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# Effects of lactulose and other laxatives on ileal and colonic pH as measured by a radiotelemetry device

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SUMMARY Using a pH-sensitive radiotelemetering device the effect of lactulose on luminal pH in the ileum, colon, and rectum has been compared with that of two other laxative agents.

Lactulose produced marked acidification of proximal colonic contents but this effect was not consistently maintained into the distal colon. Sodium sulphate acidified distal rather than proximal colonic contents. However, for a similar degree of laxation it was not possible to produce a significantly more uniform reduction of pH along the length of the colon by combining these laxatives compared with lactulose alone. Magnesium sulphate had little effect upon luminal pH except in the rectum where a significant rise occurred.

These results are discussed in relation to both normal colonic physiology and to their possible relevance to the treatment of chronic hepatic encephalopathy by colonic acidification.

Lactulose is an unabsorbed disaccharide (1:4 $\beta$-galactoside-fructose), which produces a fermentative diarrhoea analogous to that induced by lactose in patients with hypolactasia. Lactose-induced diarrhoea is characteristically associated with acid faeces containing high concentrations of organic acids, especially lactate (Haemmerli, Kistler, Ammann, Marthaler, Semenza, Auricchio, and Prader, 1965) although these findings cannot always be demonstrated in adults (McMichael, Webb, and Dawson, 1965). The beneficial effects of lactulose in patients with hepatic encephalopathy have been attributed to a similar acidification of colonic contents (Elkington, 1970). In clinical trials, faecal acidification has been demonstrated in some (Elkington, Flock and Conn, 1969; Bircher, Haemmerli, Scollo-Lavizarri, and Hoffmann, 1971) but not all patients (Zeegen, Drinkwater, Fenton, Vince, and Dawson, 1970; Brown, Trey, and McDermott, 1971) who responded to this treatment. In normal subjects, reduction of faecal pH by lactulose may be small in magnitude or even negligible (Agostini, Down, Murison, and Wrong, 1972). These apparent discrepancies presumably reflect the fact that faecal pH must depend on a variety of opposing factors, especially the rate of production of organic acids, their subsequent absorption by the colonic mucosa (Dawson, Holdsworth, and Webb, 1964), and the buffering of colonic contents by mucosal secretion of bicarbonate (Giller and Phillips, 1972; Bown, Sladen, Rousseau, Gibson, Clark, and Dawson, 1972).

Studies in experimental animals published many years ago indicate that unabsorbed sugars may produce consistent acidification in the caecal lumen with less marked effects in the distal colon (Cannon and McNease, 1923; Beach and Davis, 1925). Such an effect in man has not previously been investigated. The introduction of extremely stable pH-sensitive radiotelemetry devices allows the pH to be measured in the ileum and along the length of the colon and we have already published some preliminary observations on normal subjects (Meldrum, Watson, Riddle, Bown, and Sladen, 1972). In the present report, the effect of lactulose on luminal pH in the ileum and colon of normal subjects has been compared with that of two other laxative agents. First, magnesium sulphate was used because it does not acidify faeces and may even produce an alkaline pH (Zeegan *et al*, 1970). Secondly, sodium sulphate was examined because this produces a more consistent acidification of faeces than lactulose, probably by a totally different mechanism (Down, Agostini, Morison, and Wrong, 1972; Agostini *et al*, 1972). Finally, the effects of a mixture of lactulose and sodium sulphate

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were investigated in an attempt to produce uniform acidification along the length of the colon.

## Methods

The studies were performed on adult volunteers, particularly members of the department but also patients without evidence of gastrointestinal disease. The subjects gave informed consent to the procedures. The pH-sensitive radiotelemetry capsule (Rigel Research Ltd) or 'pH pill' was initially calibrated in standard buffer solutions at 37°C and then swallowed and allowed to pass through the gut. Its passage was checked by occasional abdominal radiographs in most of the subjects and 5-10-minute recordings of luminal pH were charted by an F.M. receiver on to a pen recorder at approximately hourly intervals. The details and validation of this method have previously been published (Meldrum *et al*, 1972). In the later studies on the authors (G.E.S., R.L.B., and J.A.G.) it was found that the position of the pill could be reasonably well localized by finding the site of maximum signal strength. Repeated pill passages were made on these subjects without the necessity for any further radiological exposure.

