Progress report

Lactulose

Lactulose is a synthetic disaccharide comprising galactose and fructose in combination as 1,4-beta-galactosido-fructose. It is prepared from lactose and supplied for clinical use as a flavoured syrup* containing approximately 50% lactulose, together with smaller amounts of galactose and of unchanged lactose (about 7 g of each per 100 ml).

The intestinal mucosa possesses no disaccharidase capable of splitting lactulose into its component monosaccharides¹, and only insignificant amounts are absorbed unchanged². On reaching the colon, however, this sugar is metabolized by bacterial enzymes into carbon dioxide and low molecular weight acids (chiefly lactic and acetic)^{2,3}. Thus in sufficient dosage lactulose lowers the faecal pH, and produces an osmotic and fermentative diarrhoea analogous to that observed in lactase-deficient subjects following the oral administration of lactose^{4,5}.

Clinical interest in lactulose first arose when Petuely⁶ induced an increase in the faecal population of *Lactobacillus bifidus* by the administration of this sugar to adults and to bottle-fed infants. He postulated that this effect might prevent enteritis during broad-spectrum antibiotic therapy, and showed that lactulose could also be employed to treat chronic constipation⁴. Lactulose has been studied as a laxative in a double-blind controlled trial and has been found effective⁷. However, at present it appears to possess no significant advantages as an aperient over cheaper alternatives, and has therefore not achieved general acceptance for this purpose⁸.

A novel and ingenious therapeutic concept was introduced by Bircher and his colleagues⁹, namely, the use of lactulose to control chronic portal-systemic encephalopathy. The rationale of this form of treatment was credited by Bircher¹⁰ to Ingelfinger¹¹ who had suggested that since lactulose produced an increase in colonic lactobacilli (which lack urease and other ammonia-generating enzymes^{1,2,12,13}), there might in theory be a beneficial action in chronic portal systemic encephalopathy. In this disabling complication of advanced cirrhosis, nitrogenous substances, formed in the colon by bacterial action on protein, bypass the liver through natural or surgically formed vascular shunts and affect the brain¹⁴. Conventional therapy has hitherto required dietary protein restriction, purgation, and the administration of a broad-spectrum antibiotic, each of which has disadvantages. Prolonged dietary protein restriction is inconvenient and may be harmful; vigorous evacuation of the bowel by purgation or enemas may produce or exacerbate electrolyte disturbance¹⁵. Continuous administration of a broad-spectrum antibiotic such as neomycin may result in moniliasis, staphylococcal enterocolitis, or malabsorption of both sugars and fat^{16,17,18,19}. Other measures less frequently employed include the oral administration of cultures of *Lactobacillus acidophilus*¹³, which involves the consumption of large quantities of protein, and surgical exclusion of the colon^{20,21}, which carries a considerable

*Duphalac, Duphar Laboratories Ltd.

operative mortality. Thus the introduction of lactulose by Bircher and his coworkers⁹ was welcome.

Clinical Studies in Chronic Portal-systemic Encephalopathy

In the initial clinical study⁹ lactulose was administered to two patients in a dose sufficient to produce two soft bowel motions daily but insufficient to produce watery diarrhoea. Comparison was made with sorbitol as a control substance. (This sugar is not fermented in the bowel and has an osmotic action only on stool consistency.) Bircher and his colleagues⁹ reported that lactulose was as effective as neomycin in correcting encephalopathy, and possibly more so, since the dietary protein intake was greater during lactulose therapy. The only side effects were watery diarrhoea if the dose was too great—the optimum dose in their patients was 100–150 ml of the syrup daily in divided doses—and some initial abdominal distension and flatulence, which resolved within a few days. These workers⁹ postulated that the action of lactulose in preventing hepatic coma resulted primarily from a change in the colonic bacterial flora, in accordance with Ingelfinger's original hypothesis¹¹. Subsequently Markoff²² briefly reported the successful use of lactulose in one patient.

These promising reports stimulated several groups to study lactulose in greater detail. Fung and Khoo²³ compared the response of two patients to lactulose and to conventional therapy, including neomycin. They concluded that lactulose was superior, since it provided better control of asterixis, allowed a normal protein intake, and was free from significant side effects in a dose of 90 ml daily. Lande and Clot-Paimboeuf²⁴ reported improvement with lactulose in 10 out of 12 patients, but made no control comparisons. Rottiers and his associates²⁵ reported uncontrolled observations on 11 patients with chronic portal-systemic encephalopathy, six of whom benefited from treatment with lactulose. The best responses were observed in patients whose clinical condition was stable, particularly when encephalopathy followed portacaval anastomosis.

