Haemoperfusion Through Cation Exchange Columns in the Treatment of Ammonia Intoxication in Dogs[1] (35507)

J. S. JUGGI[2]
(Introduced by G. C. Ring)
Department of Physiology, Medical College, Patiala, Punjab, India

One of the major sources of ammonia in the body is the gastrointestinal tract. Eck (1) and his associates from Pavlov's laboratory devised an ingenious surgical approach to study the metabolism of this moiety of ammonia in the body. The classical Eck fistula (the portacaval shunt), ever since its inception, has been extensively used both experimentally, for the metabolic studies and clinically, for the relief of portal hypertension.

Ammona intoxication occurs in the Eck fistula dogs upon the oral administration of protein substances, blood, or nitrogenous compounds (2). In patients with surgically constructed portacaval shunts, ammonia toxicity has been found to occur from ingestion of high protein diet or from the oral administration of ammonium cation exchange resins (3). Spontaneous portal–systemic venous collatral channels develop in some patients with advanced liver disease and ammonia intoxication is the consequence of massive hemorrhage from gastroesophageal varices (4). In all these experimental or clinical situations, levels of blood ammonia in the systemic circulation are elevated and approach toxic concentrations affecting the brain and produce a characteristic neuropsychiatric syndrome of hepatic coma (5, 6). While efforts to reduce or eliminate the sources of ammonia within the gastrointestinal tract are an important aspect of long-term management of these conditions, measures must also be taken to lower the elevated ammonia levels of the systemic circulation as an immediate phase in the treatment of ammonia intoxication.

Schechter *et al.* (7) perfused hyperammonemic blood, both experimentally and clinically, through the columns containing the sodium form of a strong cation exchange resin. This resin, though effective in extracting ammonia from the systemic circulation, was found by them and by subsequent workers (8, 9) to sequester other cations from the influent blood resulting in the development of a dangerous hypokalemia, hypocalcemia, and hypomagnesemia. This necessitated the modification of the cation exchange resins for their safe use in the extracorporeal circuits. As a result of the detailed and systematic *in vitro* studies a mixture of four forms of the strong cation exchange resin, Amberlite IR-120, was developed (10, 11). This mixture with a total quantity of 750 mEq was found to be efficient in removing 90% of the ammonium ion from the hyperammonemic artificial serum without affecting any significant change in its other constituents. This report presents the laboratory experience with such a mixture in the treatment of ammonia intoxication of portacaval shunt dogs produced by a challenging dose of oral ammonium chloride.

Materials and Methods. Twelve healthy mongrel dogs, weighing 12 to 18 kg, were selected and side to side portacaval shunts were constructed under intravenous pentobarbital sodium (25 mg/kg). The dogs were allowed 9–12 days to recover from the operation before the specific experiments were performed.

The first experiment consisted of a comparative study of ammonia tolerance in six normal and six operated dogs lightly anesthetized with intravenous pentobarbital sodium (20 mg/kg). After taking the fasting (18 hr) blood sample in each dog, ammonium

[1] Supported by a grant from the Indian Council Medical Research, New Delhi.

[2] Present address: Department of Physiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

TABLE I. Blood Ammonia Levels (μg of NH_3–N%; mean ± SE).

	Fasting (min): 0	30	60	90	120
Normal dogs with oral NH_4Cl (6)	23 ±3	91 ±6	82 ±10	56 ±7	27 ±3
Shunt dogs with oral NH_4Cl (6)	53.5 ±5	167 ±11	161 ±14	129 ±10	96 ±6
Shunt dogs with oral NH_4Cl and with concomitant hemoperfusion (after 30 min) (6)	57 ±4	173[a] ±13	74[b] ±7	34[b] ±3	14[c] ±3

[a] Start of hemoperfusion through the resin mixture columns.
[b] During perfusion.
[c] End perfusion.

chloride (100 mg/kg as a 1% aqueous solution) was given by gastric tube. Samples of blood were withdrawn at intervals of 30 min for a total of 120 min and analyzed for ammonium.