It should be stressed that the positions of the pill can only be regarded as approximate, especially in the small bowel. In the proximal small bowel, transit of the pill was often rapid and readings at different sites were sometimes missed. Occasionally the pill did not leave the stomach until the subject retired to bed and was in the low small intestine or proximal colon by the next morning. For these reasons, the number of proximal small intestinal observations was limited and, in some of the laxative studies, the readings were so few that they have been disregarded altogether. The lower ileum, right and left colon, and rectum were identified with reasonable accuracy. In many studies the pill remained for several hours in a single position which was most frequently in the proximal colon. Mean values of repeated pH measurements were obtained from the charts. During prolonged recordings at a single site occasional deflections of pH were observed, but these were ignored if their duration was a small fraction of the total period of observation. In the rectum, a brief fall of pH was observed in four subjects just before defaecation in the lactulose studies. This seemed to occur when the stools were fluid and urgent and was attributed to the rapid passage of proximal colonic contents to the rectum. This fall was ignored and the rectal pH was taken as the more stable value preceding such an 'acid dip'. In three subjects, very prolonged hold-up in the proximal colon (up to five days) and unusually variable pH measurements at this site made the results difficult to interpret and these studies were excluded.

In the control studies, the subjects ate a normal diet and continued with their usual activities or were active in the ward. In the laxative studies, the agent was taken for three or more days before the study in a sufficient dose to produce two to four semiformed stools daily. Urgency and liquid stools were avoided as far as possible. When the bowel habit was reasonably stable, the pH pill was swallowed and the study performed in the usual way. The agents and dose ranges were as follows:

1 Lactulose syrup (Duphar) contains 50% w/w lactulose in water plus small amounts of lactose and galactose. This is equivalent to 66·5 g lactulose/100 ml. The dosage was 15-20 ml syrup three times daily (30-40 g lactulose daily or 80-110 mmoles daily).

2 Magnesium sulphate mixture (BPC) contains $MgSO_4$ $7H_2O$ 4·0 g/10 ml and $MgCO_3$ 0·5 g/10 ml. The usual dosage was 5 ml twice or three times daily (22-23 mmol of magnesium salt daily).

3 Sodium sulphate solution, made up to contain 57·8 g/l and the dosage was 30 ml twice or three times daily (25-37·5 mmoles daily).

4 A mixture of 10 ml of lactulose and 15 ml of sodium sulphate solution three times daily.

During these studies the subjects were not distressed and were able to continue their normal activities. The three authors each underwent the four study programmes so that some within-subject control data were available. Each study was separated by at least one week from the previous one. Daily stool weights were also measured during the period of transit of the pH pill in the three authors. The remaining subjects were usually only used for a single study.

## Presentation of Results and Statistical Methods

In view of the logarithmic nature of pH units, the uncertainty of the distribution of pH values, and the relatively small numbers involved (n = 11 or less), the results have been presented as median values with ranges and the statistical significance of differences assessed by non-parametric methods, ie, sum of ranks or, for paired data, signed rank tests (Langley, 1968).

## Results

The median pH values in control studies during treatment with lactulose, magnesium sulphate, sodium sulphate, and the mixture of lactulose and sodium sulphate are shown in table I. Discrepancies in the numbers of observations indicate that reliable information was not available at all sites along the

