Supine heart rate versus supine systolic blood pressure: change from placebo to nifedipine (60 mg/day).

In our previous report⁴ we showed that both nifedipine and propranolol were effective in managing angina of effort but that the combination was significantly better than either drug alone. Though it has been suggested that a reduction in blood pressure in patients with coronary artery disease may precipitate angina or ischaemia by reducing myocardial blood flow, the phase which produced the greatest fall in blood pressure also produced the greatest reduction in angina. Hypertension and ischaemic heart disease often co-exist and hypertension predisposes to and possibly aggravates atherosclerotic vascular disease.¹² A regimen that lowers blood pressure and effectively improves ischaemia is thus advantageous. The combination of propranolol and nifedipine satisfies this need.

The hypotensive potential of beta-blocking agents was first noted during a clinical trial of propranolol in patients with angina pectoris.¹³ The favourable haemodynamic responses to

calcium antagonists will probably also prove valuable in managing patients with hypertension.

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Acute haemolysis due to concentrated dialysis fluid

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Abstract

Fatal acute haemolysis occurred in a 65-year-old man undergoing regular home haemodialysis for terminal renal failure. Circumstantial evidence indicating that the haemolysis resulted from exposure to concentrated dialysis solution was supported by in-vitro studies. Frank haemolysis in blood samples occurred at a dilution of >1/2 of dialysis fluid. Osmotic fragility tests of surviving red blood cells showed 47% haemolysis at a dilution of 1/2 and >90% haemolysis at a dilution of 1/1. Urgent design modifications to the proportionating machine are being undertaken to prevent such an accident recurring.

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Introduction

Acute haemolysis is a rare complication of haemodialysis. There are a wide variety of medical and drug-related causes of haemolysis which may occur incidentally in patients undergoing maintenance haemodialysis. Several technical causes may also complicate haemodialysis and result in acute haemolysis. These include dialysis against hypotonic dialysis fluid, contamination of dialysis fluid by toxic concentrations of copper, zinc, chloramine, nitrate, and formaldehyde¹ and haemolysis due to over-heated dialysate.² We report the case of a patient who developed acute haemolysis as a result of exposure to very concentrated dialysis fluid.

Case report

A 65-year-old man had started regular twice weekly haemodialysis in July 1977 because of terminal renal failure due to rapidly progressive glomerulonephritis. He started on home dialysis in May 1978 and dialysed for 10 hours twice weekly using a Meltec Multipoint dialyser (1.05 m²) and a single pass Dylade DII proportionating machine. On the day of admission to hospital in May 1981

he had started dialysis at home as usual. During the first two hours dialysis was uneventful but a blood-to-dialysate leak developed and he changed to a disposable Gambro dialyser. During the third hour of dialysis the conductivity monitor intermittently registered a high (+10) reading and his attempts to correct this were unsuccessful. He was then instructed to stop the dialysis but while doing so became unconscious and had several generalised fits. He was admitted to hospital shortly afterwards deeply unconscious and having repeated fits. His blood pressure was 180/120 mm Hg and he was hyperventilating. The concentration of plasma sodium was 177 mmol (mEq)/l, potassium 4.9 mmol(mEq)/l, and blood urea 23 mmol/l (138.6 mg/100 ml). The plasma was grossly haemolysed and the haemoglobin concentration was 5.6 g/dl having previously been 9 g/dl. He was given 10 mg diazepam intravenously and started on haemodialysis immediately. After dialysis for six hours on a Major Gambro dialyser, the plasma sodium concentration had fallen to 143 mmol(mEq)/l. A dialysis fluid sample from the proportionating machine in his home was analysed and the sodium concentration was found to be 1050 mmol(mEq)/l with a potassium concentration of 28.8 mmol(mEq)/l. His plasma continued to show obvious although decreasing haemolysis over the next three days. He remained unconscious for the next two days. There was a pronounced rise in the serum alanine transferase activity to 740 IU/l and in the serum inorganic phosphate to 3.7 mmol/l (11.46 mg/100 ml), both returning to normal values in about a week. He slowly improved and two weeks after the accident was conscious, reasonably alert, and could carry on a conversation. He was unable to walk, however. Regular dialysis was continued but over the next month his condition deteriorated. He became completely apathetic with very little spontaneous movement. Serial CT brain scans showed increasing cerebral atrophy. Eventually he was unable to recognise his family, and after full discussion we decided to stop dialysis. He died about two and a half months after the accident. At necropsy there was evidence of acute pancreatitis as well as end-stage kidneys and cerebral atrophy.