In the second experiment, ammonium chloride induced hyperammonemia of the remaining six operated dogs was treated by hemoperfusion through the resin mixture columns. The perfusion column was of hemorepellent vinyl plastic, 45 cm long and 3.8 cm in diameter and fitted with polyurethane foam filters at the proximal and distal ends. The column was filled with 750 mEq of the resin mixture. The mixture was prepared from various forms of the strong cation exchange resin, Amberlite IR-120, BSS 22/60, with an exchange capacity of 3.77 mEq/g of air dried resin. The proportion of the various resin forms in the mixture, as worked out from the results of the *in vitro* studies (11) was (mEq): sodium form, 380.3; potassium form, 18.15; calcium form, 327.95; and magnesium form, 23.6. The filled resin columns, inlet and outlet sets, were sterilized in an autoclave before use. The resin column was clamped in an upright position and inlet tubing was connected with its proximal end and outlet tubing with its distal end. A modified Debaky pump was used in the inlet circuit for pushing blood through the column in an antigravity direction. Priming of the circuit was done by 250 ml of fresh heparinized blood obtained from the healthy donor dogs. The experimental dogs were lightly anesthetized and heparinization was achieved by injecting heparin (200 IU/kg) intravenously. The arterial cannula of the inlet tubing was inserted in the exposed femoral artery and the venous cannula of the outlet tubing was inserted in the exposed femoral vein of the dogs. After withdrawing the arterial blood sample (30 min subsequent to the oral administration of ammonium chloride), hemoperfusion was started and was continued for 90 min at a flow rate of 40–60 ml/min. Three blood samples, *viz.*, 60 min (during perfusion), 90 min (during perfusion) and 120 min (at the end of perfusion) after the oral administration of ammonium chloride were withdrawn from the arterial inlet circuit and were analyzed for ammonium. Preperfusion and end-perfusion samples of the blood were also collected for the estimation of sodium, potassium, calcium, and magnesium by the standard analytical techniques. Ammonium was determined by the microdiffusion method of Conway and Cooke (12) as adopted by Singh *et al.* (13).

Results. Table I shows that the fasting blood ammonia levels in the portacaval shunt dogs are considerably higher than in the normal dogs. Peak levels of blood ammonium were found to occur 30 min after the ammonium chloride administration both in the normal and in the shunt dogs. However, compared to the normal dogs, these levels in the shunt dogs did not return to the fasting values even after 120 min. This reflects the impaired intrahepatic clearance of ammonium load which is typically seen in these dogs (2). In the second series of experiments, oral ammonium chloride induced hyperammonemia of the portacaval shunt dogs was success-

TABLE II. Effect of the Hemoperfusion on the Cationic Constituents of Blood (mEq; mean values for six dogs).

	Sodium	Potassium	Calcium	Magnesium
Preperfusion	139.67	4.47	4.98	2.2
End-perfusion	138.43	4.64	5.4	2.05

fully corrected by hemoperfusion through the resin mixture columns. At the end of the perfusion, the mean preperfusion level of 173 μg of NH_3–N% was brought down to 14 μg of NH_3–N%, which is even lower than the mean fasting blood ammonia level in these dogs.

No significant changes were observed in the end-perfusion levels of plasma sodium, potassium, calcium, and magnesium (Table II). The hemoperfusion was uneventful. All the dogs recovered promptly and there were no adverse effects of the extracorporeal perfusion in the postperfusion period.

