THE EFFECT OF LACTULOSE ON THE FAECAL FLORA OF PATIENTS WITH HEPATIC ENCEPHALOPATHY

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SEVERAL workers (Fung and Khoo, 1968; Bircher *et al.*, 1969; Elkington, Floch and Conn, 1969; Ma, McLeod and Blackburn, 1969; Zeegen *et al.*, 1970) have found lactulose therapy beneficial in the treatment of hepatic encephalopathy which is thought to result, at least in part, from cerebral intoxication caused by the failure of a damaged or by-passed liver to continue the normal detoxification of substances such as ammonia elaborated by bacteria in the gut. Lactulose is a synthetic disaccharide that is not hydrolysed by the disaccharidases of the small intestine of man (Dahlqvist and Gryboski, 1965). It passes unabsorbed into the ascending colon, where it is split by the action of bifidobacteria, lactobacilli and faecal streptococci to yield mainly lactic and acetic acids (Hoffmann *et al.*, 1964), the accumulation of which causes the colonic pH to fall and fermentative diarrhoea to develop.

The present study evaluates the effect of lactulose on the faecal flora of the patients studied by Zeegen *et al.* (1970) and examines the possibility that the changes observed were due solely to purgation.

MATERIALS AND METHODS

Five patients, three men and two women, were studied in hospital. All had suffered from periodic encephalopathy over periods varying from a few months to several years. Each patient was studied during an initial stabilisation period of constant protein intake (70 or 80 g per day) and subsequently during successive periods of administration of lactulose or magnesium sulphate. Lactulose was given first in three cases and magnesium sulphate first in the other two. Three patients were given lactulose therapy twice. Neomycin was given over a further period of 5 days to one patient (no. 5). The dose of lactulose was adjusted to produce two to three soft or semi-formed stools a day: usually between 100 and 150 ml of syrup (50% lactulose) in divided doses three or four times a day was required. Magnesium sulphate was used in doses adjusted to produce a similar quantity of stool: usually 15 ml of a solution containing 6 g of magnesium sulphate twice or three times daily.

Bacteriological examination of faeces. Fresh specimens were obtained daily or at regular intervals and were examined immediately upon arrival at the laboratory as described previously (Hamilton *et al.*, 1970; Zeegen *et al.*, 1970). The average period over which each patient was studied was 50 days and a total of 160 specimens was examined.

Expression of results. The results were analysed by a slightly modified version of Goldsmith's (1965) autocorner's computer programme. This takes into account the fact that considerable spontaneous variation in faecal bacterial counts may be found in the same person on successive days. The deviation of each individual reading from the mean of the whole series was calculated and its significance assessed by application of the Student "t"

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test at the 1% level. A change in level was printed only if significant differences were maintained for four or more successive readings.

RESULTS

The table lists the highest mean counts recorded for individual organisms in each patient during the various treatments. A typical computer plot which shows the significant increases and decreases in the counts of different groups

FIGURE.—Mean counts of lactobacilli, bifidobacteria, clostridia, *Esch. coli* and *Bacteroides* spp., as indicated by computer analysis, during successive periods of treatment of one patient on a constant 70-g protein intake with (a) diet alone, (b) diet+magnesium sulphate, (c) diet+lactulose.

of organisms over the various treatment periods for one patient is shown in the figure. Usually there was a single mean value that was maintained during each treatment, but occasionally significant changes occurred within a treatment period—as shown in the figure where two significant mean values for lactobacilli were obtained during lactulose treatment.

During the stabilisation period no significant increase occurred in the count of any organism. The highest mean aerobic lactobacillus count during lactulose therapy exceeded that of the stabilisation period in three patients (nos. 1, 2 and 3), two of whom (nos. 1 and 2) responded clinically to lactulose. Among the three patients who showed significant increases in lactobacillus counts while receiving lactulose, the counts at the end of the period of treatment

TABLE

Highest mean counts of lactobacilli, bifidobacteria, clostridia, enterococci, Escherichia coli and Bacteroides spp. as recorded by computer analysis when five patients with hepatic encephalopathy were treated with (i) diet alone, (ii) diet+lactulose, and (iii) diet+magnesium sulphate. Counts above the broken line in each group are from patients who responded clinically to lactulose

Group of organisms	Patient no.	Highest mean count of stated organism per g of faeces in patients treated by		
		diet alone	lactulose	magnesium sulphate
Lactobacilli	1	9.0×10^7	9.9×10^9	8.5×10^6
	2	0	7.7×10^6	4.0×10^4
	3	0	6.6×10^4	0
	4	5.3×10^6	2.3×10^6	2.3×10^6
	5	9.9×10^7	8.2×10^7	1.1×10^6
Bifidobacteria	1	2.0×10^8	9.9×10^8	2.4×10^8
	2	5.0×10^7	1.0×10^7	8.2×10^5
	3	6.2×10^7	9.9×10^9	6.2×10^7
	4	1.0×10^7	8.2×10^7	4.5×10^6
	5	1.0×10^8	9.9×10^8	3.0×10^7
Clostridia*	3	5.3×10^7	1.9×10^5	1.9×10^5
	4	5.0×10^4	6.1×10^5	6.1×10^5
	5	2.3×10^5	2.3×10^4	2.3×10^5
Enterococci†	1	3.0×10^7	5.5×10^8	3.3×10^6
	2	8.9×10^7	7.5×10^7	3.7×10^6
	4	5.0×10^5	2.4×10^4	1.9×10^4
	5	3.2×10^3	8.7×10^5	5.7×10^3
<i>Escherichia coli</i>	1	7.2×10^8	1.0×10^8	7.7×10^6
	2	5.0×10^3	1.6×10^9	1.0×10^7
	3	1.0×10^8	2.0×10^6	2.0×10^6
	4	7.1×10^4	5.2×10^5	3.0×10^8
	5	7.7×10^6	9.1×10^6	1.0×10^7
Bacteroides	1	3.5×10^{10}	1.0×10^{11}	7.4×10^8
	2	5.0×10^7	7.5×10^6	7.9×10^5
	3	5.7×10^8	9.9×10^9	5.7×10^8
	4	5.0×10^6	1.3×10^7	1.3×10^7
	5	9.2×10^8	6.1×10^6	4.3×10^8

