Mannitol and frusemide in the treatment of diuretic resistant oedema in nephrotic syndrome

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Abstract

Three children (two girls aged 7 and 9 years, and one boy aged 4 years) with diuretic resistant oedema in steroid resistant nephrotic syndrome were treated with a combination of intravenous mannitol and frusemide. All three responded with loss of oedema of 10% to 30% of body weight over one week. There were no complications of hypertension or hypovolaemia. Mannitol-frusemide combination is a safe, inexpensive, and effective treatment for diuretic resistant oedema. Its use in other conditions and in developing countries (where the availability and purity of 20% albumin is limited) needs to be explored.

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In childhood nephrotic syndrome the most common complications are those secondary to hypovolaemia and oedema. Hypovolaemia is of major importance and warrants treatment with intravenous albumin to correct circulating volume.¹ Oedema, on the other hand, is frequently unsightly but rarely a clinical problem. In patients who are slow to respond to steroids or steroid unresponsive, gross oedema can be complicated by infection and skin breakdown. Standard treatment has been loop diuretics with aldosterone antagonists such as spironolactone. If these fail, then intravenous 20% albumin with frusemide is usually used.² This treatment is not without risks, as in many nephrotic patients the intravascular volume is normal or increased rather than low,³ so intravenous albumin can precipitate intravascular fluid overload, hypertension, and cardiac failure.⁴

Patients resistant to this treatment are often given powerful thiazide diuretics such as metolazone. In extreme cases, haemofiltration has been recommended.² We report our experience using a combination of mannitol and frusemide in grossly oedematous patients with nephrotic syndrome who had normal glomerular filtration rates (GFR) but were resistant to standard treatment.

Case 1

A 4 year old Asian boy presented with steroid resistant nephrotic syndrome. On admission he was grossly oedematous with massive ascites and enormous scrotal enlargement with skin breakdown and oozing. His total urine output was 200 ml per day despite diuretics. Renal

biopsy showed a picture of focal segmental glomerulosclerosis. Renal function was normal (creatinine 38 µmol/l). The child's nutritional state was poor, he refused food, and we had to provide at least 600 ml of nasogastric feed to ensure reasonable calorie and protein intake. Standard infusions of 20% albumin (5 ml/kg/dose) with frusemide (2 mg/kg/dose) led to an additional diuresis of only 200 ml. An infusion of 20% mannitol (5 ml/kg over one hour) also led to a diuresis of 200 ml. An identical mannitol infusion with a concurrent dose of 2 mg/kg frusemide led to a diuresis of 700 ml over several hours. He was treated with daily mannitol infusions with frusemide, and over one week lost all his ascites and oedema, with a weight reduction from 18 kg to 15 kg while being given adequate nutrition. There were no adverse events related to the infusions.

Case 2

A 9 year old girl presented with a short history of oedema. She had heavy proteinuria and low serum albumin but a normal creatinine. She was treated at her local hospital with steroids, intravenous albumin, diuretics, and fluid restriction. After four weeks her proteinuria persisted and despite diuretics she weighed 38.5 kg having been admitted at a weight of 30 kg. She was given daily infusions of 20% mannitol (5 ml/kg over one hour) with frusemide (2 mg/kg/dose). She had brisk diuresis, her weight falling to 28 kg over eight days. Renal biopsy showed mesangiocapillary glomerulonephritis type 2 (dense deposit disease).

Case 3

A 7 year old girl with nephrotic syndrome was referred for renal biopsy because of persistent proteinuria after four weeks of oral prednisolone. On admission she was grossly oedematous despite diuretic and intravenous albumin treatment. She had heavy proteinuria but normal renal function (creatinine 60 µmol/l). She was treated with mannitol and frusemide and had brisk diuresis. Over five days she lost 2.4 kg, reaching a weight of 20.8 kg. Renal biopsy showed focal segmental glomerulosclerosis.

Discussion

The pharmacology of mannitol has recently been extensively reviewed.⁵ Mannitol has several potential advantages in patients with nephrotic syndrome. Experimentally it increases GFR in patients with poor renal perfusion by increasing renal blood flow. The diuretic activity of mannitol acts throughout the nephron. Its effect on proximal tubular salt

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and water reabsorption allows more sodium to be delivered into the loop of Henlé where frusemide prevents sodium and water uptake in the thick ascending limb and mannitol does the same in the thin ascending limb. Moreover, the dilution of the tubular fluid through the osmotic effects of mannitol in the proximal tubule will lower the intraluminal albumin concentration and therefore reduce the binding of frusemide to albumin, enhancing its activity.

The response to intravenous 20% albumin in this situation is unpredictable and the use of albumin and frusemide to promote a diuresis leads to a lesser urine output. Although hypovolaemia with tachycardia, poor peripheral perfusion, and cold extremities can be recognised clinically, recognising which patients will develop volume overload (11%) and hypertension (46%) with albumin and frusemide is more difficult.⁴ In addition, it is expensive and carries the risks of transmission of infectious diseases. Diuretic combinations using frusemide and metolazone are associated with frequent electrolytic disturbances, prolonged diuresis after cessation of treatment that can lead to hypovolaemia, and are not effective in nephrotic patients with low serum albumin concentrations.⁶

In this small series there were no episodes of hypertension, as the transit time was short and the diuresis prompt. Moreover, mannitol is a safe and inexpensive treatment that allows for

use more than once daily if required. It would be inappropriate to use the mannitol-frusemide combination in a patient with either clinical evidence of hypovolaemia or a significantly reduced GFR. However, in the normovolaemic or hypervolaemic patient with nephrotic syndrome and a normal GFR it is a safe and inexpensive way of producing rapid diuresis, much greater than that attained with other agents. We believe this combination of diuretics will prove invaluable in the management of diuretic resistant oedema without hypovolaemia in nephrotic syndrome and perhaps other conditions with similar clinical problems. It will be of great value in developing countries where the availability and purity of 20% albumin is limited.

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