Discussion. Direct removal of excessive ammonium from the systemic circulation has been attempted in various ways. Extracorporeal homologous and heterologous liver perfusions (14) and cross circulations (15) have been utilized with some success. These procedures are complicated with variable and unpredicatable effectiveness. Hemodialysis through the Kolff-type artificial kidney has been found to be successful in lowering elevated blood ammonia levels (16). However, the technique is time consuming, the equipment is elaborate and expensive and requires several trained individuals for its performance. A simple and inexpensive approach has been the hemoperfusion through the cation exchange resins. One important and serious side-effect of cation exchange perfusions has been the cationic sequestering effect of the sodium form of the resin (7–9). This resin exchanges sodium not only for ammonium but also for the other cations in the perfused blood. Many workers (7–9, 17, 18) have given, intravenously, salts of potassium, calcium, and magnesium during and following each perfusion in an attempt to replace the loss of these cations in the blood. This, in addition to increase in sodium, would increase the total electrolyte concentration of blood which may not be desirable. The ideal arrangement would be to lower the elevated blood ammonia levels without affecting any significant change in the other cationic constituents of the blood. This has been achieved by the use of the mixture of four forms of the strong cation exchange resin in the perfusion columns instead of the sodium form of the resin. The resin mixture has been shown to be effective in the correction of oral ammonium chloride-induced hyperammonemia of the portacaval shunt dogs (Table I). Other cationic constituents of the blood were not significantly altered (Table II).

Sandler *et al.* (19) made a detailed study of the effects of the extracorporeal perfusion of blood through the ion exchange columns on the formed elements of blood and on blood clotting. They could find no serious alterations in the blood composition and all their animals recovered within 24–72 hr of the perfusion. The animals of the present study were carefully watched and no undesirable effects of the perfusion were noted in the postperfusion period. These data suggest that clinical experience, employing hemoperfusion through the cation exchange resin mixture column, is warranted.

Summary. A mixture of the sodium, potassium, calcium, and magnesium forms of the strong cation exchange resin, Amberlite IR-120, has been used in perfusion columns instead of the sodium form of the resin alone. This resin mixture has been shown to be efficient in correcting ammonium chloride-induced hyperammonemia of the portacaval shunt dogs. There have been no adverse effects of the hemoperfusion; and other cationic constituents of the blood were not significantly affected. Clinical therapeutic experience with cation exchange perfusions has been suggested.

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1. Eck, N. V. K. (cited by Child, C. G.), Surg. Gynecol. Obstet. **96**, 375 (1953).

2. Bollman, J. L., Physiol. Rev. **41**, 607 (1961).

3. McDermott, W. V., Jr., and Adams, R. D., J. Clin. Invest. **1**, 1 (1954).

4. Kiley, J. E., and Welch, C. S., N.Y. State J. Med. **60**, 834 (1960).

5. McDermott, W. V., Jr., Surg. Gynecol. Obstet. **109**, 139 (1959).

6. Read, A. E., Sherlock, S., Laidlaw, J., and Walker, J. G., Quart. J. Med. **36**, 135 (1967).

7. Schechter, D. C., Nealon, T. F., Jr., and Gibbon, J. H., Jr., Surgery **44**, 892 (1958).

8. McCann, W. J., N.Y. State J. Med. **61**, 879 (1961).

9. Nealon, T. F., and Ching, N. P. H., Biochem. Clin. **3**, 263 (1964).

10. Chaudhry, N. C., Juggi, J. S., and Singh, I. D., Lancet **1**, 1262 (1962).

11. Juggi, J. S., PhD thesis, Punjabi University, Patiala, Punjab, India (1967).

12. Conway, E. J., and Cooke, R., Biochem. J. **33**, 457 (1939).

13. Singh, I. D., Barclay, J. A., and Cooke, W. T., Lancet **1**, 1004 (1954).

14. Eiseman, B., Proc. Symp. Colston Res. Soc. **19**, 279 (1967).

15. Burnell, J. M., Dawnorn, J. K., Epstein, R. B., Gutman, R. A., and Leinbach, G. E., N. Engl. J. Med. **276**, 935 (1967).

16. Kiley, J. E., Pender, J. C., and Welch, H. F., N. Engl. J. Med. **259**, 1156 (1958).

17. Moore, E. J., Lehman, T. H., and Hodges, C. V., Surg. Gynecol. Obstet. **112**, 67 (1961).

18. Ching, N. P., Nealon, T. F., Jr., and Gibbon, J. H., Jr., J. Amer. Med. Ass. **183**, 350 (1963).

19. Sandler, J. L., Cohn, H. E., Clark, J. E., Weiss, A. J., and Nealon, T. F., Jr., Trans. Amer. Soc. Artif. Intern. Organs **7**, 3 (1961).

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