J. Pharm. Pharmac., 1976, **28**, 192–195 *Received August* 12, 1975

Intestinal pH and propulsion: an explanation of diarrhoea in lactase deficiency and laxation by lactulose

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Acidification of the lumen of guinea-pig isolated intestine increases peristaltic activity. A low colonic pH might therefore contribute directly to the diarrhoea induced by lactose in lactase-deficient subjects, and to the laxative effect of lactulose.

Subjects deficient in lactase may experience bloating, cramps and diarrhoea after ingesting milk, due to the unhydrolysed and poorly-absorbed lactose. The diarrhoea may result from an osmotic effect of the lactose itself or its poorly-absorbed acidic products of fermentation (Weijers, van de Kamer & others, 1961; Christopher & Bayless, 1971), possibly together with an alteration of sodium and water absorption due to the lowered colonic pH (Rousseau & Sladen, 1971).

Laxation by lactulose (1-4-β-galactosidofructose) may operate through an analogous mechanism. The drug is a synthetic dissaccharide which, in oral doses of 10–20 g, relieves chronic constipation (Wesselius-de Casparis, Braadbaart & others, 1968). It is neither hydrolysed by intestinal dissaccharidase (Dahlqvist & Gryboski, 1965) nor absorbed in the gut, but it is converted in the colon mainly to lactic and acetic acids by various bacteria including *Lactobacillus acidophilus*. Apart from the increased osmotic effect, the pH in the proximal colon falls markedly (Bown, Gibson & others, 1974), and larger doses may reduce stool pH. Weijers & others (1961) inferred that the acidic products formed from lactose in the colon stimulate propulsion, and K. S. Liem (Philips-Duphar) suggested to us that lactulose may relieve constipation partly by stimulation of propulsion due to the lowered pH. The experiments described below support this view.

METHODS

Adult albino guinea-pigs of either sex were killed by a blow on the head and segments of ileum or colon were set up as described by Bennett, Eley & Scholes (1968), with the following slight modifications: the Marriotte bottle controlling the intraluminal pressure (zero pressure at rest to 1–5 cm H_2O) contained bicarbonate-free Krebs solution. In the later experiments, the bottle was raised at a constant rate by a linear motor for 1·5 min every 8 min (15 s to raise 4 cm, 15 s to lower), and the solution expelled during peristalsis was collected in a tube 25 cm long, 8 mm internal diameter, with a side-arm at the bottom to measure the hydrostatic head of pressure with a transducer. The waste outlet at the bottom of the collecting tube was closed by a relay before raising the intraluminal pressure, and opened after returning to zero pressure. In this way it was possible to record simultaneous changes in longitudinal muscle, circular muscle (pressures measured intraluminally by one or two fine polyethylene tubes) and propulsion of fluid.

In the ileum experiments, drugs were infused intraluminally at the rate of 2·25 to 18 ml h^{-1}. The intraluminal pH was measured in a small sample aspirated through one of the fine intraluminal tubes or by an electrode sited in the outflow tube (dead space about 1 ml). Intraluminal infusion was not entirely satisfactory because the local concentration of drug administered depended on the amounts of fluid in the gut at rest and during peristaltic activity. In the colon studies lactic acid or sodium lactate was added to a second Marriotte bottle, so the concentrations were known exactly.

Formula of the Krebs solution (g $litre^{-1}$): NaCl, 7·1; $CaCl_2.6H_2O$, 0·55; KCl, 0·35; KH_2PO_4, 0·16; $MgSO_4.7H_2O$, 0·29; $NaHCO_3$, 2·1; dextrose, 1·0. Bicarbonate-free Krebs solution was neutralized with NaOH. Drugs used: acetic acid, hydrochloric acid, lactic acid, lactulose (Philips-Duphar).

The results were analysed statistically using Fisher's exact probability test, except where otherwise stated.

