Extracorporeal methods of reducing high blood ammonia levels

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EDITORIAL SYNOPSIS Laboratory studies have been made to evaluate two methods for removing ammonia from blood:—

1 The twin-coil artificial kidney was found to produce significant reductions in the ammonia content of out-dated human banked blood. After one passage through the coil, levels of up to 9 μg. of ammonia nitrogen per millilitre were reduced to normal, and this effect was maintained when up to 5 litres were passed.

2 Ion-exchange resins, in particular a British resin ZK.225 having a 20% divinyl-benzene linkage, were also found to be effective. When passed from an artery directly through an autoclaved resin column to a vein, significant amounts of ammonia were removed from the blood of a dog with pronounced hyperammonaemia.

No serious systemic, biochemical, or haematological effects were observed when the blood of three normal dogs was passed through resin columns. All survived, and to date no reason has been found why such a technique could not be used in clinical practice.

McDermott (1957) has suggested that two varieties of hepatic coma occur. He describes an exogenous type characterized by high blood ammonia levels arising either after ingestion of more protein than the functioning hepato-cellular mass can deal with or from gastrointestinal haemorrhage. In these cases Webster and Gabuzda (1958) found a good correlation between depth of coma and cerebral uptake of ammonia. A second or endogenous type, however, is noted in which coma may occur spontaneously and which is not associated with increased cerebral uptake of ammonia.

The exogenous group respond well to broad-spectrum antibiotics such as neomycin (Dawson, McLaren, and Sherlock, 1957; Fisher and Falcon, 1957), whereas the latter group do not do well with any measures (Webster and Gabuzda, 1958). Failures occur, however, in treatment of the exogenous group and there is of necessity a period of delay, during which coma persists, before antibiotic therapy can become effective.

More direct methods of removing ammonia from the blood might have a place in the treatment of this phase. We report here some results of laboratory studies in which both the Kolff twin-coil artificial kidney and columns of ion-exchange resins (Schechter, Nealon, and Gibbon, 1958) have been used in attempts to reduce the ammonia content of perfused blood.

MATERIALS AND METHODS

Out-of-date banked human blood which has a high ammonia content was used for both series of experiments.

Ammonia was estimated on whole blood by a modification of Billing of the method of Seligson and Seligson (1951).

ARTIFICIAL KIDNEY STUDIES A stoppered reservoir containing varying volumes of blood was used as a 'patient' and the blood was pumped through a standard coil as used for haemodialysis. The concentration of ammonia in the reservoir blood was estimated and checked at intervals. As the dialysis progressed the ammonia concentration in the blood leaving the coil was measured. Effluent blood was discarded. The flow rate was 100 ml. per minute.

ION-EXCHANGE RESIN STUDIES One hundred gram columns of resin, prepared in 25 ml. heparinized saline, were packed as shown in Fig. 1. The container was made of 1 in. internal diameter P.V.C. tubing and a nylon mesh.
Filter from a standard plastic intravenous infusion set was incorporated. The packed columns were autoclaved. Banked human blood of known ammonia concentration was passed directly by gravity through the columns at measured flow rates and the concentration of ammonia in the effluent estimated.

Three different resins were used: 1 Dowex 50, an American polystyrene divinyl benzene copolymer in the sodium form; 2 ZK. 226, a British carboxylic resin in the potassium form; and 3 ZK. 225, a British polystyrene resin in the sodium form. Different percentage divinyl benzene linkages of this resin were also studied. A mesh size of 14 to 52 was used throughout.

In three experiments healthy mongrel dogs (weights 17 to 22 kg.) were anaesthetized with nembutal, and heparin, 2 mg. 1 kg., was given intravenously. Blood was passed directly from the femoral artery through a column of ZK. 225 resin to the femoral vein. Flow was controlled by a screw clip on the venous line and was regulated by direct calibration so that the estimated blood volume passed through once in approximately one hour. Blood pressure was recorded throughout on a mercury manometer. Haematological and biochemical screening was carried out by routine clinical laboratory methods.

A similar experiment was carried out on a fourth dog while it was receiving a continuous intravenous infusion of ammonium acetate (1 ml. per minute of a 95 g. per litre solution containing 19,000 μg. of ammonia nitrogen per ml.).

RESULTS

ARTIFICIAL KIDNEY STUDY The results of six experiments carried out with quantities of blood varying from 1 to 5 litres are shown in Fig. 2. It may be seen that after up to 5 litres of blood containing over 8 μg. of ammonia nitrogen per millilitre had passed through the coil the amounts of ammonia in the effluent were still within the normal range.

