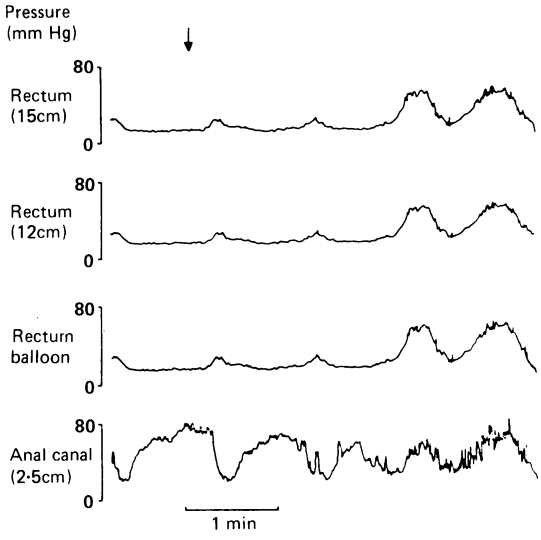

Figure *Rectal and anal pressure activity recorded in one subject who experienced severe urgency during rectal infusion of 3 mmol/l deoxycholic acid. Regular rectal contractions were associated with deep anal relaxations. These gave way to giant contractions occurring throughout the anorectum. Arrow indicates onset of urgent desire to defecate.*

subjects, and the subject who had to abandon the 1 mmol/l bile acid study, experienced an extreme urge to defecate, that occurred between two and 30 minutes after the start of the infusion and exhibited large amplitude pressure waves in the rectal channels (amplitude 30 (5) mmHg, duration 0·7 (0·1) min, frequency 1·7 (0·4)/min, Figure) associated with severe urgency and termination of the study. No subject had to abandon a saline infusion study. Seven subjects reported a sustained unpleasant rectal sensation lasting for approximately one day after infusion of 3 mmol/l deoxycholic acid.

More subjects experienced a desire to defecate during or shortly after infusion of 1 mmol/l deoxycholic acid (64%) and 3 mmol/l (70%) compared with saline (18%, $p<0.05$).

RECTAL DISTENSION

One millimole per litre deoxycholic acid infusion had no effect on the lowest distension volume to induce anal relaxation or rectal contraction (Table), but decreased the volume required to cause sustained anal relaxation ($p<0.05$). Steady state and peak pressures recorded in the balloon channel during inflation were unchanged by deoxycholic acid infusion, and values for rectal compliance were unaltered. Deoxycholic acid (1 mmol/l) did not affect the volume required to induce a feeling of rectal distension but it significantly reduced the volumes required to sustain this feeling for the whole period of distension ($p<0.01$, Table). Deoxycholic acid (1 mmol/l) also reduced the rectal volume required to induce a desire to defecate ($p<0.01$) and to sustain this sensation for one minute ($p<0.001$, Table).

Discussion

This study has shown that concentrations of deoxycholic acid as low as 1 mmol/l, at neutral pH, increased the sensitivity of the rectum of normal volunteers, reducing the distension volume required to produce a desire to defecate and to sustain a feeling of rectal distension for the duration of the stimulus. This observation may be relevant to the pathogenesis of the symptoms and enhanced rectal sensitivity[8] in a subset of patients with the irritable bowel syndrome, in whom absorption of bile acids is impaired.[1]

A small increase in bile acid concentration from 1 to 3 mmol/l produced such extreme rectal discomfort and urgency in seven normal subjects that continence was threatened and the study had to be abandoned. These symptoms were associated with large rectal contractions and may occur as a result of non-specific irritation to the colonic epithelium. Previous studies have shown that exposure of the rabbit colon to 2·5 mmol/l chenodeoxycholic acid causes ultrastructural changes to the colonic enterocytes associated with mucus and fluid secretion.[12]

The effect of infusion of bile acids on colonic motility has been studied before by other investigators,[7,8] but in most cases the concentrations were higher than those used in this study and the propagation of contractions was not investigated. The reason that we were able to observe changes in rectal sensitivity and motility at such low concentrations may be related to the higher volumes used in our

Table *Effect of infusion of 500 ml normal saline containing 1 mmol/l deoxycholic acid on the anorectal responses to rectal distension in normal volunteers*

Threshold volume (ml)	*Saline (n=10)*	*1 mmol/l deoxycholic (n=10)*	*p*
Initial perception	47 (14)	33 (9)	NS
Sustained perception	104 (17)	56 (10)	p<0·01
Initial desire to defecate	123 (12)	76 (12)	p<0·01
Sustained desire to defecate	205 (22)	119 (20)	p<0·001
Initial anal relaxation	33 (6)	31 (5)	NS
Sustained anal relaxation	152 (24)	83 (14)	p<0·05
Rectal contraction	77 (26)	70 (11)	NS

Results are expressed as mean (SEM).

studies. Increasing the volume of the solutions would distribute the bile acid over a much greater area of colonic epithelium, stimulating a larger receptor 'field'. This experimental design simulates disease conditions more closely than infusion of small volumes of more concentrated bile acids because unabsorbed bile acids would be diluted in a large volume of ileal effluent and colonic secretions, and would stimulate the entire colon.

The results of this study suggest that very small concentrations of secondary bile acids, distributed in a large volume of colonic fluid, can enhance the sensitivity and reactivity of the rectum of normal volunteers. This emphasises the need to consider the role of bile acids in any patient suffering from urgency, diarrhoea and other symptoms indicative of the irritable bowel, because such symptoms may respond to treatment with bile acid binding agents.

Dr Edwards is supported by a grant from the Special Trustees of the Former United Sheffield Hospitals.

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