Mannitol-Induced Acute Renal Failure

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Abstract. The osmotic diuretic mannitol may be used in diverse clinical settings, such as providing “renal protection” in patients at risk for acute renal failure, decreasing intracranial pressure in patients with intracranial trauma, and preventing the dialysis-disequilibrium syndrome. Mannitol is commonly used after cardiac catheterization, cardiovascular surgery, and exposure to intravenous contrast dyes. This study presents a case in which a long-term renal transplant recipient receiving cyclosporine therapy concomitantly developed acute renal failure after the administration of high-dose mannitol in an attempt to induce an osmotic diuresis. The diagnosis of “osmotic nephrosis” was confirmed by renal biopsy, and the condition was reversed by cessation of the agent. Studies in experimental animals indicate that cyclosporin A can potentiate the tubular toxicity of mannitol, but such an association has not been verified in humans. Numerous studies confirm the nephrotoxic potential of high-dose mannitol, especially in patients with renal insufficiency. The clinical utility of the osmolar gap in preventing mannitol nephrotoxicity is emphasized. (J Am Soc Nephrol 8: 1028–1033, 1997)

Case Report
A white man 68 yr of age with a recent past history of cytomegaloviral pneumonia was admitted to the Cardiology Service at St. Luke’s Episcopal Hospital with gradually worsening dyspnea. The patient had received a cadaveric renal transplant in 1988 for end-stage renal disease secondary to autosomal dominant polycystic kidney disease. He was continuing a regimen of cyclosporine and prednisone. The history included a prior myocardial infarction, coronary angioplasty, and coronary artery bypass surgery in 1992, 2 yr before the present admission. Congestive heart failure, which developed after the coronary artery bypass surgery, had been controlled previously with oral medications. However, on physical examination the patient exhibited signs consistent with congestive heart failure, including elevated jugular venous pressure, a third heart sound, and a palpable and tender liver. Peripheral edema was not present. A chest x-ray revealed pulmonary vascular congestion. An electrocardiogram taken at admission revealed no acute changes. Medications on admission included 0.25 mg of digoxin, 100 mg of amiodarone, 40 mg of furosemide, 325 mg of aspirin, 5 mg of prednisone, and 325 mg of cyclosporine (all daily). Intravenous furosemide was initiated immediately. Subsequently, intravenous high-dose mannitol was initiated for the treatment of refractory heart failure, which did not respond to the loop diuretic. The blood urea nitrogen (BUN) concentration was 58 mg/dl (21 mmol/L), and serum creatinine concentration was 3.4 mg/dl (300 μmol/L). The patient’s previous medical records revealed a baseline serum creatinine concentration of 2.8 mg/dl (247 μmol/L). Cyclosporine was discontinued on the second hospital day, and azathio- pron and higher doses of prednisone were administered. A random cyclosporin A level was 303 ng/ml. Acute renal failure, secondary to cyclosporine nephrotoxicity, was suggested, and a nephrology consultation was finally obtained on hospital day 4. Acute ureteral obstruction was ruled out by renal ultrasonography, and a computerized tomographic renal scan was unremarkable.

It was noted that the BUN and creatinine levels continued to increase after discontinuing cyclosporine, despite adequate hydration. Mannitol had been continued throughout. A renal biopsy (hospital day 4) revealed glomerulosclerosis, patchy interstitial fibrosis, moderate tubular atrophy, and arteriolar wall thickening, all consistent with chronic rejection. In addition, however, multiple, large, homogeneous vacuoles (isometric tubular vacuolization) packed the cytoplasm of multiple tubular epithelial cells, especially in the proximal tubules. Proximal tubular epithelial cells were markedly enlarged, to the extent that the tubule lumen was not easily discernible. Arteriolar hyalinization, as would be expected with cyclosporine nephrotoxicity, was absent. The 99mTc-DTPA clearance was 27 ml/min. Mannitol was discontinued on hospital day 4. Unfortunately, plasma and urine osmolality was not measured.

Also of interest is the relationship, evident in our patient, between discontinuation of the mannitol and resolution of acute renal failure, as opposed to the failure to respond to cessation of cyclosporin A.

