The Role of Mannitol as a Nephroprotectant in Patients Receiving Cisplatin Therapy

Katherine P Morgan, Larry W Buie, and Scott W Savage

**Request**

Does concomitant mannitol infusion with cisplatin reduce renal damage?

**Response**

**BACKGROUND**

Cisplatin is a platinum-based chemotherapeutic compound that is frequently used with proven survival benefits for patients diagnosed with malignancies including testicular, head and neck, lung, ovarian and cervical cancers, and lymphoma. Cisplatin works as an alkylating agent by creating interstrand and intrastrand crosslinks, resulting in DNA dysfunction and arresting DNA replication. The adverse effect profile of cisplatin consists of nausea and vomiting, myelosuppression, ototoxicity, and dose-limiting nephrotoxicity. The incidence of nephrotoxicity is high, occurring in approximately one third of all patients on cisplatin therapy.

Cisplatin is renally eliminated and accumulates in the renal tubules. Uptake of cisplatin and toxic metabolites into the proximal tubules is mediated primarily through an organic cation transporter. Cisplatin concentrations in the proximal tubule cells, the major site of damage, are approximately 5 times the serum concentration. Once in the cell, cisplatin is converted to glutathione conjugate and is metabolized through γ-glutamyl transpeptidase and cysteine–S-conjugate β-lyase–dependent pathways to a reactive thiol, which is a potent nephrotoxin. Direct damage to the proximal tubules results in mitochondrial damage and generation of reactive oxygen species contributing to the epithelial dysfunction. The inflammatory response is activated, mediating renal injury by enhanced renal expression of tumor necrosis factor-α and other cytokines in the kidney. Several histologic changes occur as a consequence of these molecular effects, including necrosis of the distal tubules and collecting ducts, dilation of convoluted

**OBJECTIVE:** To review the efficacy and safety of concomitant mannitol administration with cisplatin therapy to reduce the incidence of nephrotoxicity.

**DATA SOURCES:** A literature search was performed via MEDLINE, PubMed, and the Cochrane Library (1945-August 2011) using the terms mannitol, cisplatin, nephrotoxicity, and forced diuresis. Reference citations from the publications identified were also reviewed.

**STUDY SELECTION AND DATA EXTRACTION:** The search was limited to studies conducted in humans. All studies in which mannitol was used for forced diuresis with cisplatin therapy were evaluated.

**DATA SYNTHESIS:** Cisplatin therapy can lead to transient and permanent renal impairment. Molecular and histologic changes occur in the renal tubules, which contribute to nephrotoxicity. The adverse effect profile of cisplatin is well documented, but the prevention strategies to alleviate renal impairment due to treatment are less understood. Mannitol plus hydration has been used for several years to alleviate toxicity associated with cisplatin therapy. However, the data for mannitol administration have not been convincing. When the use of mannitol and hydration is compared directly to hydration alone, mannitol shows no benefit. In some patients, not only was mannitol not protective, its administration was associated with worsening renal function.

**CONCLUSIONS:** Although mannitol plus hydration is used to decrease cisplatin-induced nephrotoxicity, there are no compelling data that the addition of mannitol is more nephroprotective than the use of hydration alone. Appropriate hydration remains the most reasonable strategy to reduce the incidence of cisplatin-induced nephrotoxicity.

**KEY WORDS:** cisplatin, mannitol, nephrotoxicity.


Published Online, 31 Jan 2012, theannals.com, DOI 10.1345/aph.1Q333

Author information provided at end of text.
Renal tubular function in patients receiving cisplatin is often compromised. This leads to a decrease in glomerular filtration rate, a decrease in proximal reabsorption of sodium and water, as well as an increase in urinary excretion of protein and electrolytes. These changes can be seen as soon as 10 days after the first course of cisplatin therapy. Residual effects of kidney damage can last up to 6 months after termination of treatment and may cause a persistent 20-30% reduction in glomerular filtration rate in some patients.