| | *Small Intestine* | | | *Colon* | | *Rectum* |
|---|---|---|---|---|---|---|
| | *Upper* | *Mid* | *Lower* | *Right* | *Left* | |
| *Control* | | | | | | |
| (n = 11) | | | | | | |
| Median | 5·9 | 6·8 | 7·5 | 6·0 | 7·0 | 6·8 |
| Range | 5·0-6·7 | 6·0-7·3 | 6·8-8·4 | 5·5-7·5 | 6·0-7·6 | 6·2-7·6 |
| n | 4 | 10 | 11 | 11 | 9 | 11 |
| P | | | P < 0·002 | | P > 0·1 | |
| Mean stool weight = 133 g/24 hr | | | | | | |
| *Lactulose* | | | | | | |
| (n = 10) | | | | | | |
| Median | 5·8 | 6·2 | 7·05 | 4·85 | 6·7 | 6·55 |
| Range | 4·7-6·2 | 6·0-6·5 | 6·7-7·9 | 3·5-6·1 | 5·6-7·3 | 6·0-7·2 |
| n | 5 | 6 | 10 | 10 | 10 | 10 |
| P | | | P < 0·002 | | P < 0·001 | |
| Mean stool weight = 230 g/24 hr | | | | | | |
| *Magnesium sulphate* | | | | | | |
| (n = 7) | | | | | | |
| Median | — | — | 7·75 | 6·4 | 7·2 | 7·85 |
| Range | — | — | 7·2-8·2 | 5·7-7·2 | 6·5-7·6 | 6·9-8·3 |
| n | — | — | 7 | 7 | 6 | 7 |
| P | | | P < 0·05 | | P < 0·05 | |
| Mean stool weight = 350 g/24 hr | | | | | | |
| *Sodium sulphate* | | | | | | |
| (n = 6) | | | | | | |
| Median | — | — | 7·5 | 6 5 | 6 0 | 6·1 |
| Range | — | — | 7·4-7·7 | 6·0-6·8 | 5·0-6·8 | 5·6-6·8 |
| n | — | — | 4 | 6 | 6 | 6 |
| P | | | P < 0·002 | | P > 0·05 | |
| Mean stool weight = 273 g/24 hr | | | | | | |
| *Lactulose and Sodium sulphate* | | | | | | |
| (n = 6) | | | | | | |
| Median | — | — | 7·6 | 4·5 | 6·3 | 6·35 |
| Range | — | — | 7·4-8·0 | 4·0-5·0 | 5·3-7·0 | 5·0-6·9 |
| n | — | — | 6 | 5 | 5 | 6 |
| P | | | P < 0·002 | | P < 0·002 | |
| Mean stool weight = 293 g/24 hr | | | | | | |

Table I *Median values and ranges of pH along the gastrointestinal tract during five different study programmes*[1]

[1]n = number of subjects in whom observations are available. P refers to the significance of paired differences. Values were recorded to one decimal place only; in order to obtain the median of an even number of observations two values were averaged and, where appropriate, the result was expressed to the nearest 0·05 of a pH unit. The mean stool weight applies to three subjects only

gastrointestinal tract in every subject, as explained in the methods section. Mean stool weights indicate that approximately the same laxative effect was obtained in each of the four treatment groups.

The pH increased along the length of the small bowel to reach peak values in the lower ileal region. In each study group there was a statistically significant fall of pH as the pill passed into the right colon. The pH subsequently tended to rise towards neutrality: the change in pH between right colon and rectum was statistically significant ($P < 0·05$) in the lactulose, magnesium sulphate, and lactulose plus sodium sulphate groups.

Comparing the control and lactulose groups, there was no significant difference between the pH values in the lower ileum ($P > 0·1$) and in the rectum ($P > 0·1$). However, lactulose induced a highly significant fall in pH in the right colon ($P < 0·002$). Indeed of the 10 observations in the right colon in this group, eight values were equal to or less than pH 5·0, ie, below the range found in the control group.

Comparing the control and magnesium sulphate groups, there was no significant difference between the results in the lower ileum ($P > 0·1$) and right colon ($P > 0·1$) but the rectal pH was significantly higher in the magnesium sulphate group ($P = 0·01$).

If the results of the lactulose and magnesium sulphate studies are compared, the pH values are significantly higher in the magnesium sulphate group in the lower ileum ($P < 0·05$), in the right colon ($P < 0·01$), and in the rectum ($P < 0·01$).

| | Small Intestine | | | Colon | | Rectum | Mean Stool Weight (g/24 h) |
|---|---|---|---|---|---|---|---|
| | Upper | Mid | Lower | Right | Left | | |
| *Subject A* | | | | | | | |
| Control | — | 6·2 | 7·5 | 5·6 | 6·9 | 7·4 | 165 |
| Lactulose | — | — | 7·9 | 5·0 | 6·9 | 7·0 | 250 |
| $MgSO_4$ | — | 6·5 | 7·6 | 6·8 | 7·5 | 7·7 | 350 |
| $Na_2SO_4$ | — | — | 7·7 | 6·8 | 6·8 | 6·0 | 310 |
| Lactulose + $Na_2SO_4$ | — | 6·7 | 7·7 | 5·0 | 6·2 | 6·3 | 230 |
| *Subject B* | | | | | | | |
| Control | — | 6·4 | 7·7 | 7·3 | 7·3 | 6·7 | 80 |
| Lactulose | 5·8 | 6·0 | 6·7 | 4·7 | 7·4 | 6·6 | 190 |
| $MgSO_4$ | — | — | 7·7 | 7·2 | 7·1 | 8·0 | 370 |
| $Na_2SO_4$ | 6·7 | — | 7·4 | 6·7 | 6·3 | 6·0 | 140 |
| Lactulose + $Na_2SO_4$ | — | — | 7·8 | 4·8 | — | 6·5 | 240 |
| *Subject C* | | | | | | | |
| Control | 8·0 | — | 7·4 | 5·8 | 6·7 | 7·4 | 154 |
| Lactulose | — | — | 7·5 | 4·9 | 5·6 | 6·4 | 250 |
| $MgSO_4$ | — | — | 8·2 | 5·7 | 6·5 | 6·9 | 330 |
| $Na_2SO_4$ | 7·1 | 7·5 | 7·5 | 6·8 | 6·7 | 6·2 | 370 |
| Lactulose + $Na_2SO_4$ | — | — | 7·7 | 4·5 | 6·4 | 6·9 | 410 |