* Clostridia were not isolated from patients no. 1 and no. 2.

† Enterococci were not isolated from patient no. 3.

were much higher in the two patients who responded (9.9×10^9 per g and 7.7×10^6 per g) than in the patient who failed to respond (6.6×10^4 per g). In two patients (nos. 2 and 3), lactobacilli were not isolated from the faeces until lactulose was administered, and in one of these (no. 3) lactobacilli disappeared when therapy ceased. Patient 3, and patients 4 and 5 in whom lactobacillus counts fell while on lactulose therapy, failed to respond clinically.

No other systematic relationship was demonstrated between changes in counts of organisms, lactulose therapy and clinical response of the patient. Counts of ammonia-producing organisms, e.g., *Escherichia coli* and *Bacteroides* spp. did not invariably fall during lactulose administration. Counts of *E. coli* decreased during lactulose therapy in one patient (no. 1) who responded clinically and in one (no. 3) who did not, and increased dramatically (from 5.0×10^3 to 1.6×10^9 per g) in another (no. 2) who responded clinically. Counts of *Bacteroides* spp. increased during lactulose therapy in one (no. 1) and decreased in the other (no. 2), both of whom responded clinically to lactulose.

During magnesium sulphate therapy the general tendency was for counts of organisms to fall. Both patients who responded to lactulose deteriorated whilst receiving magnesium sulphate, and counts of lactobacilli fell below that of the stabilisation period in one patient. The administration of neomycin to patient no. 5, after lactulose and magnesium sulphate therapy, eliminated *E. coli* from the faeces.

DISCUSSION

Clinical response to lactulose is dependent on its breakdown to organic acids by bacteria and the consequent lowering of the colonic pH, so some relationship might be expected between the effect of lactulose on the faecal flora and the clinical response of the patient. The beneficial effects of lactulose could arise (i) from fostering the growth of acidophilic organisms with consequent "displacement" of ammonia-producing species, (ii) from a reduction in the amount of ammonia produced by intestinal organisms at low pH, or (iii) from a reduction in the amount of ammonia absorbed, because ammonia is effectively trapped in the gut at low pH.

The reported effects of lactulose on the faecal flora are conflicting. Haenel, Muller-Beuthow and Scheunert (1957) and Haenel *et al.* (1958) found that generally the count of the bifidus group was not increased, and that counts of *E. coli* and streptococci were decreased. Bircher *et al.* (1969) reported an increase in numbers of anaerobic lactobacilli and a decrease in bacteroides counts after lactulose administration. Conn and Floch (1970) found that lactulose treatment resulted in moderate, but statistically insignificant, increases in the mean number of lactobacilli, a decrease in total aerobic bacteria and an increase in the total anaerobic flora.

The present results indicate that clinical improvement was not dependent upon drastic reductions in counts of ammonia-producing organisms. Counts of enterobacteria, considered to be among the most active ammonia producers (O'Grady, 1966), actually increased during some periods of lactulose therapy. Possibly it is not that the numbers of ammonia-producing organisms fall during

lactulose administration, but that their production of ammonia and other toxic substances is inhibited; in our previous study, no correlation could be demonstrated between faecal counts of ammonia-producing species and concentrations of ammonia in the blood and faeces of the subjects studied (Zeegen *et al.*, 1970).

Nor could clinical improvement be related in the present analysis to the highest count of lactobacilli recorded—a higher count was recorded for a non-responding patient than for one who responded. Perhaps there is no absolute lactobacillus count that must be exceeded in all patients for symptomatic improvement to occur, but each individual may have a threshold count above which improvement follows. The amount of acid produced, and hence the decrease in colonic pH on which the beneficial effect of lactulose presumably depends is likely to be related to the total increase in numbers of lactobacilli. In the non-responding patient in whom an increase in the lactobacillus count occurred during lactulose therapy, the highest count reached was only 6.6×10^4 per g. Such a count represents only a tiny fraction of the total flora, and the influence of this component on the remainder of the flora and its environment is likely to be correspondingly small.

SUMMARY

The changes that occurred in the faecal flora during the separate administration of lactulose and magnesium sulphate were studied in five patients with hepatic encephalopathy. Lactulose therapy produced significant increases in lactobacillus counts in three patients, and two of these patients showed clinical improvement. No systematic change occurred in the counts of other organisms during either treatment; in particular it was not possible to correlate clinical improvement with a reduction in the count of the two groups of organisms—enterobacteria and *Bacteroides* spp.—that are considered to be most active in the production of ammonia.

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