In early Phase I studies of cisplatin, dose-dependent, cumulative, and sometimes irreversible nephrotoxicity was observed as a dose-limiting toxicity. The half-life of cisplatin can be reduced significantly with hydration and diuresis, leading to less severe renal effects. Fluid hydration increases excretion and reduces formation of toxic metabolites by decreasing contact time with the renal tubules. Mannitol is an osmotic diuretic and works to increase the osmolarity of the glomerular filtrate, promoting the excretion of water and inhibiting renal tubular reabsorption of sodium, chloride, and other solutes. With these methods instituted, nephrotoxicity can be minimized, allowing for higher and more optimal doses of cisplatin to be delivered. Mannitol at higher doses and in patients with decreased renal function has also been associated with further declines in renal function and precipitation of renal failure. This may be related to afferent arteriole constriction or vacuolization of the proximal tubular epithelial cells. Despite these reports, mannitol is commonly used to decrease renal complications associated with nephrotoxic drugs, including cisplatin.

Hayes et al. were the first to explore hydration in combination with mannitol to reduce cisplatin-induced nephrotoxicity. They conducted a noncomparative study with 60 patients receiving a high-dose cisplatin bolus of at least 120 mg/m² and prehydration with 2 L of dextrose 5% in half-strength normal saline (0.45% NaCl) 12 hours prior to the cisplatin dose plus 12.5 g of intravenous bolus of 25% mannitol immediately before cisplatin administration. Infusion of half-strength normal saline at a rate of 200 mL/h for 6 hours after cisplatin infusion for fluid replacement, and a continuous intravenous infusion of 20% mannitol at a rate of 10 g/h was also run for 6 hours after the cisplatin dosing. Of the 52 patients evaluated, renal toxicity was limited to a transient rise in serum creatinine (SCr). Although no definition of nephrotoxicity was given, SCr peaked at less than 2.0 mg/dL in most patients. Ten patients had a peak SCr level greater than 2.0 mg/dL, of which 9 had significant renal abnormalities before treatment with cisplatin, placing them at higher risk of nephrotoxicity. One patient received the highest dose of cisplatin allowed (5 mg/kg), resulting in death attributed to renal and bone marrow failure. This study was the first to demonstrate some benefit from concomitant hydration and diuresis to reduce the risk of renal toxicity. Mannitol was added in most cisplatin studies for nephroprotection after these results were published.

Subsequent studies observed hydration to be effective in ameliorating cisplatin-induced nephrotoxicity. Legha and Dimery conducted another noncomparative study of high-dose cisplatin (30-40 mg/m² for 5 days) with overnight intravenous hydration with 150 mL/h of dextrose 5% in half-strength normal saline plus 20 mEq of potassium chloride that continued through day 5 of chemotherapy. The highest SCr documented was 2.7 mg/dL. Elevations in blood urea nitrogen (BUN) and SCr were reversible and normalized before the next treatment with cisplatin in all but one patient. Aggressive hydration appeared to be renally protective in these patients.

**Literature Review**

Ostrow et al. published one of the first (1981) studies comparing mannitol and furosemide to assess the effectiveness of diuresis during cisplatin therapy. Twenty-two patients with advanced neoplasms refractory to conventional therapy were given a course of cisplatin 100 mg/m² in 2 L of dextrose 5% in half-strength normal saline over 6 hours every 21-28 days. The patients received 1.5 L of intravenous normal saline 4 hours before cisplatin administration. Ten patients were randomized to receive 37.5 g of mannitol by 6-hour infusion with cisplatin and 12 patients received a 40-mg intravenous bolus of furosemide 60 minutes prior to therapy. All patients also received at least 1 L of normal saline after cisplatin therapy. Patients had normal renal function, defined as SCr less than 1.5 mg/dL, and creatinine clearance (CrCl) greater than 50 mL/min.