The neuropsychiatric state of patients with chronic portal-systemic encephalopathy is notoriously unstable, and carefully controlled investigations are essential if therapy is to be evaluated accurately. The first double-blind controlled study²⁶ compared the response of seven patients to treatment, which was randomly assigned, with lactulose and with sorbitol over short periods of one to two weeks. Five of these patients improved clinically during lactulose therapy but did not respond to sorbitol, the improvement correlating well with decreases in faecal pH and in arterial blood ammonia values. In two patients who did not improve with lactulose the faecal pH remained unaltered. Seven patients were also studied during lactulose administration lasting for several months. It was concluded that lactulose was effective in controlling chronic portal-systemic encephalopathy, enabling neomycin to be discontinued and protein intake to be doubled. In one instance chronic choreo-athetoid movements lessened. However, Ma and his colleagues²⁷, in an uncontrolled study of long-term lactulose therapy, did not observe benefit in two patients with evidence of extrapyramidal disease. These workers concluded, nevertheless, that improvement occurred in six out of eight treated patients. More recently, Bircher²⁸ has reported improvement during lactulose therapy in six patients, and Rorsman and Sulg²⁹ have reported an uncontrolled study of three patients, each of whom was controlled by lactulose as judged clinically and by electroencephalography.

Each of the foregoing studies lacked a statistical analysis of the many variables which had been followed in each subject, an omission which had

led some workers to express their conclusions with caution²⁶. This shortcoming was remedied by the elegant study of Zeegen and his coworkers³⁰, in which magnesium sulphate was used as a control. In addition to detailed investigations comprising daily faecal frequency, weight, and bacteriology, together with estimations of arterial and venous blood ammonia levels, these investigators employed a method of quantitative psychometric testing, the Reitan trail test, for serial evaluation of their patients. The difficulties of analysing daily data for different periods were overcome by using the cumulative sum technique. Clinical improvement occurred in three out of seven patients during lactulose therapy, and relapse followed substitution by magnesium sulphate. The patients who did not respond resembled those responding to treatment in respect of decreases in faecal pH and in blood ammonia, and the reason for their failure to improve was unexplained. It was concluded that lactulose can be a useful alternative to neomycin in some patients with chronic portal-systemic encephalopathy, particularly when prolonged treatment is required.

Mode of Action

The original hypothesis of Bircher and his colleagues⁹, that lactulose acted by enhancing the growth of urease-deficient organisms such as lactobacilli, has not been supported by subsequent studies. Investigations undertaken in rats by Bircher and his associates³¹ demonstrated no increase in faecal urease activity following lactulose therapy, despite a rise in the number of anaerobic lactobacilli. In normal subjects given lactulose therapy, Floch and coworkers³² were unable to detect any significant change in the pattern of faecal flora during the administration of lactulose to normal subjects, nor were significant changes observed during treatment of cirrhotic patients²⁶. In unselected hospital patients with various disorders who were given lactulose, Hoffman and his associates³³ found significant decreases in total bacterial counts, *E. coli*, and *Bacteroides*, with no more than a proportional increase in lactobacilli and no alteration in faecal ammonia values. In cirrhotic patients lactulose produced clinical improvement one to three weeks before the development of consistent changes in faecal bacteriology, and benefit was obtained even by patients whose stools contained no lactobacilli. However, Mütting³⁴ found a relative increase in lactobacilli in cirrhotic patients treated with lactulose, and Gmünder³⁵ found no decrease in colonic bacterial urease activity in rats given lactulose. Zeegen and his colleagues³⁰ observed significant increases in faecal lactobacilli during lactulose administration, but found no consistent changes in coliforms or in *Bacteroides*.

It is the opinion of most workers that changes in faecal flora cannot explain the clinical action of lactulose. Nor can the action be ascribed to the purgative effect of lactulose, since control substances such as sorbitol^{9,26} and magnesium sulphate³⁰, which have a purely laxative action, produce no clinical improvement.

