ELSEVIER

Netherlands Journal of Medicine 50 (1997) 21–24

The Netherlands
JOURNAL OF
MEDICINE

Brief report

Mannitol-induced acute renal failure

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Received 31 May 1996; revised 21 August 1996; accepted 9 September 1996

Abstract

Mannitol is widely used because of its osmotic diuretic action and its presumed antioxidant properties. In pre-existent renal dysfunction, however, mannitol may accumulate leading to potentially deleterious effects. We describe a 71-year-old woman with moderate chronic renal failure due to diabetic nephropathy who developed acute anuric renal failure after mannitol administration for post-traumatic reflex sympathetic dystrophy. After haemodialysis symptoms of acute renal failure rapidly disappeared with recovery of pre-existent renal function. Daily measurement of the osmolal gap as a simple and accurate way of monitoring patients receiving mannitol infusion is emphasized. A rapid increase in the osmolar gap should prompt adjustment of the dose or even discontinuation of mannitol, especially in the case of pre-existent risk factors.

Keywords: Mannitol; Acute renal failure; Risk factors; Osmolal gap; Haemodialysis

1. Introduction

Mannitol in clinical experience is especially well-known because of its ability to create osmotic diuresis. In this way it is frequently used to reduce intracranial [1] or intraocular pressure and to prevent the occurrence of nephrotoxicity due to chemotherapy [2] or radiocontrast [3]. In addition, the use of mannitol in acute renal failure (ARF) may convert an oliguric state to a non-oliguric [1]. Today, mannitol is also increasingly used for other indications, especially because of its assumed antioxidant properties [4–6].

As mannitol is mainly excreted by the kidney, in pre-existent renal dysfunction it may accumulate in the extracellular fluid space, leading to deleterious effects [7].

We report here a rare case of a patient who developed acute anuric renal failure following intravenous mannitol therapy for post-traumatic reflex sympathetic dystrophy (RSD) [4]. To our knowledge, this is the first report in the literature in which mannitol therapy for RSD was complicated by anuric ARF.

2. Case report

A 71-year-old woman was admitted to the surgical department of our hospital because of progressive

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PII S0300-2977(96)00060-5

pain in the right foot shortly after distortion of the right ankle. Physical examination showed a swollen, slightly discoloured foot with loss of function and abnormal sensitivity on palpation. A diagnosis of reflex sympathetic dystrophy syndrome (RSDS) was suspected for which intravenous mannitol therapy was suggested [4]. An extensive medical history revealed agenesis of the left kidney, type II diabetes mellitus for 4 years and moderate chronic renal failure which had remained stable in the last year (serum creatinine 200 μmol/l). She was also known to have had myocardial infarction 4 years prior to admission and mild congestive heart failure for which she received enalapril and bumetanide for 14 months. Medication on admission included insulin, acenocoumarol, digoxin, enalapril and bumetanide. No absolute contraindications with regard to mannitol therapy were found in this patient: blood pressure 135/60 mmHg; no signs of peripheral oedema or dehydration; normal central venous pressure (CVP) and normal diuresis (1500 ml/day). Relevant laboratory data included: creatinine 213 μmol/l; urea 12.4 mmol/l; potassium 4.8 mmol/l; sodium 141 mmol/l; glucose 5.3 mmol/l. Serum osmolality amounted to 296 mosm/kg H_2O. Therapy was started with a daily intravenous dose of 1000 ml of a 10% mannitol solution (i.e., 100 g) over 12 h in combination with a 1000 ml glucose 2.5%/NaCl 0.45% solution over 24 h. On the second day, urine production decreased from 1600 to only 500 ml/24 h finally resulting in an anuric state 12 h thereafter (Fig. 1). At that time, a cumulative dose of 250 g mannitol over a 60-h period was given (Fig. 1). Renal sonography showed a normal-sized right kidney without postrenal obstruction. No response occurred on intravenously administered diuretics. Subsequently, the patient developed angina pectoris and complaints of progressive nausea and dyspnoea. Physical examination revealed elevated blood pressure (180/95 mmHg), elevated CVP (R + 2), ankle oedema and bibasilar lung crackles. A chest X-ray showed cardiomegaly and pulmonary vascular congestion. Relevant laboratory data now included: serum creatinine 559 μmol/l, urea 25.9 mmol/l, potassium 5.7 mmol/l, sodium 121 mmol/l, glucose 3.5 mmol/l. Measured serum osmolality was 305 mosm/kg H_2O and calculated serum osmolality 272 mosm/kg H_2O, resulting in an osmolal gap of 33 mosm/kg H_2O. The patient was treated with nitroglycerine intravenously and underwent two sessions of combined haemodialysis/ultrafiltration for 4 h each (Fig. 1). This resulted in rapid recovery of the patient with return of diuresis and improvement of renal function (serum creatinine 200 μmol/l; urea 10.2 mmol/l), serum electrolytes (sodium 138 mmol/l) and measured osmolality (297 mosm/kg H_2O).