ION-EXCHANGE RESIN STUDIES In Fig. 3 results of two studies *in vitro* showing the effect of Dowex 50 resin on ammonia and potassium levels in perfused blood are given. In Fig. 4 the effect of ZK.226

**TABLE**

RESULTS OF BIOCHEMICAL AND HAEMATOLOGICAL STUDIES

<table>
<thead>
<tr>
<th>Initial Sample</th>
<th>Final Sample</th>
<th>24 Hours Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>141</td>
<td>143</td>
</tr>
<tr>
<td>Potassium</td>
<td>3-2</td>
<td>3-6</td>
</tr>
<tr>
<td>Chloride</td>
<td>108</td>
<td>110</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Total proteins</td>
<td>6-1</td>
<td>5-7</td>
</tr>
<tr>
<td>Albumin</td>
<td>3-7</td>
<td>3-7</td>
</tr>
<tr>
<td>Globulin</td>
<td>2-4</td>
<td>2-0</td>
</tr>
<tr>
<td>Fibrinogen (mg. per 100 ml.)</td>
<td>280</td>
<td>260</td>
</tr>
<tr>
<td>pH</td>
<td>7-51</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>11-2</td>
<td>9-9</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>5-9</td>
<td>5-2</td>
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</tbody>
</table>

Haematology

<table>
<thead>
<tr>
<th>Test</th>
<th>Initial</th>
<th>Final</th>
<th>24 Hours Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemolysis</td>
<td>nil</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Haemoglobin (g. per 100 ml.)</td>
<td>15-6</td>
<td>15-0</td>
<td>15-6</td>
</tr>
<tr>
<td>Haemoglobin (%)</td>
<td>102</td>
<td>102</td>
<td>107</td>
</tr>
<tr>
<td>Erythrocytes (million per c.mm.)</td>
<td>5-31</td>
<td>6-04</td>
<td>6-20</td>
</tr>
<tr>
<td>Platelets (per c.mm.)</td>
<td>42,000</td>
<td>38,000</td>
<td>99,000</td>
</tr>
<tr>
<td>Leucocytes (per c.mm.)</td>
<td>6,800</td>
<td>2,500</td>
<td>225,000</td>
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<tr>
<td>Neutrophils (%)</td>
<td>81</td>
<td>67</td>
<td>96</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>13</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>5</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Nucleated red cells per 100 leucocytes</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>E.S.R. Wintrobe method (mm.)</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Prothrombin time (sec.)</td>
<td>10</td>
<td>9</td>
<td>15</td>
</tr>
</tbody>
</table>
FIG. 3. Capacity of Dowex 50 to remove ammonia from blood.

FIG. 4. Capacity of ZK. 226 to remove ammonia from blood.

FIG. 5. Capacity of ZK. 225 to remove ammonia from blood.
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**Figs. 6 and 7.** Effect of percentage linkage on ammonia uptake by resins.

In the potassium form is shown. Theoretically it was thought likely to be effective but its ammonia-removing capacity was found to be minimal. In Fig. 5 a similar study shows the effect of ZK.225 which is comparable to that obtained with Dowex 50. Further studies (Figs. 6 and 7) were undertaken to determine the effect of divinyl benzene linkage on ammonia uptake. It appeared that the higher the percentage divinyl benzene linkage of this resin the greater its affinity for ammonia.

Autoclaving was not found to alter the performance of ZK.225 in this respect.

**Fig. 8.** Chromatogram before and after.

The table shows the biochemical and haematological findings in a typical experiment from the group of three studies on normal dogs in which a 100 g. column of ZK.225 resin having a 20% divinyl benzene linkage was used. The animals survived. No significant abnormality was observed and electrophoretic patterns (Fig. 8) seemed unchanged. Resin columns were washed with sterile heparinized saline before autoclaving and pyrogenic effects were not observed in this small series. At
the flow rates used arterial blood pressures fell 5 to 10 mm. Hg. Chromium 51-tagged red cell survival studies on two further dogs gave similar pre- and post-perfusion red cell survival rates.

Fig. 9 shows the effect of a similar column on the blood ammonia concentration of a fourth dog receiving a continuous intravenous infusion of ammonium acetate. Note the rate of increase when the column is excluded from the circulation.

DISCUSSION

Kiley, Welch, Pender and Welch (1956), using a Kolff twin-coil artificial kidney on animals with the 'meat intoxication syndrome', obtained clear reductions in blood ammonia levels. Our laboratory data confirm that significant amounts of ammonia can be removed from blood by this apparatus or more simply by columns of ion-exchange resin.

In liver failure, however, ammonia is probably widely diffused throughout the body. Indeed it has been calculated that the intracellular concentration of ammonia may be several times higher than that of the blood (Lawrence, Schwartz, and Randall, 1958). If this is so, a sustained reduction of the blood level in ammonia intoxication may be difficult to achieve and any effect obtained could rapidly be reversed by back diffusion from cells and tissue fluid to blood, a phenomenon seen after dialysis of urea with the artificial kidney.

Schechter et al. (1958) using Dowex 50 resin have achieved some success in lowering blood ammonia levels of dogs with Eck fistulae. They report a clinical case in which minimal reduction was obtained in the blood ammonia level before technical difficulty required the perfusion to be stopped. The claim that the patient was improved thereafter receives only limited support from the data given which do not seem to exclude the possibility that a spontaneous remission was already taking place.

Both the above methods are open to criticism because they require heparinization of the blood which would be undesirable in a patient with gastrointestinal haemorrhage. This difficulty could, however, be overcome by regional heparinization within the apparatus as is done during dialyses with the artificial kidney.

Such early efforts to produce an 'artificial liver' may seem of interest. The method might be worthy of trial in the treatment of deeply comatose patients with high blood ammonia levels or in that phase before antibiotics can exert their full effect.

We gratefully acknowledge the help of Dr. Barbara H. Billing, of the Department of Medicine, Royal Free Hospital, London, to whom we are indebted for the method of estimating ammonia used in the study.

REFERENCES

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