Table II *Individual pH measurements along the gastrointestinal tract in three subjects during five different study programmes*[1]

[1]Mean 24 h-stool weights during the period of passage of the pH pill are also shown.

With regard to sodium sulphate, the pH in the left colon ($P < 0·05$) and rectum ($P < 0·01$) was significantly lower than in the controls. When compared with lactulose, however, only in the rectum ($P = 0·05$) did the sodium sulphate produce a significantly lower pH.

With the mixture of lactulose and sodium sulphate the pH in both right colon ($P < 0·001$) and rectum ($P < 0·05$) was lower than in the control group. However, comparison of the lactulose and lactulose plus sodium sulphate groups showed no significant difference of pH at any site along the colon ($P > 0·05$).

Results of individual studies are shown in table II for the three subjects on whom repeated studies were made. Each subject showed the same trends as above, ie, a fall of pH between lower ileum and right colon, which was most marked in the lactulose studies and a tendency for the pH to rise as the pill passed from right colon to the rectum. In two subjects rectal pH was particularly high in the magnesium sulphate studies and, in all three, rectal pH was lowest in the sodium sulphate studies. Sodium sulphate did not produce obvious acidification in the lower ileum or right colon. Compared with lactulose alone, the mixture of lactulose and sodium sulphate did not produce a more uniform pattern of acidification along the length of the colon.

## Discussion

These studies show that lactulose produces consistent and marked acidification of proximal colonic contents, but that changes in the rest of the colon are less consistent. There are no other comparable studies in man, and all published data relate to faecal pH. However, very similar observations were made in animals 50 years ago. In rats fed with lactose, which they absorb poorly, the pH of faecal contents fell from an average of 7·0 (in controls) to 4·6 whereas the pH in the left colon fell from 7·1 to 6·2 (Cannon and McNease, 1923) and similar observations were made on chickens (Beach and Davis, 1925). Proximal acidification presumably reflects the major site of bacterial fermentation of unabsorbed sugar. In the present studies, it has been assumed that the marked fall in pH takes place between the ileum and right colon. As already mentioned, the exact location of the pill is not possible in the right iliac fossa and it may be that acidification starts in the terminal ileum. Bacteriological studies on normal ileal contents show high counts of many faecal type organisms including lactobacilli (Hamilton, Dyer, Dawson, O'Grady, Vince, Fenton, and Mollin, 1970) but such studies have not been performed on subjects taking lactulose. This is of more than purely theoretical interest because continuous ileal acidification may impair vitamin $B_{12}$ absorption in man (Palva, Salokannel, Timonen, and Palva, 1972) and this could be a hazard of long-term lactulose administration. However, in the present study luminal pH at a site definitely proximal to the ileocaecal area was not significantly depressed in the lactulose-treated group compared with controls. The lowest pH observed in the lower small intestine was 6·7 and evidence *in vitro* suggests that the uptake of vitamin

$B_{12}$ is maximal at or above pH 6·6 and absent below pH 5·5 (Carmel, Rosenberg, Law, Streiff, and Herber, 1969). It, therefore, seems unlikely that vitamin $B_{12}$ absorption would be affected in this way.