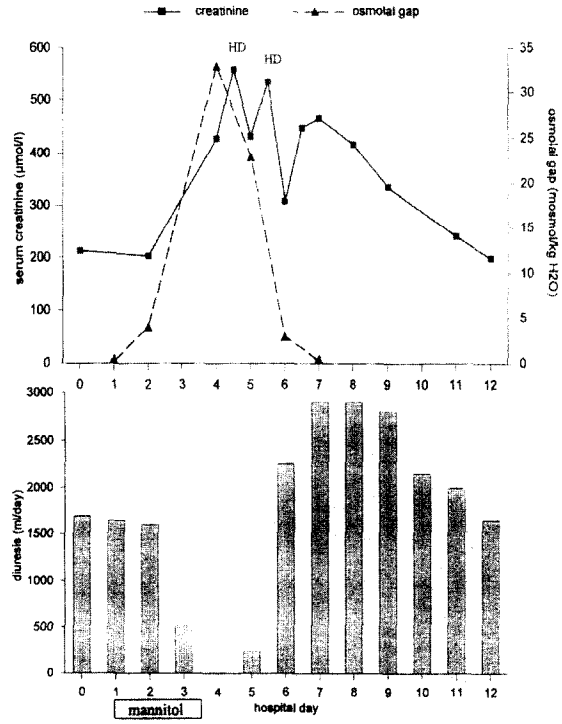

Fig. 1. Clinical course of our patient showing changes in creatinine, osmolal gap and diuresis plotted against time and mannitol administration. HD = haemodialysis.

3. Discussion

Mannitol is a metabolically inert sugar which is widely used to create osmotic diuresis in the case of cerebrovascular accident, glaucoma or threatening renal damage [1]. In the Netherlands mannitol is also increasingly used as a hydroxyl radical scavenger in the treatment of reflex sympathetic dystrophy (RSD) [4]. Of note, however, no clinical data have yet proven its therapeutic effect in this disorder.

In normal renal function 90% of intravenously administered mannitol is excreted within 24 h [8]. However, when infusion of mannitol exceeds maximum renal excretion accumulation in the extracellular space occurs [9]. This may result in intoxication characterized by intracellular dehydration and extracellular volume overload. As illustrated in the present case, the clinical picture consisted of cardiac failure with pulmonary and peripheral oedema, mental confusion and lethargy, nausea and vomiting. Blood investigations revealed (pseudo)hyponatraemia and hyperosmolality with a high osmolal gap.

Development of ARF may be the first manifestation of mannitol intoxication [7,10]. In addition, data suggest that this rapid decline in renal function also acts as a luxating event necessary for mannitol intoxication to occur [7,10–13]. In this, recognized risk factors are diabetes mellitus, use of diuretics and angiotensin-converting enzyme inhibitors (ACE-I), hypertension, intravenously administered radiocontrast, surgery shortly prior to mannitol administration and postrenal obstruction [7,10,13]. Indeed, in the present case volume depletion (chronic use of diuretics, relatively low blood pressure) and disturbed renal autoregulation (diabetes mellitus, use of ACE-I) may have led to an already compromised renal perfusion pressure on admission, thereby increasing the risk of mannitol intoxication. Several mechanisms of mannitol-induced ARF have been postulated (Table 1). Due to mannitol, intraluminal sodium concentration may increase at the level of the macula densa, resulting in intense tubuloglomerular feedback with afferent arteriolar vasoconstriction, thereby reducing glomerular filtration rate (GFR) [10]. The occurrence of ARF after administration of unfilterable large-molecular-weight dextrans [12] was explained by an elevation of plasma oncotic pressure resulting in reduction of the net glomerular pressure and so in a decrease of GFR. With mannitol, the same principle has been postulated [7,12]. Of note, however, the latter can probably occur only in the case of an enormous dose, for mannitol is well filtered. Another mechanism may be vacuolization and swelling of renal tubular cells, resulting in narrowing of the proximal tubules after administration of mannitol ('osmotic nephrosis') [7,11]. Finally, mannitol may have a direct haemodynamic effect on the renal vasculature. High concentrations may cause afferent arteriolar vasoconstriction with subsequent reduced GFR [13]. Rate and dose of mannitol infusion seem to play an important role. When infusion exceeds the maximal renal excretion rate, accumulation occurs, leading to vasoconstriction and thereby ARF with subsequent intoxication [7].

The most reliable method of monitoring mannitol therapy is the osmolal gap (mosm/kg H_2O) which consists of the difference between measured and calculated ($= 2 \times$ Na-serum + urea-serum + glucose [mmol/l]) osmolality. To reduce the risk of mannitol intoxication, a maximal osmolal gap of 55 mosm/kg H_2O, corresponding to a maintenance mannitol level of less than 1000 mg/dl (molecular weight of mannitol 180 Da), has been advocated [7]. As in the present case, however, intoxication has been reported to occur with maximal osmolal gaps as low as 22, 40 and 45 mOsm/kg H_2O, respectively [7,14,15]. Of importance, renal function impairing factors were present in all these cases. This suggests a lower osmolal gap threshold for ARF and mannitol intoxication to occur in these patients. Indeed, in patients with pre-existent normal renal function and without evidence of renal function impairing factors, osmolal gaps were reported to be as high as 85, 101 and 106 mOsmol/kg H_2O, respectively [16,9,7].

