Faecal ammonia and pH during lactulose administration in man: comparison with other cathartics

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SUMMARY The effect of lactulose on faecal pH and ammonia has been studied in three normal subjects with the aid of dialysis of faeces *in vivo*. Observations were also made with sodium sulphate and the two hexahydric alcohols, mannitol and sorbitol, given in doses sufficient to cause a similar increase in stool weight.

All four cathartics rendered the stool more acid, but there was no increase in the concentration of faecal ammonia. Lactulose, despite increasing faecal volume, did not cause an increase in the absolute amount of ammonia lost in the faeces, but the other purgatives did show a modest rise.

The results are inconsistent with the theory that lactulose benefits the clinical picture of portosystemic encephalopathy by trapping ammonia in an acid stool. An alternative suggestion is advanced, namely, that any cathartic (including lactulose) reduces ammonia absorption from the colon by decreasing colonic transit time, and so reducing the amount of ammonia generated by autolysis of colonic bacteria.

Lactulose (1-4 β galactosido-fructose) was introduced in 1966 by Bircher, Müller, Guggenheim, and Haemmerli, in the treatment of portosystemic encephalopathy. This step had been suggested by Ingelfinger (1964-65) who recognized that the disaccharide is not hydrolysed in the ileum and when taken by mouth will reach the colon unchanged, where it promotes the growth of lactobacilli, organisms which lack urease, and other ammonia-generating enzymes (Phear and Ruebner, 1956; Macbeth, Kass, and McDermott, 1965). Ingelfinger (1964) suspected that a reduction in the number of proteolytic bacteria in the colon, in favour of lactobacilli, would reduce the formation of ammonia, leading to a decrease in portal venous ammonia.

Clinical trials have since tended to confirm the value of lactulose in portosystemic encephalopathy (Bircher, Haemmerli, Scollo-Lavizzari, and Hoffmann, 1971a). Lactulose has also been shown to lower faecal pH (Mayerhofer and Petuely, 1959), a finding which has led to an alternative suggestion, that its effect on non-ionic diffusion of ammonia might explain its efficacy in portosystemic encephalopathy. It was argued (Elkington, Floch, and Conn,

1969) that by inducing an acid intraluminal reaction, lactulose would increase the ratio of ionized to unionized ammonia in the colon, thereby reducing the proportion of ammonia available for reabsorption by passive non-ionic diffusion, and so enhancing the excretion of ammonia in the faeces. This theory has been generally accepted (Haemmerli and Bircher, 1969; *Lancet*, 1970; Elkington, 1970), although the only studies in which faecal ammonia has been measured during lactulose therapy did not show the expected increase in ammonia loss (Zeegen, Drinkwater, Fenton, Vince, and Dawson, 1970; Bircher, Haemmerli, Trabent, Largiadèr, and Moccetti, 1971b).

Lactulose is thought to decrease faecal pH by providing a substrate for bacteria which is converted to organic acids, especially acetic and lactic acid (Hoffmann, Mossel, Korus, and van de Kamer, 1964). If inhibition of passive absorption of ammonia by this acid reaction is the main mechanism by which lactulose exerts its beneficial effect, it should be possible to show that the acid stools passed during lactulose administration contain an increased amount of ammonia. In the present study, we have made use of dialysis *in vivo* of faeces (Wrong, Metcalfe-Gibson, Morrison, and Howard, 1965), a

method which provides samples suitable for both pH and ammonia determinations, to settle this point.

Sodium sulphate, taken orally, also produces an acid stool, and we have shown that small doses of this substance increase faecal ammonia (Down, Agostini, Murison, and Wrong, 1972). By trapping ammonia in the colon this substance might be as effective as lactulose in the treatment of porto-systemic encephalopathy; we therefore compared its effect on faecal pH and ammonia with that of lactulose.

The isomeric hexahydric alcohols, mannitol and sorbitol, have long been used as mild aperients (Krantz and Carr, 1954). Both substances are thought to act as osmotic cathartics, but it is not clear how much of this effect is due to the unchanged alcohol, and how much to the products of bacterial decomposition. Both substances are known to be converted to organic acids by bacteria found in the colon (Cowan and Steel, 1965), and as they are cheaper and more readily available than lactulose, they might be preferable in the treatment of porto-systemic encephalopathy if they could be shown to have similar effects on faecal pH and ammonia; we have therefore studied them in the present experiments.