The tendency for pH to rise between proximal colon and rectum probably results from a combination of absorption of organic acids and neutralization of luminal contents by bicarbonate secretion. In a single study, short-chain fatty acids were absorbed from the human colon at rates which increased with increasing chain length and partition into chloroform (Dawson *et al*, 1964). However, lactulose fermentation produces mainly lactic acid (Hoffmann, Mossel, Korus, and Van de Kamer, 1964) and direct evidence relating to colonic absorption of lactate in man is not available. Perfusion studies in the rat suggest that very little colonic absorption of lactic acid would occur (Heller and Kern, 1968). On the other hand, lactose-induced diarrhoea in patients with hypolactasia is not invariably associated with a marked increase in faecal lactic acid concentration (McMichael *et al*, 1965), suggesting that most of it could be absorbed. This aspect of the problem remains unsettled. Bicarbonate is secreted into the colonic lumen against both chemical and electrical gradients (Giller and Phillips, 1972) and experimentally it can be very difficult to maintain a continuously low pH along the colonic lumen in perfusion studies (Bown *et al*, 1972). These two factors will tend to maintain a near neutral faecal pH unless colonic transit is very rapid. Consideration of transit time and faecal volumes may explain previously discrepant observations on faecal pH in patients and normal subjects taking lactulose.

In a study of three normal subjects (Agostini *et al*, 1972) the pH of faecal dialysates was reduced to a small extent (0·3 unit) in one subject and to a negligible extent in another subject by lactulose in a dose which produced only a modest increase in faecal volume. In the third subject, the faecal volume was more than doubled, compared with the control period, and the mean pH was significantly reduced by 0·7 unit. In clinical trials of patients with hepatic encephalopathy, much more striking acidification of faeces has been reported in some studies (Elkington *et al*, 1969; Bircher *et al*, 1971) but the dose of lactulose used was generally greater than that used by Agostini *et al* (1972) and the stool volumes were probably larger. Zeegen *et al* (1970) measured the pH of faecal dialysates and faecal volume in four subjects taking lactulose and extremely variable results were obtained. The patient with the least impressive fall in faecal pH had the smallest faecal volumes (mean 206 g). It must be concluded that changes in faecal pH are often a poor indication of fermentative processes in the proximal colon, particularly if faecal volumes are only modestly increased.

The present findings are in agreement with previous evidence from Wrong and his colleagues that magnesium salts increased and sodium sulphate decreased faecal pH (Down *et al*, 1972). These workers used magnesium carbonate, but postulated that this is converted to magnesium chloride in the stomach and subsequently recombines with bicarbonate in the colon. Removal of bicarbonate as insoluble magnesium carbonate might theoretically enhance the rate of colonic secretion of bicarbonate. The same arguments could apply to magnesium sulphate, assuming that magnesium is preferentially precipitated out as the carbonate in the colon. The acidifying effect of sodium sulphate appears to take place in the left colon and probably results from the virtually complete removal of absorbable anion (mainly chloride) by more proximal colon. In human colon perfusion studies, replacement of chloride by sulphate inhibits bicarbonate secretion and this has been used as evidence for an anion exchange mechanism (Bown *et al*, 1972). Down *et al* (1972) suggested that unabsorbable sulphate would increase the electrical gradient across the colonic mucosa and, by increasing luminal negativity, inhibit bicarbonate secretion, but they did not confirm this by measurement of rectal potential difference. In either situation, inhibited bicarbonate secretion might account for the distal acidification of colonic contents.

It remains to be established whether or not lactulose produces a beneficial effect in patients with chronic hepatic encephalopathy by acidifying colonic contents. The present results suggest that acceptable doses of lactulose will not consistently reduce faecal pH. Agostini *et al* (1972) showed that, even when faecal pH was lowered by lactulose, there was no demonstrable increase in the faecal excretion of ammonia. It seems unlikely that the trapping of ammonia in an acid stool is relevant in this context. An alternative explanation is that acidification of the colonic lumen might inhibit the bacterial production of ammonia from urea or other nitrogenous substrates and there is evidence from studies *in vitro* to support this (Vince, Dawson, Park, and O'Grady, 1973). In this case proximal colonic as opposed to faecal acidification might be particularly relevant, because this would be the major site of bacterial activity. Agostini *et al* (1972) have suggested that sodium sulphate may be a cheaper and more convenient alternative to lactulose in these patients, because it produces consistent faecal acidification. The present study shows that these two agents produce quite different profiles of acidification along the colonic lumen. If acidification of proximal colonic contents is beneficial in these patients, then sodium

sulphate should prove to be less effective than lactulose. Moreover, the present results suggest that the combination of these two laxatives is unlikely to be more effective than lactulose alone.

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