Full recovery from mannitol intoxication may occur after simple discontinuation of intravenous administration of mannitol. Successful treatment has also been reported with low-dose dopamine [17]. Haemodialysis, however, is the most accurate ther-

Table 1
Possible mechanisms of mannitol-induced acute renal failure

Mechanism	Result
Increased intraluminal sodium concentration at the level of the macula densa	Intense tubuloglomerular feedback
Elevation of plasma oncotic pressure	Reduced *net* glomerular pressure
Renal tubular cell swelling	Narrowing proximal tubules
Afferent arteriolar vasoconstriction	Reduced *net* glomerular pressure

apy in restoring normal osmolality and should be the treatment of choice in the case of serious clinical deterioration. Although peritoneal dialysis is also capable of clearing mannitol, the half-life of mannitol increases 3.5 times compared to haemodialysis [18]. As illustrated in the present case, only occasionally are more than 2 sessions of haemodialysis required. The rapid recovery of GFR after haemodialysis rules out structural damage of the glomerular basement membrane by mannitol as a cause of the ARF.

The case described herein typically represents a patient at high risk for developing ARF and mannitol intoxication. Indeed, pre-existent moderate renal failure, use of diuretics and compromised cardiac function are recognized risk factors for this event to occur. Although the dose of mannitol and resulting osmolal gap in our patient were low compared to the literature and advised regimens [7], severe mannitol intoxication still developed.

Nowadays, mannitol seems increasingly to be recognized as adjuvant therapy, especially because of its assumed antioxidant features [4]. In spite of the potentially beneficial effects in a great variety of diseases [4–6], the important side-effects of mannitol as illustrated in the present case should be kept in mind. Therefore, caution and careful monitoring of all patients receiving mannitol is warranted. This should include checking the volume status, pre-existent conditions or medication potentially impairing renal function and measurement of serum sodium, creatinine and urea prior to and during mannitol administration. In addition, daily measurement of the osmolal gap should be regarded as a simple and accurate way to monitor serum mannitol concentrations [7]. Indeed, a rapid increase in the osmolal gap should prompt adjustment of the dose or even discontinuation of mannitol. This may be particularly true in the case of pre-existent risk factors.

References

[1] Warren SE, Blantz RC. Mannitol. Arch Intern Med 1981;141:493–497.

[2] Hayes DM, Cvithovic E, Golbey RB, Scheiner F, Helson L, Krakoff IH. High dose *cis*-platinum diammine dichloride: amelioration of renal toxicity by mannitol diuresis. Cancer 1977;39:1372–1381.

[3] Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994;331:1416–1420.

[4] Goris RJA. Treatment of reflex sympathetic dystrophy with hydroxyl radical scavengers. Unfallchirurg 1985;88:330–332.

[5] Laskowski H, Minczykowski A, Wysocki H. Mortality and clinical course of patients with acute myocardial infarction treated with streptokinase and antioxidants: mannitol and ascorbic acid. Int J Cardiol 1995;48:235–237.

[6] Furukawa VT, Katayama Y, Suda H, Itoh T. Spinal cord protection: development of a paraplegia-preventive solution. Ann Thor Surg 1994;58:116–120.

[7] Dorman HR, Sondheimer JH, Cadnapaphornchai P. Mannitol-induced acute renal failure. Medicine 1990;69:153–159.

[8] Dominguez R, Corcorann AC, Page IH. Mannitol: kinetics of distribution, excretion and utilization in human beings. J Lab Clin Med 1947;32:1192–1202.

[9] Morgan AG, Bennet JM, Polak A. Mannitol retention during diuretic treatment of barbiturate and salicylate overdosage. Q J Med 1968;37:589–606.

[10] Goldwasser P, Fotino S. Acute renal failure following massive mannitol infusion. Arch Intern Med 1984;144:2214–2216.

[11] Stuart FP, Torres E, Fletcher R, Crocker D, Moore FD. Effects of single, repeated and mannitol infusion in the dog: structural and functional changes in kidney and brain. Ann Surg 1970;172:190–204.

[12] Moran M, Kapsner C. Acute renal failure associated with elevated plasma oncotic pressure. N Engl J Med 1987;317:150–153.

[13] Lilien OM. The paradoxical reaction of renal vasculature to mannitol. Invest Urol 1973;10:346–353.

[14] Aviram A, Pfau A, Czaczkes JW, Ullman TD. Hyperosmolality with hyponatremia, caused by inappropriate administration of mannitol. Am J Med 1967;42:648–50.

[15] Rello J, Triginer C, Sanchez JM, Net A. Acute renal failure following massive mannitol infusion. Nephron 1989;15:377–378.

[16] Lin SL, Hung KY, Lin Wu FL, Wei SC, Wu KD. Mannitol-induced acute renal failure. Nephrol Dial Transplant 1995;10:120–122.

[17] Docci D, Berardi E, Baldrati L. Mannitol-induced acute renal failure. Nephron 1994;68:141.

[18] Borges HF, Hocks J, Kjellstrand CM. Mannitol intoxication in patients with renal failure. Arch Intern Med 1982;142:63–66.