Methods

Three healthy males, aged 31-46 years, were studied during the course of their normal activities while taking a normal mixed diet. *In-vivo* dialysis of faeces was performed as already described (Wrong *et al*, 1965), each subject swallowing 8-10 dialysing capsules a day, and faecal dialysate being analysed from all stool specimens until capsules no longer appeared in the stool. After control observations, each subject swallowed 30-50 g lactulose daily (average dose 40 g) in divided doses for 14 days; the dose was adjusted to produce two to three soft stools per day, as has been recommended in the treatment of porto-systemic encephalopathy (Bircher *et al*, 1971a). The drug was taken either as pure lactulose in water or as Duphalac. All stools were weighed and their

consistency classified as 'formed', 'semi-formed', 'semi-fluid', and 'fluid'. Daily stool weight was calculated by averaging stool weight over each experimental period of study, and daily loss of ammonia was estimated by assuming that stools were 75% water ('formed'), 80% ('semi-formed'), 85% ('semi-fluid'), and 90% ('fluid'), and that faecal ammonia was evenly distributed in the watery component. These percentages of stool water correspond to those found by measurement of typical specimens in our laboratory. Faecal dialysate ammonia, total organic anion, and osmolality were measured as already described (Wrong *et al*, 1965), and faecal pH by glass electrode under anaerobic conditions. At least two weeks after the lactulose experiment, each subject was restudied while taking sodium sulphate, 6-8 g/day (mean 6.2 g) in divided doses for seven days, followed by mannitol, 10-50 g/day (mean 34 g) for 10 to 20 days, and finally sorbitol, 20-80 g/day (mean 35 g) for nine to 25 days. The actual dosage of each of these substances was adjusted during each experiment in an attempt to yield approximately the same weight of stool.

Results

Lactulose increased the daily weight of faeces (Table I), and made them more liquid, but there was a

Subject	Control	Lactulose	Na ₂ SO ₄	Mannitol	Sorbitol
1	181	384	292	289	300
2	144	180	386	239	262
3	105	170	214	143	138

Table I Mean stool weights (g/day) in subjects taking different cathartics

tendency for the stools to become more solid as lactulose was continued. Mean faecal pH fell significantly in subjects 1 and 2 (Table II) but not in subject 3. Mean faecal ammonia concentration was less than control values in all three subjects during lactulose ingestion, not more as predicted by theory (Table III). Faecal ammonia concentrations were also less than those found in earlier studies on formed

Subject	Control	Lactulose	Na ₂ SO ₄	Mannitol	Sorbitol
1	7.17 ± 0.33	6.46 ± 0.39 P < 0.01	6.40 ± 0.61 P < 0.01	6.90 ± 0.45 P < 0.02	6.36 ± 0.46 P < 0.01
2	7.40 ± 0.25	7.13 ± 0.41 P < 0.01	6.24 ± 0.34 P < 0.01	7.07 ± 0.45 P < 0.01	6.94 ± 0.61 P < 0.01
3	7.28 ± 0.50	7.25 ± 0.49 P NS	6.50 ± 0.61 P < 0.01	7.28 ± 0.20 P NS	6.71 ± 0.34 P < 0.01

Table II Mean stool pH and SD in subjects taking different cathartics

¹P values refer to the difference between the mean value for each study and the mean value of control observations in that subject. NS = not significant.

Fig. 1 Effect of lactulose on faecal pH and ammonia concentration. Subject 1, ●; subject 2, ■; subject 3, ▲. The regression line shown was calculated from data obtained from formed stool of the three subjects in a previous study (Down et al, 1972) and shows a significant negative correlation between total ammonia concentration and pH ($r = -0.65$, $P < 0.01$, $y = 4.07 - 0.415x$, where $x = \text{pH}$ and $y = \log [\text{total ammonia}]$). The ammonia concentrations during lactulose treatment were lower than in formed stool, and showed no significant correlation with pH ($r = 0.02$, $P > 0.1$).

stools, throughout the whole pH range observed (Fig. 1). The absolute amount of ammonia lost in the stool per day, derived from stool weight and consistency as described above, did not differ significantly from control observations (Table IV). There was a significant increase in organic anion excretion in all three subjects while taking lactulose (Tables V and VI). Faecal osmolality showed no difference during lactulose administration (control mean 318 mOsm/kg $\pm$ 28, lactulose 318 mOsm/kg $\pm$ 21).