On the seventh hospital day, the patient spontaneously diuresed. Renal perfusion improved markedly and renal failure began to resolve as indicated by the changes in urine output, serum creatinine (Table 1), and decreasing signs of congestive heart failure. At discharge 10 d later, the serum creatinine concentration had declined to 1.7 mg/dl (200 μmol/L).
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Discussion

Review of the Clinical and Pathologic Manifestations

Because mannitol is an osmotic diuretic and an obligate
extracellular solute, it has been recommended for prevention of
acute renal failure secondary to mechanisms as diverse as
prerenal causes (for example, clamping of the abdominal aorta
before aneurysmal repair and edematous conditions) and acute
toxic renal failure (for example, salicylates, barbiturates, and
bromides) leading to tubular necrosis (1). In earlier uncon-
trolled studies, mannitol was reported to reduce the nephrotox-
icity of radiodinst modules in patients with chronic renal
insufficiency (1). On the basis of this report and other evidence
suggesting a possible beneficial effect of mannitol in prevent-
ing cell swelling (2), mannitol was widely used in the setting of
early or impending acute renal failure. More recent controlled
studies, however, failed to substantiate a beneficial prophylac-
tic effect for patients at risk for contrast nephropathy (3).

Indeed, intravenous saline administration was observed to im-
port a beneficial effect in preventing contrast nephropathy,
whereas furosemide and mannitol had a deleterious effect (3).

It has been assumed that altered vascular reactivity in response
to mannitol can explain the absence of renal protection in
patients with diabetes who were given mannitol to prevent the
onset of acute renal failure when exposed to radiocontrast (4).

The incidence of acute renal failure was much higher in pa-

patients who received mannitol, dopamine, or atrial natriuretic
peptide compared with those who received only intravenous
normal saline in this setting (4).

Currently, mannitol is most commonly used to: (1) reduce
intracerebral edema resulting from trauma or surgery; (2) re-
duce intraocular pressure in acute congestive glaucoma; and
(3) prevent and treat dialysis-disequilibrium syndrome (1,5).

Mannitol has been recommended, along with volume expan-
sion and sodium bicarbonate, in the prevention of myoglobin-
induced acute renal injury (6). Moreover, intravenous mannitol
infusion before vascular clamp release and before the initiation
of cyclosporin A has been suggested for the prevention of post-
transplant acute renal failure (7,8). Such applications may
require high doses of mannitol and may precipitate acute renal
failure (5).

Typically, mannitol-induced acute renal failure occurs in
patients receiving larger cumulative doses of this agent than
can be excreted. The mean reported total dose of mannitol that
precipitated acute renal failure in patients with previously
compromised kidney function is 295 ± 134 g (5). In contrast,
in individuals with previously normal baseline renal function,
the mean total dose of mannitol that precipitated acute renal
failure was 626 ± 270 g over 2 to 5 d (5). In patients concomitantly
on cyclosporine, however, the mannitol dose necessary for precipita-
tion of acute renal failure appears to be much less, although this level has not been established. In our
patient, a total dose of 236 g of mannitol administered over
approximately 4 d was associated with "acute on chronic" renal
failure. Laboratory findings included a rapidly rising creat-
ine, which peaked at 7.0 mg/dl (620 μmol/L), and BUN, which
peaked at 82 mg/dl (29 mmol/L). Previous studies report
peaks for creatinine at 4 to 7 mg/dl and BUN at 40 to 60 mg/dl
(5).

An elevated serum potassium is common when intoxication
results from higher doses because of the solvent drag phenom-
enon associated with mannitol. Early in the course of the
infusion, hypokalemia may be observed. Hyponatremia, hypo-
icarbonatemia, hypocalcemia, hypophosphatemia, and acido-
sis are other features of mannitol excess (9). Hypocalcemia and
hypophosphatemia result from increased urinary excretion.
The urinalysis may reveal tubular epithelial cells with vacu-
olization at a magnification of ×1400 (5). Urine chemistries,
including electrolytes, the renal failure index, and fractional
excretion of sodium, cannot be interpreted, because mannitol is
an osmotic diuretic (9). Clinical features of central intracellular
dehydration include lethargy, stupor, and deterioration of men-
tal function (5). In severe cases, signs of acute congestive heart
failure and pulmonary edema with low blood pressure, pulmo-
nary rales, dyspnea, and reduced urinary output are seen (5).