A third mechanism by which lactulose may act is through trapping ammonia in the acidified contents of the bowel. Rottiers and coworkers²⁵ have shown that the administration of lactulose improves both oral and intravenous ammonia tolerance, suggesting that lactulose indeed influences ammonia metabolism directly. Ammonia exists in blood predominantly as ammonium ion (NH_4^+) and in small amounts as non-ionized ammonia (NH_3). The ratio of these substances is largely determined by the blood pH, since the dissociation constant of ammonia (pK_a 8.90 at 37°C)³⁶ is sufficiently close to the physiological pH of blood for any change in the latter to affect the $\text{NH}_4^+/\text{NH}_3$ ratio appreciably. Ionizable compounds in compartments

separated by a membrane completely permeable to the non-ionized species and relatively impermeable to the ionized species will be unequally distributed when a *pH* gradient exists between the two compartments. Such unequal distribution occurs between blood and cerebrospinal fluid^{37,38}, blood and urine^{39,40}, blood and gastric juice⁴¹, and between intra- and extracellular fluids where *pH* gradients exist^{42,43}. The same principle should operate between blood and the lumen of the gastrointestinal tract, acidification of the colonic contents increasing the *pH* gradient and reducing ammonia absorption from the bowel. Indeed, the observations of Summerskill, Price, and their respective associates^{44,45} on the transfer of ammonia between blood and gut can be explained largely by differences in *pH*. Castell and Moore⁴⁶ have demonstrated in patients with ileosigmoid anastomoses that absorption of ammonia from the isolated colon varies directly with the *pH* of the perfusate. In similar studies in dogs, the distribution of ammonia between colonic contents and colonic venous blood correlated directly with faecal *pH*, and below a faecal *pH* of 6.2 the usual flux of NH_3 from colonic lumen to the blood was reversed^{47,48}. Clinical observations have shown a fall in stool *pH* from 7.0 to 5.0 during lactulose therapy without alteration in blood *pH*²⁶. This *pH* gradient propels NH_3 from blood to the lumen of the colon, while NH_3 in the colon (whether derived from influx or from proteolysis) is converted to the non-absorbable NH_4^+ ion and is thus retained in the bowel^{26,47,48}. This process of ammonia abstraction, termed 'acid dialysis' by Haemmerli and Bircher⁴⁷, converts the colon from the principal organ of ammonia formation to the principal organ of ammonia sequestration and excretion. The fall in blood ammonia observed by Demeulenaere⁴⁹ following rectal administration of lactulose, too rapid to be a consequence of the breakdown of lactulose, probably results from the acid *pH* (3.8) of the syrup⁵⁰, which is necessary to ensure its stability.

Side Effects and Dosage

Lactulose is absorbed in insignificant amounts only, which are rapidly excreted by the kidney. It has no effects beyond the lumen of the bowel. On first receiving the syrup, patients frequently note borborygmi, an increase in flatus, and occasionally colicky abdominal discomfort, but these symptoms usually remit within a few days either spontaneously or on adjustment of the dose. Diarrhoea is the most important side effect, but also responds to reduction in the dose of lactulose. Most investigators have started treatment with 25-30 ml of syrup three times daily, and have adjusted the dose so as to obtain two or three semi-formed stools daily with a *pH* of 5.5 or less checked by indicator paper. Occasional patients require 150 ml daily or more, and a few are sensitive to daily doses of less than 100 ml. Acidification of the stool may be achieved without any looseness of the motion, but some patients may develop severe diarrhoea before the stool becomes acid and require withdrawal of lactulose. Patients may object to the sweet taste of the syrup or to the flavouring, but the majority find it an acceptable and palatable form of treatment. Long-term administration of lactulose has no adverse effects.

Conclusions

Lactulose is a useful addition to the existing treatment of cirrhotic patients with neuropsychiatric disorders. Most patients respond, particularly those with mild and relatively stable symptoms; such patients may receive lactulose

indefinitely, and enjoy improved tolerance of dietary protein. However, unpredictable and inexplicable failures to respond occur, and lactulose cannot replace conventional measures for controlling chronic portal-systemic encephalopathy on all occasions in every patient. Though more expensive than neomycin³⁰, lactulose is free from significant side effects, and therefore falls into place as a valuable alternative to antibiotics when prolonged therapy is required. The probable mode of action is through acidification of the contents of the large bowel, resulting in the trapping and reabsorption of ammonia at this site. It is not recommended for the treatment of coma associated with fulminant hepatitis, in which ammonia intoxication is less important than in chronic portal-systemic encephalopathy⁵¹.

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