Successful use of vancomycin hydrochloride in the treatment of lactulose resistant chronic hepatic encephalopathy

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Abstract
Vancomycin hydrochloride (2 g daily) was administered to 12 patients with cirrhosis and lactulose resistant portal systemic encephalopathy in a double blind crossover trial. All 12 patients showed a remarkable clinical improvement after vancomycin treatment. The mean (SE) electroencephalographic (EEG) frequency changed from 6-3 (0-2) to 8-5 (0-2) cps (p<0.001) and the mean arterial ammonia concentration from 152 (4) μg/ml to 97 (8) μg/ml (p<0.001). Their clinical condition deteriorated when treatment was switched to lactulose, returning to the previous slower EEG frequency and high arterial ammonia concentrations. Vancomycin seems to be effective in chronic portal systemic encephalopathy in patients who are not helped by lactulose alone.

In recent years, chronic recurrent portal systemic encephalopathy in patients with cirrhosis has generally been treated with restriction of dietary protein and oral lactulose. There are, however, occasional patients with portal systemic encephalopathy who do not respond to oral lactulose treatment and develop hepatic encephalopathy despite this drug. Although a specific amino acid solution, Fischer's solution, has also been advocated in severe hepatic encephalopathy in patients with cirrhosis, it is difficult, in practice, to administer over a long period of time.

We have recently shown that vancomycin hydrochloride, a non-absorbable antibiotic which is effective against anaerobic Gram negative rods but ineffective against aerobic ones, is useful in controlling portal systemic encephalopathy in patients with cirrhosis. It has also been shown that changes in blood ammonia concentrations correspond very well with changes in the number of anaerobic Gram negative rods in faeces.

We therefore gave vancomycin hydrochloride to cirrhotic patients with portal systemic encephalopathy that was resistant to oral lactulose. We examined changes in their faecal bacterial flora and report the effectiveness of this antibiotic in these subjects.

Methods

Patients
Fourteen of 29 consecutive patients with cirrhosis and portal systemic encephalopathy admitted to Kanagawa Cancer Center Hospital and Kawasaki Kyodo Hospital between 7 April 1986 and 10 March 1988, whose portal systemic encephalopathy was resistant to continuous lactulose administration, were admitted to the study. There were 13 men and one woman. The proportion of lactulose resistant patients was high because many had been transferred to these two centres from outlying hospitals. The diagnosis of liver cirrhosis was made by laparoscopy and examination of liver biopsy specimens. Rupture of oesophageal varices occurred in one man soon after vancomycin hydrochloride administration, and he was excluded from the study. One woman was unable to continue taking vancomycin because of severe nausea and she was also excluded. Twelve patients finished the study.

None of the 12 patients had abused alcohol for more than two years and the liver lesion was biochemically and histologically inactive in all but one, who showed only mild activity. All patients had given informed consent and the research was carried out according to the declaration of Helsinki.

Study design
Before the trial the patients were admitted to hospital for two weeks (the control period) for assessment of their clinical condition. During this period lactulose was given to all patients and the amount was adjusted individually to induce two to four bowel movements a day. Protein intake was restricted to about 50 g daily and there were no changes in diet during the trial period. At the end of the two week assessment period, the mental status of the patients was evaluated and graded according to the criteria suggested by Parsons-Smith et al., modified by Conn et al. The mean electroencephalographic (EEG) frequency was estimated, the fasting arterial ammonia concentration was measured by a modified method of Okuda and Fujii, and a bacteriological study of stools was done.

The trial then started. During the first eight weeks all patients were given 1000 mg of vancomycin hydrochloride (VCM, Shionogi Pharmacological Co, Tokyo, Japan) orally twice daily — at 6 am and at 6 pm. The vancomycin was diluted in distilled water to a volume of 30 ml. At this dose vancomycin has a mildly laxative property and produces one to three semi-formed stools per day. Once the vancomycin administration had been established, the patients were discharged and followed for eight weeks as outpatients. During this period, clinical and EEG assessments were made twice weekly. After
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Figure 2:

Table 1: Changes in the grade of encephalopathy in the 12 patients with lactulose resistant chronic hepatic encephalopathy given vancomycin hydrochloride (according to the criteria suggested by Parsons-Smith et al and modified by Conn et al)

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Mean (SE) 2-0 (0-3) 0-2 (0-2)  

p<0.001
usually evident after two to three days of treatment. In 10 patients the encephalopathy resolved completely and in the remaining two only grade 1 encephalopathy persisted. The grade of encephalopathy after vancomycin (0-2 (0-2)) was significantly (p<0.001) less than that beforehand (2-0 (0-3)). The EEG frequency after vancomycin (8.5 (0-2) cps) was significantly (p<0.001) larger than that beforehand (6.3 (0-2) cps) (Table II).