In the presence of nephrotoxicity, the serum level of man-
nitol may be extremely high (>1000 mg/dl), but overdose may
be recognized more readily by the accompanying increase in
serum osmolality, which is best appreciated by calculation of
the osmolar gap. The osmolar gap is the most practical variable
to monitor in a patient receiving high doses or prolonged
therapy of mannitol (9). Every effort should be made to keep
the osmolar gap below 55 mmol/kg H₂O, because values in this
range are associated with a lower incidence of acute renal
failure (9). Other variables that may be monitored are hourly
vital signs, urine output, and serum levels of potassium, so-
dium, glucose, calcium, and phosphate (9). As a general rule,
mannitol, especially in large doses, should not be administered
to patients with chronic renal insufficiency.
The most dramatic finding can be seen on the renal biopsy, where extensive vacuolization of the proximal tubular epithelial cells, and occasionally distal tubular epithelial cells, is evident. This unique appearance, as demonstrated in our patient (Figure 1), has been described previously as “osmotic nephrosis” (5,9,10) (Table 2).

**Review of Pathophysiology**

Mannitol, a 6-carbon alcohol with a molecular weight of 182, is prepared commercially by the reduction of dextrose (1). In 1940, Smith and associates showed that mannitol clearance reflected the GFR in humans (11). Mannitol is metabolically inert; after intravenous infusion it remains largely in the extracellular space and is excreted unchanged in the urine (11). Mannitol has a myriad of effects on tubular transport and hemodynamics, including: (1) osmotic inhibition of water reabsorption in excess of sodium in the proximal tubule; (2) a diminished gradient for passive sodium resorption in the thin ascending limb of the loop of Henle; and (3) an increment in renal blood flow (9). The GFR may either be augmented (by extracellular volume expansion and increased renal plasma flow) or reduced (by increased intratubular pressure and efferent arteriolar dilatation) (9).

Recent evaluations of mannitol pharmacokinetics reveal that the elimination half-life of mannitol varies with the GFR and volume of distribution. Variation in GFR probably explains the wide variation in the \( t_{1/2} \) from 39 to 103 min of a dose of between 0.5 and 0.71 g/kg (5).

As early as the 1960s, light and electron microscopic studies revealed the effects of intravenous administration of mannitol, hypertonic glucose, and dextran on proximal convoluted tubular epithelial cells (12). The term “osmotic nephrosis” was first used to indicate the observation that proximal tubular epithelial cells were substantially vacuolized. It was not determined whether these vacuoles contained the injected substance. Vacuolization was much more pronounced when mannitol was injected than when a comparable amount of glucose was injected (12). It is widely assumed that the vacuolization is indicative of endocytosis of the agent. The vacuoles, which are numerous and pack the cytoplasm, are almost always uniform in size. The swollen tubular epithelial cells may or may not occlude the tubular lumen (Figure 1, A and B). Ultrasonography...
Table 2. Review of osmotic nephrosis literature

<table>
<thead>
<tr>
<th>Author (Reference No.)</th>
<th>Description of Study</th>
<th>Year</th>
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<tbody>
<tr>
<td>Maunsbach et al. (12)</td>
<td>Intramuscular and subcutaneous injections of hypertonic solutions such as mannitol cause vacuolization of proximal tubular epithelial cells. First English language article describing this effect. (Referenced are five German and French papers describing same).</td>
<td>1962</td>
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<tr>
<td>DiScala et al. (24)</td>
<td>Vacuolation occurs in proximal convoluted tubules after single injection of mannitol, without loss of renal function</td>
<td>1965</td>
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<tr>
<td>Stuart et al. (17)</td>
<td>An in-depth evaluation in dogs of (1) single exaggerated dose; (2) repeated low dose; and (3) massive dose of intravenous mannitol. Observations confirmed that mannitol induces isometric tubular vacuolization. The degree of vacuolization was related to amount of mannitol infused.</td>
<td>1970</td>
</tr>
<tr>
<td>Dorman et al. (5)</td>
<td>Photomicrographs of urinary sediment showing vacuolated tubular epithelial cells after massive mannitol administration, in addition to vacuolization in tubules on biopsy.</td>
<td>1990</td>
</tr>
<tr>
<td>Brunner et al. (10)</td>
<td>In rats, combined infusion of cyclosporin A and mannitol has a much more nephrotoxic effect than either agent alone. Tubular vacuolization is slight with either agent but pronounced when both are infused.</td>
<td>1986</td>
</tr>
<tr>
<td>Hamburger et al. (26)</td>
<td>Histology of mannitol-induced acute renal failure in rabbits. Earliest publication describing tubular vacuolization.</td>
<td>1954</td>
</tr>
<tr>
<td>Taggert et al. (27)</td>
<td>Description of mannitol-induced tubular vacuolization in rabbits and reversibility on discontinuation of mannitol.</td>
<td>1968</td>
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Phy and other diagnostic modalities reveal no mechanical obstruction, however. Although the isometric tubular vacuolization seen on renal biopsy in osmotic nephrosis is also seen with cyclosporine nephrotoxicity (28), the degree of vacuolization is generally much more extensive and uniform with mannitol intoxication (10). Moreover, studies in rats (10) have revealed potentiation of the degree of vacuolization when mannitol and cyclosporine were administered concomitantly (Table 2). Although animal studies clearly demonstrate potentiation of the nephrotoxicity of mannitol by cyclosporine (Table 2), few, if any, human studies confirm this association (13).