Sodium sulphate increased stool weight significantly and there was a marked fall in faecal pH as expected (Tables I and II), although the lowest value was only 5.6. Faecal ammonia concentrations varied between subjects, with a fall in subjects 1 and 2 and a rise in subject 3 (Table III); taken together, the three subjects did not show a significant change in ammonia concentration. As in the lactulose studies, ammonia concentrations were lower than previously observed in formed stool of similar pH from the same three subjects (Fig. 2). There was a small increase in

Subject	Control	Lactulose	Na ₂ SO ₄	Mannitol	Sorbitol
1	23.4 $\pm$ 15.6	7.7 $\pm$ 5.9 P < 0.01	13.2 $\pm$ 6.7 P < 0.10 Means all < control	20.6 $\pm$ 10.8 P < 0.25	19.7 $\pm$ 11.2 P < 0.25
2	8.7 $\pm$ 2.3	7.6 $\pm$ 4.0 P < 0.15	7.7 $\pm$ 2.5 P < 0.15 Means all < control	7.1 $\pm$ 3.7 P < 0.10	6.6 $\pm$ 2.9 P < 0.01
3	11.8 $\pm$ 6.1	9.0 $\pm$ 5.5 P < 0.10 Mean < control	16.7 $\pm$ 6.1 P < 0.05	13.5 $\pm$ 7.2 P < 0.20 Means > control	13.6 $\pm$ 6.9 P < 0.20

Table III Mean stool ammonia concentration (m-equiv/l and SD) in subjects taking different cathartics

Subject	Control	Lactulose	Na ₂ SO ₄	Mannitol	Sorbitol
1	3.19 $\pm$ 2.13	2.60 $\pm$ 2.27 P < 0.25 Mean < control	2.91 $\pm$ 1.40 P NS Mean < control	4.56 $\pm$ 2.34 P < 0.03	4.78 $\pm$ 2.65 P < 0.03 Means > control
2	0.95 $\pm$ 0.23	1.13 $\pm$ 0.60 P < 0.10	2.50 $\pm$ 0.82 P < 0.01 Means all > control	1.38 $\pm$ 0.65 P < 0.01	1.33 $\pm$ 0.55 P < 0.01
3	0.96 $\pm$ 0.52	1.26 $\pm$ 0.85 P < 0.10	2.93 $\pm$ 1.11 P < 0.01 Means all > control	1.50 $\pm$ 0.84 P < 0.01	1.34 $\pm$ 0.56 P < 0.03

Table IV Mean daily faecal loss of ammonia (m-equiv/day and SD) in subjects taking different cathartics

Fig. 2 Effect of sodium sulphate on faecal pH and ammonia concentration. Details as in Figure 1.

The ammonia concentrations during sodium sulphate treatment were lower than in formed stool, and showed no significant correlation with pH ($r=0.14$, $P>0.1$).

the absolute amount of ammonia lost in the faeces in subjects 2 and 3 (Table IV). Faecal organic anion concentration fell in all three subjects (Table V), but the total daily loss was greater than in control studies (Table VI). Faecal osmolality showed no significant change (control mean $318 \text{ mOsm/kg} \pm 28$, sodium sulphate $319 \text{ mOsm/kg} \pm 26$).

The effects of mannitol and sorbitol were similar; both caused an increase in stool weight although the stools were often well formed, and both lowered faecal pH, particularly sorbitol (Tables I and II). Mean faecal ammonia concentrations did not differ

significantly from control data (Table III). As with the other two cathartics, the faecal concentrations of ammonia were lower than in formed stools of similar pH from these subjects (Figs. 3 and 4), but there was a small increase in the daily loss of ammonia (Table IV). Faecal organic anion concentration varied with each subject (Table V), but the daily faecal loss more than doubled in subjects 1 and 2 (Table VI). Faecal osmolality showed a slight increase with both substances (control mean $318 \text{ mOsm/kg} \pm 28$, mannitol $322 \text{ mOsm/kg} \pm 20$, $P<0.05$; sorbitol $344 \text{ mOsm/kg} \pm 45$, $P<0.02$).

Subject	Control	Lactulose	Na_2SO_4	Mannitol	Sorbitol
1	154 ± 35	224 ± 37 $P<0.01$	129 ± 32 $P<0.15$	198 ± 37 $P<0.01$	203 ± 27 $P<0.01$
2	148 ± 20	211 ± 37 $P<0.01$	123 ± 54 $P<0.15$	164 ± 13 $P<0.1$	172 ± 33 $P<0.03$
3	170 ± 42	177 ± 34 $P \text{ NS}$	111 ± 33 $P<0.01$	130 ± 27 $P<0.01$	169 ± 25 $P \text{ NS}$

Table V Mean stool organic anion concentration (m-equiv/l and SD) in subjects taking different cathartics

Subject	Control	Lactulose	Na_2SO_4	Mannitol	Sorbitol
1	20.8 ± 4.9	75.7 ± 28.4 $P<0.01$	28.5 ± 6.4 $P<0.01$	43.9 ± 11.6 $P<0.01$	49.4 ± 6.0 $P<0.01$
2	17.2 ± 3.0	31.1 ± 7.1 $P<0.01$	39.9 ± 16.0 $P<0.01$	32.4 ± 3.6 $P<0.01$	35.8 ± 11.0 $P<0.01$
3	14.1 ± 4.3	30.2 ± 7.5 $P<0.01$	19.3 ± 5.6 $P<0.05$	14.2 ± 2.2 $P \text{ NS}$	17.2 ± 1.9 $P<0.05$

Table VI Mean daily faecal loss of organic anion (m-equiv/day and SD) in subjects taking different cathartics

Fig. 3.