RESULTS

Guinea-pig ileum. Fifteen segments of ileum from 14 guinea-pigs were infused intraluminally with lactic acid 0·05–2% v/v or equivalent amounts of sodium lactate or lactulose, acetic acid 0·4 or 0·5% v/v, HCl 0·012 or 0·5% w/v, or control infusion of bicarbonate-free Krebs solution.

Lactic acid 0·05–0·5% reduced the pH to 3–6. It usually increased the peristaltic activity induced by raising the intraluminal pressure, as shown by increased fluid propulsion and circular muscle contractions. However, occasionally there was no effect or even a reduction, and in three experiments responses were reduced after an initial stimulation. The median and semiquartile ranges of % increase in fluid propulsion were 21% (0 to 80; 20 observations in 8 experiments). Control infusions of bicarbonate-free Krebs solution often had no effect or tended to reduce propulsion (0% (0 to −10), n = 18), so that the stimulant effect of lactic acid was statistically significant ($2P < 0·006$). Sodium lactate in amounts equivalent to those of lactic acid in the same experiment, and 0·4–4% lactulose, tended to reduce propulsion (median and semiquartile ranges −23% (0 to −32), n = 8, and −14% (0 to −25), n = 9 respectively), but the effect was not statistically different from the corresponding controls (−7% (0 to −26), n = 12) and (0% (0 to 0), n = 6).

Hydrochloric acid (0·012 or 0·5%) infused intraluminally lowered the pH to 3–5 and also stimulated propulsion by 33% (19 to 107) (12 observations in 7 experiments) (Fig. 1). Its effect was statistically significant ($2P = 0·004$). With both lactic acid and hydrochloric acid, the peristaltic contractions of the circular muscle usually increased, but there was usually little change in longitudinal muscle activity.

Guinea-pig colon. The peristaltic activity was much slower in the colon than in the ileum, and the tissue was particularly susceptible to mechanical changes due to intraluminal infusion. The pilot experiments with this method gave inconsistent results, and a different method was used with a second Marriotte bottle containing bicarbonate-free Krebs solution at the desired pH.

Lactic acid (pH 3·5–5; usually 4·5–5) stimulated propulsion of fluid in 10 out of 12 trials on 10 tissues ($2P = 0·036$, binomial test) (Fig. 2). The median and semiquartile ranges of the increases were 27% (9 to 93). By contrast, equivalent amounts of sodium lactate inhibited propulsion in 10 out of 12 trials on 9 tissues (−29% (13 to −49), $2P = 0·036$, binomial test). The difference between the effects of lactic acid and sodium lactate was significant ($2P = 0·004$). HCl pH 4·3–4·8 increased pro-