Suggested mechanisms for potentiation of toxicity of mannitol by cyclosporin A include reduction in cortical blood flow in response to the vasoconstrictive properties of cyclosporin A (14). In mice in which the exposure to mannitol was not preceded by exposure to cyclosporin A, there was no decrease in renal cortical blood flow. These experiments and others (10,28) suggest that mannitol and cyclosporin A together may exert an additive effect, which could result in significant vasoconstriction, favoring the development of tubular toxicity.

The first described toxicity of mannitol was congestive heart failure. These same studies indicated that if mannitol was used to load the kidney to diagnose acute renal failure, it could actually exacerbate the condition (15). Subsequently, it was noticed that mannitol exerted a direct, dose-dependent vasoconstrictor effect on the renal artery (16). However, studies in dogs revealed that although the proximal tubular cells were full of vacuoles, the luminal area was not compromised, and the proximal intratubular pressure was not elevated, even during peak renal failure. Thus, the onset of acute renal failure suggested that there was more than merely an anatomical component to this event (10,17). In addition, the fact that the acute renal failure is so often reversible after initiation of hemodialysis also suggests that the pathology is less likely to be anatomical than physiological (5).

Another possible, but as yet unproven, mechanism is that mannitol causes acute renal failure because of tubuloglomerular feedback in response to the increase in tubule fluid osmolality delivered to the macula densa (18). In a rat micropuncture study, however, mannitol alone, when used to increase osmolality of tubule fluid to 400 mosmol, did not decrease the single-nephron GFR until chloride ions were added to the solution (19). Thus, an increase in tubular osmolality, in conjunction with increased chloride delivery to the macula densa, could activate the tubuloglomerular feedback system and decrease single-nephron GFR.

It has been proposed that mannitol causes acute renal failure simply by depleting intravascular volume as a result of the osmotic diuresis (20). Concomitant administration of diuretics (furosemide or acetazolamide) or other potentially nephrotoxic agents (cyclosporine) increases the likelihood of mannitol-induced renal failure (10, 21–23, 28).

Thus, mannitol-induced acute renal failure is a complex pathophysiological process, which may occur as the result of several possible mechanisms. Confounding factors are the concomitant administration of other nephrotoxic drugs and agents, as well as volume depletion and pre-existing renal disease, which potentiates the nephrotoxicity of mannitol.
Monitoring Mannitol Therapy and Treatment of Renal Failure

When treating a patient with high doses of mannitol, it is important to monitor regularly the serum concentrations of sodium, potassium, calcium, and phosphate; osmolality and the osmolar gap; and hourly urine output. If the serum osmolar gap exceeds 55 mosmol/kg H₂O or if the serum concentration of mannitol exceeds 1000 mg/L, mannitol should be discontinued. The serum mannitol concentration may be estimated using the formula:

\[ [\text{Mannitol}] = \text{Osmolar gap} \times \frac{182}{10} \]

where 182 represents the molecular weight of mannitol.

High-dose mannitol therapy should be used judiciously, particularly in the face of pre-existing renal insufficiency. Emphasis should be placed on the prevention of mannitol-induced acute renal failure by recognition of the setting in which this complication may occur, and by avoiding larger doses and continuous therapy in patients at risk.