Fig. 3 Effect of mannitol on faecal pH and ammonia concentration. Details as in Figure 1.

The ammonia concentrations during mannitol treatment were lower than in formed stool, and showed no significant correlation with pH ($r=0.11$, $P>0.1$).

Fig. 4.

Fig. 4 Effect of sorbitol on faecal pH and ammonia concentration. Details as in Figure 1.

The ammonia concentrations during sorbitol treatment were lower than in formed stool, and showed no significant correlation with pH ($r=0.20$, $P<0.1$).

Discussion

The prevailing belief that lactulose leads to increased faecal loss of ammonia by causing an acid stool has been disproved by the present experiments. This view was based on the observation that lactulose leads to a more acid stool, and on very substantial evidence that ammonia is absorbed from the colon by non-ionic diffusion, but it has never been confirmed by actual measurement of faecal ammonia. The results of the present study, in which neither the concentration nor the total loss of ammonia in the

stool increased during lactulose therapy, despite a marked lowering of faecal pH, were unexpected, and a number of possible explanations need consideration.

Dialysis *in vivo* of faeces might not provide samples suitable for ammonia determination under the circumstances of these experiments. Ammonia concentrations in faecal dialysate might be lower than the actual concentration in faeces because of very rapid transit of dialysing capsules in a diarrhoeal stool, with failure to equilibrate fully with the surrounding fluid faeces. We suspect that this expla-

nation is incorrect for two reasons; first, that dialysing capsules always took at least 24 hours to pass through the alimentary tract, even during diarrhoea caused by administration of lactulose and other cathartics, a time which is much greater than the two hours which capsules take to equilibrate with their surroundings (Wrong *et al*, 1965). (It is of interest that capsules took this time to travel through the alimentary tract even when diarrhoea occurred within a few hours of a single dose of lactulose.) Secondly, on frequent occasions when dialysate ammonia concentrations from a fluid stool were very low, we were able to measure faecal ammonia by introducing liquid faeces directly into the Conway units, and on all occasions the ammonia concentrations measured in this way were close to those of faecal dialysate.

A second possible explanation for our findings is that diarrhoea increases the speed of colonic transit so markedly that bacterial hydrolysis of urea is incomplete, and so less ammonia is produced in the colon. To confirm whether this is so, we have measured the urea concentration of many samples of faecal dialysate of low ammonia concentrations, but in no case have we found more than 0.5 mM/l urea, which is the smallest amount that we can detect with certainty by the Conway method when ammonia is also present. Thus we are unable to confirm that a reduced hydrolysis of urea is the cause of our results.

A third possible explanation for our findings is that ammonia absorption from the colon is not really determined by non-ionic diffusion, in which case one would not expect to find an increase in faecal ammonia with more acid stools. However the evidence for absorption of colonic ammonia by this mechanism is extremely good, consisting of work both *in vivo* and *in vitro* on man and animals, including the demonstration that ammonia absorption is greater from alkaline colonic perfusates (Price, Sawada, and Voorhees, 1970; Castell and Moore, 1968), and that under normal circumstances stool pH and ammonia concentrations are negatively correlated (Down *et al*, 1972).

We think that the explanation which is most consistent with the known facts is that diarrhoea itself reduces colonic production of ammonia, even when it does not interfere with urea hydrolysis or mucosal absorption. In favour of this view we note that sodium sulphate, mannitol, and sorbitol, in doses sufficient to cause diarrhoea, usually reduced the concentration of ammonia in the stool, in some cases reducing the total daily faecal loss of ammonia, despite their acidifying effect. This observation is the more remarkable when it is recalled that smaller doses of sodium sulphate, insufficient to cause

