Effect of lactulose on cerebral metabolism in patients with chronic portosystemic encephalopathy

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SUMMARY Cerebral blood flow and cerebral metabolism were studied in six patients with moderately severe portosystemic encephalopathy before and after a 10-day course of lactulose. As a result of therapy there was a mean increase in cerebral oxygen utilization but no changes in either mean glucose consumption or in mean cerebral blood flow. It appears therefore that the abnormalities in cerebral metabolism that have been previously described in patients with hepatic encephalopathy can be improved by the oral administration of lactulose.

In patients with severe hepatic encephalopathy there is a fall in cerebral blood flow and in cerebral oxygen consumption (Fazekas, Ticktin, Ehmantraut, and Alman, 1956; Posner and Plum, 1960) together with an abnormality in the handling of glucose by the brain (James, Nashat, Sampson, Williams, and Garassini, 1969). Since clinical impressions of improvement are difficult to evaluate and to quantitate, these metabolic changes can be used as an index of the efficacy of various forms of treatment. Cerebral metabolic studies have already been used by us for the assessment of various forms of treatment, namely, the effect of induced metabolic alkalosis on hepatic encephalopathy (James et al, 1969) and for the assessment of extracorporeal pig's liver perfusion in hepatic coma (Parbhoo, Kennedy, James, Chalstrey, Ajdukiewicz, Brook, Xanalatas, Soyer, and Sherlock, 1971).

The rates of cerebral oxygen and glucose consumption were studied in six patients with moderately severe portosystemic encephalopathy before and after a 10-day course of oral lactulose (60 ml of 50% w/w solution per day).

All the patients studied had evidence of chronic liver disease and of some neurological abnormality as characterized by a flapping tremor, exaggeration of the deep tendon reflexes, or somnolence. Grade 1 or grade 2 changes were seen in the electroencephalogram. No change in therapy or diet was made one week before the study or during the 10-day period of the study.

Methods

CEREBRAL BLOOD FLOW
Cerebral blood flow was measured by the inhalation

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<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Cerebral Blood Flow (ml/100 g/min) Before</th>
<th>Cerebral Oxygen Consumption (ml/100 g/min) Before</th>
<th>Cerebral Glucose Consumption (mg/100 g/min) Before</th>
<th>pCO₂ (mm Hg) Before</th>
<th>Clinical Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Female</td>
<td>53</td>
<td>Cryptogenic cirrhosis</td>
<td>34</td>
<td>32</td>
<td>1.6</td>
<td>2.8</td>
<td>6.2</td>
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<tr>
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<td>44</td>
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<tr>
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<td>Cryptogenic cirrhosis</td>
<td>52</td>
<td>52</td>
<td>2.9</td>
<td>3.6</td>
<td>4.2</td>
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<tr>
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<tr>
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<td>40</td>
<td>Alcoholic cirrhosis</td>
<td>68</td>
<td>44</td>
<td>1.9</td>
<td>4.0</td>
<td>4.8</td>
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<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>56</td>
<td>54</td>
<td>2.0</td>
<td>3.2</td>
<td>4.8</td>
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<td>Standard error of mean</td>
<td>7.5</td>
<td>7.5</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table I Effect of 10 days' lactulose therapy on cerebral metabolism in patients with chronic portosystemic encephalopathy

1Significantly different from control value at 5% level,

Cerebral Blood Flow
A very wide scatter in values from 34 ml/100 g/min to 76 ml/100 g/min was found in these patients. Lactulose therapy did not occasion a change in most instances. There was a fall in cerebral blood flow in patient 6, but a concurrent fall in arterial pCO₂ may well have been responsible for this change.

Cerebral Metabolism
In all patients there was an increase in cerebral oxygen consumption. Since there was no commensurate increase in cerebral blood flow it can be seen that this increase was due to an increased arterial venous difference in oxygen content. There was no consistent change in cerebral glucose consumption, however, but an improvement in most cases of the oxygen glucose index. If this index is calculated, in the conventional way as

\[ A - V \text{O}_2 \text{ (m mole)} \times 100\% \]

\[ 6 \times A-V \text{glucose (m mole)} \]

then a mean value of 49% increased to a value of 80% as a result of therapy.

These changes in cerebral metabolism were not accompanied by significant changes in arterial pCO₂ or in arterial hydrogen ion concentration.

Discussion
It was a surprise to find that despite a low oxygen consumption before treatment in these patients cerebral blood flow was normal or even slightly high. The normal value for cerebral blood flow in our hands in 48.0 ml ± 2.0 (SEM). Certainly this group of patients with portosystemic encephalopathy had a much higher mean flow than the patients with hepatic encephalopathy previously described by us of 35 ml/100 g/min ± 3 (SEM) (James et al, 1969). However, Polli and his colleagues (Polli, Porro, and Maiolo, 1969) have shown that immediately after a portosystemic shunt there is an increase in cerebral blood flow. This is at a time before the patient exhibits clinical signs of encephalopathy. Once the neurological signs become manifest, brain oxygen consumption falls and there is presumably a secondary fall in cerebral blood flow. The time sequence of these events has, however, never been studied in patients.

The high cerebral blood flow noted on this occasion may be due to the fact that this group of patients was not as ill as that previously studied and the depression in oxygen consumption not yet as marked. It is certainly true that those patients, namely, patients 1 and 2, who had the lowest cerebral oxygen consumption also had the lowest flows. The very high values for cerebral blood flow noted in patient 4 may be in part due to the fact that he had some degree of renal failure in addition to liver disease.

It has been suggested that the beneficial action of lactulose in patients with portosystemic encephalopathy may be due either to the suppression of ammonia-forming organisms in the gut (Bircher, Muller, Guggerheim, and Haemmerli, 1966) or to a decrease in absorption of ammonia from the intestines as the result of an increased hydrogen ion gradient (Summerskill, Aoyagi, and Evans, 1966). However, it
can be as easily argued that lactulose could reduce
the formation of many other toxic products from
bacterial protein breakdown in the gut and that
the pH gradient would also reduce the absorption
of any toxin of a weak base
Whatever the mode of action of lactulose in
patients with portosystemic encephalopathy there
would appear to be no doubt that the administration
of lactulose is able to reverse at least partially
the abnormalities in cerebral metabolism.

We wish to thank Professor Sheila Sherlock for her
helpful advice and encouragement. This work was
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References
Treatment of chronic portal-systemic encephalopathy with
lactulose. Lancet, 1, 890-892.
(1956). Cerebral metabolism in hepatic insufficiency. Amer. J.
James, I. M., Nashat, S., Sampson, D., Williams, H. S., and Garassini,
M. (1969). Effect of induced metabolic alkalosis in hepatic
Linden, R. J., Ledsome, J. R., and Norman, J. (1965). Simple methods
for the determination of the concentrations of carbon dioxide
Parbhoo, S. P., Kennedy, J., James, I. M., Chalstrey, L. J.,
Ajdukiewicz, A., Brook, P. J., Xanatlas, C., Soyer, P., and
Sherlock, S. (1971). Extracorporeal pig-liver perfusion in
treatment of hepatic coma due to fulminant hepatitis. Lancet,
1, 659-665.
bolism after portacaval shunt. Lancet, 1, 153.
and acetazolamide in hepatic encephalopathy. J. clin. Invest.,
39, 1246-1258.
in the upper gastrointestinal tract of man: quantitations and
Mallett, B. L., and Veall, N. (1965). The measurement of regional
cerebral clearance rates in man using Xenon-133 inhalation
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