However, when present, mannitol toxicity may be treated successfully by stopping the agent and by restoring extracellular fluid volume. Recovery may occur spontaneously, as evidenced by a diuresis in association with a decline in the osmolar gap (5). If a diuresis does not ensue, hemodialysis may be required.

Summary

High-dose mannitol therapy may be complicated by acute renal failure, particularly in patients with baseline renal functional impairment. Mannitol induces extensive isometric proximal tubular vacuolization, which may occlude the lumen of the tubule. In higher doses, this agent may cause intense afferent arteriolar constriction, particularly when administered in conjunction with cyclosporin A. Common side effects of high-dose mannitol therapy include an acute expansion in extracellular fluid volume, congestive heart failure, hyperosmolality, hyponatremia, hypokalemia, and alteration in sensorium due to intracellular dehydration in the brain. Mannitol therapy should be monitored by measuring the serum osmolar gap; if the osmolar gap exceeds 55 mosmol/kg of water, mannitol should be discontinued. In its early stages, acute renal failure may usually be reversed by discontinuing mannitol or by initiating hemodialysis, if necessary, to eliminate the agent.

References

23. Plouvier B, Baclet J, DeConinck P: Une association nephrotox-
Nephrology Training Program at the University of Texas Medical School at Houston

The Nephrology Training Program at the University of Texas Medical School, Houston, Texas, offers broad-based clinical experience in all aspects of clinical nephrology, which is coupled with opportunities for formal training in basic research and clinical investigation. The program offers multiple pathways for a trainee's chosen career in nephrology and emphasizes preparation for a career in academic nephrology, including mastery of fundamental and clinical investigative techniques. The traditional clinical training program is of 2 yr duration and prepares the fellow for a career in clinical nephrology. The academic track is a 3- or 4-yr curriculum and emphasizes mastery of research techniques. The clinical investigator track includes, in the third year, didactic study at the University of Texas School of Public Health and clinical research under the direction of a faculty member in either the Clinical Research Center or the outpatient setting. A critical care pathway, administered in conjunction with the Division of Pulmonary and Critical Care Medicine, allows the graduate dual board certification in Critical Care Medicine and Nephrology. More recently, a new combined 4-yr program in Medicine-Pediatric Nephrology has been initiated, in cooperation with the Division of Pediatric Nephrology. A prerequisite for this track is completion of a 4-yr medicine-pediatric residency. Finally, a fellowship in Transplant Medicine and Immunology is also available in the third year and is coordinated in cooperation with the Division of Immunology and Organ Transplantation. For fellows in all tracks, didactic lectures complement a strong emphasis on clinical case discussion and problem solving. The core curriculum, which is presented concurrently over a 2-yr period, is intended to provide the nephrology fellow with a strong foundation in all aspects of nephrology, hypertension, transplantation, dialysis, and the renal biopsy. Other educational opportunities include weekly Renal Grand Rounds, the usual array of clinical and research journal clubs, biopsy conference, and research conference.

A rich experience in clinical nephrology is available through rotations on the nephrology consultation services at Hermann Hospital, the Lyndon Baines Johnson General Hospital, and the M. D. Anderson Cancer Center. A dedicated renal inpatient unit is staffed by the faculty of the Division of Renal Diseases and Hypertension at Hermann Hospital. A large outpatient hemodialysis and peritoneal dialysis population is maintained in two free-standing outpatient dialysis units. Approximately 127 patients undergo acute hemodialysis each year, providing fellows with extensive experience in the assessment and management of acute renal failure. Postdoctoral fellows also spend at least 3 mo yearly as members of the transplant team, which performs approximately 120 renal transplants annually. Moreover, over 1000 patients are followed in the renal transplant clinics. Regular ambulatory clinics in evaluation of the renal referral patient emphasize the diagnosis and management of glomerulonephritis, hypertension, and general nephrology. Trainees are supervised individually in their own longitudinal ambulatory clinic, where they monitor patients for 2 yr of their training.

The 12 full-time faculty members of the Division of Renal Diseases and Hypertension participate in extramurally funded research and are involved in national and international academic and educational pursuits. A strong emphasis is placed on state-of-the-art investigations, which are at the forefront of academic nephrology, including molecular and cell biology, transport physiology, and the pathophysiology of acid-base and electrolyte disorders. Funding for continued research training is available on a competitive basis from local and extramural agencies, as well as industry-sponsored fellowship awards within the division.