diarrhoea, give rise to a more acid stool containing higher concentrations of ammonia (Down *et al*, 1972), the reverse of the finding observed in this study with larger doses. The effect of diarrhoea is not likely to be an increase in ammonia *absorption*, for lactulose has been shown to reduce the peripheral blood ammonia concentration in portosystemic encephalopathy (Elkington *et al*, 1969; Simmons, Goldstein, and Boyle, 1970; Zeegen *et al*, 1970; Bircher *et al*, 1971b), and both lactulose (Elkington *et al*, 1969; Combes, Walker, and Potter, 1969; Ma, McLeod, and Blackburn, 1969; Siebner, 1969; Rorsman and Sulg, 1970; Simmons *et al*, 1970; Bircher *et al*, 1971a; Brown, Trey, and McDermott, 1971) and other purgatives (Dawson, McLaren, and Sherlock, 1957) are known to cause clinical improvement in this syndrome. Rather, the effect of these purgatives is likely to be an effect on ammonia production, even though they do not apparently alter urea hydrolysis. A critical observation is the fact that normal stool, when isolated from the body, continues to generate ammonia even though it contains no urea from which this ammonia can be derived by hydrolysis (Ing, Down, Murison, and Wrong, unpublished). It is unlikely that proteolytic enzymes of intestinal mucosal origin are still active in faeces, and we suspect that this ammonia is produced by bacterial autolysis. Much of the ammonia present in normal stool may be derived in the distal part of the colon from this source, rather than from urea hydrolysis directly, even though this bacterial protein may have been largely synthesized from ammonia produced by hydrolysis of urea higher up in the colon. The proximal colon and caecum are likely to be more fertile ground for bacterial growth than the distal colon, as they probably contain more substrate, particularly in the form of carbohydrate and fat, which become progressively diminished by bacterial activity in the lower reaches of the colon. Bacterial metabolism of ammonia to form bacterial protein is therefore likely to exceed autolysis in the proximal colon, whereas in the distal colon the reverse situation will prevail, with the result that the ammonia concentrations normally present in the colonic contents will be higher in distal than in proximal colon. If this theory is correct, and it needs confirmation by analysis for ammonia in samples from different parts of the colon, any procedure provoking diarrhoea would lower faecal concentrations of ammonia by causing the excretion of a stool resembling proximal colonic contents, and simultaneously it would lower colonic absorption of ammonia by reducing the concentration of ammonia in the more distal colon.

The fate of mannitol and sorbitol in man is still

conjectural. Both are poorly absorbed (Flinn, Merrill, and Welzant, 1961) and produce osmotic diarrhoea. Colonic bacteria, particularly the coliform-aerogenes groups, are known to ferment both substances with the production of organic acids (Cowan and Steel, 1965). We found evidence of a fermentative diarrhoea in two of our three subjects; both increased their stool weight, and showed a reduction in faecal pH with a rise in organic anion concentration, indicative of an increase in organic acid produced by fermentation of these sugar alcohols. The fact that neither substance induced diarrhoea in subject 3 was probably due to greater absorption, as there was no increase in faecal organic anion, suggesting less fermentation in the colon.

According to the above theory, both mannitol and sorbitol should be as effective as lactulose in patients with portosystemic encephalopathy. However, a review of the literature does not appear to support this concept, for in two carefully designed studies (Elkington *et al.*, 1969; Bircher *et al.*, 1971a), sorbitol was used as a control 'to exclude the effect of non-specific diarrhoea', and it did not improve the symptoms of portosystemic encephalopathy. On the other hand, some workers have suggested that sorbitol may be as effective as lactulose in certain patients with portosystemic encephalopathy, ascribing the benefit to its cathartic effect (Combes *et al.*, 1969; Brown *et al.*, 1970). Of course, clinical trials are difficult because patients suitable for study are uncommon, and the neuropsychiatric state of such patients is notoriously unstable.

If it were possible to treat portosystemic encephalopathy by trapping ammonia in the colon, in our view sodium sulphate might be the agent most suitable; not only is it a potent cathartic, but it also acidifies the stool more effectively than the other substances we have studied, and it is very cheap. Although it did not lead to increased faecal losses of ammonia, we suspect that the stool contained more ammonia than it would after a cathartic which produces an alkaline stool, such as magnesium chloride (Metcalf-Gibson, Ing, Kuiper, Richards, Ward, and Wrong, 1967), and absorption of ammonia was probably much reduced by the combination of catharsis and an acid stool. However, we doubt whether portosystemic encephalopathy can really be influenced by the trapping of ammonia in the colon. Colonic breakdown of urea is known to contribute 120-300 m-moles of ammonia to the portal circulation a day (McDermott, Adams, and Riddell, 1954; Walser and Bodenlos, 1959; Wolpert, Phillips, and Summerskill, 1971), ie, 12-30 times as much as the greatest daily faecal loss of ammonia seen in any of the present studies. We doubt whether trapping of such a small

proportion of the ammonia produced in the colon would benefit patients with portosystemic encephalopathy.

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