Subsequent investigation of the Dylade DII proportionating machine showed that the water supply to the Duplex pump was restricted, which could have resulted in the production of dialysis fluid with an abnormally high conductivity. The machine's conductivity alarm system functioned normally. When triggered the effluent pump stopped and the machine went into bypass. Seepage through the 1 psi (0.07 kg/cm²) check valve and non-occlusive effluent pump, however, allowed a low flow of dialysis solution of incorrect composition to pass through the dialyser. Urgent design modifications to prevent a recurrence of this situation are being undertaken by the manufacturers.

Results of incubating 1 ml samples of the patient's blood with 1 ml aliquots of dialysis fluid at different dilutions

Dialysis fluid dilutions	Calculated sodium concentration in dialysis fluid (mmol/l)	Frank haemolysis	Osmotic fragility of surviving red blood cells (% NaCl)
1/0	4655	+	90
1/1	2327	+	96
1/2	1551	+	47
1/4	931		1
1/8	517		1
1/12	358		0.5
1/16	273		1
1/24	186		1
1/32	141		0
1/34	133		0

IN-VITRO STUDIES

The circumstantial evidence strongly suggested that this patient had been exposed to a concentrated dialysis solution, which was probably responsible for the acute haemolysis. A blood sample was obtained from the patient about two weeks after haemolysis had disappeared and various in-vitro studies were carried out. Serial dilutions of Renalyte (35 × concentrated dialysis fluid) were made with distilled water. Aliquots of 1 ml of each dilution were then incubated at 37°C for 30 minutes with 1 ml of the patient's blood and centrifuged at 5000 rev/min for 20 minutes. The supernatant was examined for frank haemolysis and then removed. The remaining red blood cells were resuspended in 1 ml normal saline and an osmotic fragility test carried out on the resuspended red blood cells by spectrophotometry. The

results are shown in the table. Frank haemolysis was noted in blood samples exposed to dialysis fluid at a concentration of $\geq 1/2$. Furthermore, the surviving red blood cells exposed to these high concentrations of dialysis fluid showed a pronounced increase in osmotic fragility. In the normal state 0%-5% of red blood cells are haemolysed by 0.5% saline. In this study surviving red cells which had been exposed to a 1/2 dilution of Renalyte showed 47% haemolysis and those exposed to a 1/1 dilution $>90\%$ haemolysis. The precise mechanism of the haemolysis is not clear and, apart from osmotic forces, some of the other constituents of the Renalyte may have contributed to the haemolysis. The composition of undiluted Renalyte is as follows: sodium 4655 mmol(mEq)/l, potassium 52.5 mmol (mEq)/l, calcium 52.5 mmol/l, magnesium 17.5 mmol/l, acetate 1365 mmol/l, chloride 3482.5 mmol/l, and dextrose 70 g/l.

Comment

To our knowledge this is the first instance of massive haemolysis occurring as a result of exposure to a concentrated dialysis fluid. The in-vitro studies indicated that red blood cells were severely damaged by exposure to such solutions. Haemolysis is not mentioned as a feature of hypernatraemia in the review by Friedler *et al.*³ Furthermore, it did not occur in six patients⁴ who were accidentally exposed to concentrated dialysis fluid, although the sodium concentration in the dialysis fluid was only 215 mmol/l and the highest serum sodium concentration was 165 mmol(mEq)/l. In our case study the sodium concentration of the dialysis fluid was 1050 mmol/l, and the patient's plasma sodium on admission was 177 mmol/l. His serum potassium concentration was normal, which is surprising since the samples were haemolysed and the potassium concentration in the dialysis fluid was 28.8 mmol/l. The finding of pancreatitis at necropsy is interesting and may have been related to the acute haemolysis. Walker *et al.*⁵ have reported two patients being treated with dialysis who developed acute intravascular haemolysis due to exposure to hypotonic dialysis fluid, and in both pancreatitis also occurred.

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No piece of indolence hurts the health more than the modern custom of lying a bed too long in a morning. This is the general practice in great towns. The inhabitants of cities seldom rise before eight or nine o'clock; but the morning is undoubtedly the best time for exercise, while the stomach is empty, and the body refreshed with sleep. Besides, the morning air braces and strengthens the nerves, and, in some measure, answers the purpose of a cold bath. Let any one who has been accustomed to lie a-bed till eight or nine o'clock, rise by six or seven, spend a couple of hours in walking, riding, or any active diversion without doors, and he will find his spirits cheerful and serene through the day, his appetite keen, and his body braced and strengthened. Custom soon renders early rising agreeable, and nothing contributes more to the preservation of health.

(Buchan's *Domestic Medicine*, 1786)