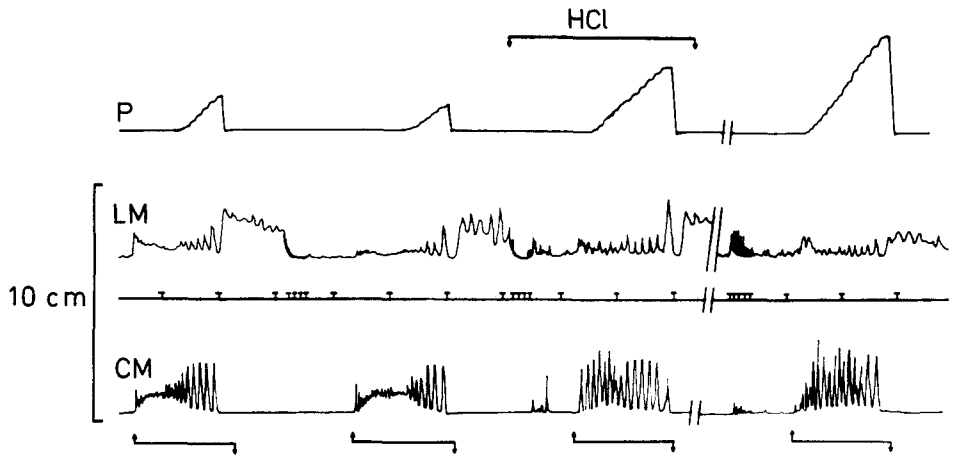

FIG. 1. Raising the intraluminal pressure at the arrows (bottom) by 4 cm water in guinea-pig isolated ileum, evoked peristaltic contractions of the longitudinal muscle (LM) and circular muscle (CM) and propulsion of fluid (P). Infusion of HCl (0·5%, 4·5 ml h^{-1}) reduced the intraluminal pH to 4·6, and stimulated circular muscle peristaltic activity and fluid propulsion. The acid was washed out during the break in the trace (8 min). The responses subsequently returned to normal. The longitudinal muscle occasionally remained contracted for a short time after lowering the intraluminal pressure, as shown in the present trace. Time marker (3rd trace down), min; 5 mm = 1ml fluid propelled.

pulsion by 45–47% (3 experiments). As in the ileum, both acids usually increased circular muscle peristaltic contractions but had little effect on the longitudinal muscle activity.

DISCUSSION

Several findings support the hypothesis that a reduced pH is associated with, and may cause, diarrhoea. When intestinal lactase is deficient, lactose reaching the colon causes diarrhoea associated with acid stools. Lowering the intraluminal pH to levels which can occur in fermentative diarrhoea (Weijers & others, 1961), and in the

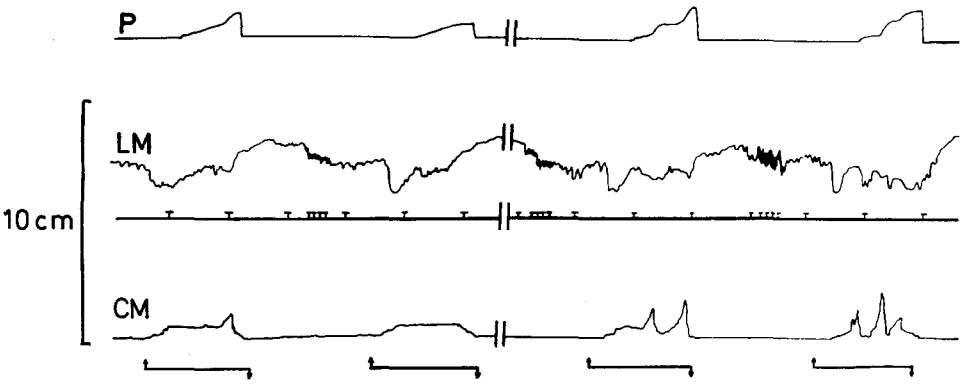

FIG. 2. Raising the colonic intraluminal pressure at the arrows (bottom) by 5 cm water pressure stimulated slow peristaltic activity (cf. Fig. 1). At the break in the trace bicarbonate-free Krebs solution acidified to pH 5 with lactic acid was delivered into the colon from a second Marriotte bottle. This reduced the intraluminal pH to 5·7, and stimulated the circular muscle peristaltic contractions (CM) and propulsion of fluid (P). Time marker (3rd trace down), min; 8·5 mm = 1 ml fluid propelled; LM, longitudinal muscle.

ascending colon with lactulose (down to pH 3·5, Bown & others, 1974), stimulates circular muscle activity and propulsion of fluid in guinea-pig isolated ileum and colon. The effect seems due to the hydrogen ions since both lactic and hydrochloric acids were effective, whereas sodium lactate tended to be inhibitory. It therefore appears likely that reduction of stool pH by the acids formed in the colon from lactose or lactulose contributes directly to the laxative effect seen in patients. This is in addition to the osmotic effects of unabsorbed products and altered sodium and water absorption due secondarily to the lowered pH. Perhaps in an analogous way, diarrhoea in the Zollinger-Ellison Syndrome results partly from the entry of large volumes of acid gastric juice into the upper small intestine. Intraluminal pH might normally affect motility in other parts of the intestine.

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