In the crossover double blind study, the tendency was the same. In group A, the mental status deteriorated when patients were crossed to lactulose, and improved again when they crossed back to vancomycin. In group B, the improvement in mental status persisted for about two months, and thereafter it deteriorated in five of six patients when they were crossed to lactulose.

**Discussion**

The management of chronic recurrent portal systemic encephalopathy is difficult and unsatisfactory. It consisted of restriction of dietary protein and antibiotic suppression of the intestinal bacteria, usually by neomycin until 1967 when lactulose was introduced. This synthetic disaccharide (1,4-galactoside fructose), which is neither absorbed nor hydrolysed in the upper intestinal tract of man, passes unchanged into the lower bowel where it is metabolised by bacteria with the production of lactic, acetic, and formic acids and carbon dioxide. It is initially suggested that acidification favoured growth of lactobacilli and other acidophilic fermentative bacteria and suppression of acidophilic proteolytic bacteria resulting in a decrease in ammonia production in the colon.

It has recently been suggested, however, that a major effect of lactulose is to augment the incorporation of nitrogen (especially ammonia) into faecal bacteria for synthesis of bacterial protein, although nitrogen in the soluble frac-
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We recently showed that vancomycin, a non-

absorbable antibiotic that suppresses anaerobic Gram negative rods but not aerobic ones, is very effective in chronic recurrent portal systemic encephalopathy.4,7

We therefore administered vancomycin to patients with intractable chronic recurrent portal systemic encephalopathy which developed in spite of the oral lactulose treatment. This study shows that vancomycin is surprisingly effective in these patients. It improved their clinical symptoms, EEG abnormalities, and blood ammonia values.

Recently, it has been shown in vitro that an appreciable proportion of the non-sporing anaerobes, especially bacteroides, produce urease,26 and that Gram negative anaerobic rods (chiefly bacteroides) are more active than aerobic enterobacteria in the production of ammonia from nutrient medium containing peptides and amino acids.12 Indeed the Bacteroides sp isolated in this study belonged to the most active species in ammonia production. Moreover, in 1982 Morgan et al27 showed clinically that in the treatment of hepatic encephalopathy in a series of 11 mildly or moderately affected and seven severely affected patients with histologically confirmed cirrhosis, metronidazole, which is active against bacteroides and other anaerobes, was as effective as neomycin and that metronidazole could also reduce the production of endogenous ammonia by its effect on the anaerobic intestinal flora.

More recently we have shown that bacteroides may be the main producers of ammonia in hepatic encephalopathy in cirrhotic patients, and that suppression of these bacteria by vancomycin brings about recovery from hepatic encephalopathy in many patients.13

One of the reasons for the effect of vancomycin in lactulose resistant intractable portal systemic encephalopathy could be its ability to decrease Gram negative faecal anaerobes, especially bacteroides. This study showed a dramatic decrease in the anaerobic Gram negative rods after vancomycin treatment. In contrast, their counts were much higher in patients on lactulose. On the other hand, aerobic Gram negative rod counts remained in the same range during both treatments.

At this point one must consider the mode of action of lactulose and neomycin. Lactulose and neomycin were originally thought to exert their influence on hepatic encephalopathy by interfering with the bacterial flora but Leeuwen et al19 recently showed a potential additional effect; interference with glutamine dependent non-bacterial ammonia production. It is possible that vancomycin also has a strong inhibitory effect on the non-bacterially mediated degradation of glutamine to ammonia but no data are available on this point at present.

Although further study is required to elucidate the precise mechanism by which vancomycin is effective in lactulose resistant portal systemic encephalopathy, we conclude that this antibiotic is useful in the control of chronic portal systemic encephalopathy in which lactulose alone is ineffective.

We thank emeritus Professor Kunio Okuda of Chiba University for his indispensable assistance in the preparation of the manuscript.

18 Van Leeuwen PAM, Bogaart EJM, Janssen MA, de Boer JEG, van Eek HMA, Soeters PB. Ammonia production and glutamine metabolism in the small and large intestine of the