Nephrotoxicity, defined as CrCl less than 50 mL/min and SCr greater than 2 mg/dL, occurred in 28% of the 22 courses and in 19% of the 25 courses in patients treated with mannitol and furosemide, respectively. The mean decrease in CrCl in the mannitol group was 34 mL/min, compared to 26 mL/min in the furosemide group. Although there was an increase in the number of patients with reported nephrotoxicity in the group receiving mannitol, there was no significant difference observed with regard to increase in SCr (p = 0.45) or decrease in CrCl (p = 0.25) between the 2 groups. The results of this study showed no superiority between the 2 diuretics in reducing the nephrotoxicity associated with cisplatin and did not assess the effectiveness of hydration therapy alone as a comparator. It is unclear how long after cisplatin therapy the SCr data were collected for patient evaluation. Cisplatin nephrotoxicity may not occur directly after administration and it is difficult to determine the true effects of cisplatin without this information. There also was no description of the patient baseline characteristics, including the baseline mean SCr or CrCl for the patient population, so clinical relevance is difficult to assess. Although this study provided minimal in-
Forty-two patients were randomized to hydration only, receiving an additional 2 L of dextrose 5% in half-strength normal saline over 24 hours prior to 100 mg/m² of cisplatin administered over 10-15 minutes. Thirty-three patients were randomized to hydration only, receiving an additional 2 L of dextrose 5% in half-strength normal saline. Thirty-four patients received 12.5 g of mannitol prior to cisplatin, followed by 25 g of mannitol in 1 L of 5% dextrose in water over 6 hours. In both groups an additional 2 L of dextrose 5% in half-strength normal saline was administered; additional infusions were administered over the following 24 hours to replace fluids lost via emesis or excessive urine output. This study preceded the use of modern antiemetic therapy, and nausea and vomiting occurred in 77% of patients. Patients included in this study had a BUN 20 mg/dL or less, SCr of 1.7 mg/dL or less, or CrCl at least 60 mL/min, although no baseline values were reported. Nephrotoxicity was defined as mild (CrCl 40-50 mL/min, BUN 23-40 mg/dL, SCr 1.5-2 mg/dL), moderate (CrCl 30-40 mL/min, BUN 41-60 mg/dL, SCr 2-4 mg/dL), severe (CrCl 20-30 mL/min, BUN >100 mg/dL, SCr >4 mg/dL), and life-threatening (CrCl <20 mL/min). Creatinine, BUN, and electrolyte concentrations were collected daily for 3 days after cisplatin therapy for follow-up evaluation.

Thirty percent of the patients in the hydration-alone group and 15% in the mannitol group had renal toxicity after the first dose. Overall rates of renal insufficiency seen in the hydration group versus the mannitol group were 39% and 32%, respectively. Patients appeared to have a better response to mannitol after the first dose, but no statistical analysis was performed to validate these results and there was no apparent protective effect from mannitol for subsequent doses. The patient population was minimally discussed, so the generalizability of these results remains uncertain. Seventeen patients in the hydration group received only 1 course of cisplatin, compared with 11 patients in the mannitol arm. The potential protective effects beyond the first dose can therefore not be assessed accurately since the beneficial effects of mannitol after the first dose may be misleading because of the small population size.

In 2003, Santoso et al. performed a randomized trial to distinguish the nephroprotective benefits from those of normal saline alone versus the addition of mannitol or furosemide in patients receiving cisplatin therapy. Forty-nine women with gynecologic tumors received cisplatin 75 mg/m² plus paclitaxel or fluorouracil and were randomized into 3 hydration arms: 500 mL of normal saline over 2 hours, 500 mL of normal saline over 2 hours plus furosemide 40 mg 30 min before cisplatin infusion, and 500 mL of normal saline over 2 hours plus mannitol 50 g mixed with cisplatin. All patients received cisplatin mixed in 1 L of normal saline and an additional 500 mL of normal saline after the cisplatin infusion. Patients were excluded if their SCr concentration was 2 mg/dL or greater, if they had diabetes or renal disease, or if they were taking concomitant nephrotoxic drugs. The 24-hour CrCl rate was measured at baseline, before each cycle of cisplatin, and 6 days after each cycle of cisplatin. Patients were instructed to collect their urine samples and to increase fluid intake after chemotherapy administration.

There were 15 patients in the normal saline arm, 17 in the normal saline and furosemide arm, and 17 in the normal saline and mannitol arm. The mean (SD) measured 24-hour CrCl rates before the first infusion of cisplatin were 84.5 (33.5), 82.5 (24), and 87.4 (25.6) mL/min for the normal saline, normal saline plus furosemide, and normal saline plus mannitol groups, respectively. The mean (SD) measured 24-hour CrCl rates after completion of the treatment course of cisplatin were 80.4 (33.5), 81.4 (23.3), and 60.6 (26.8) mL/min. No definition of nephrotoxicity was provided, but a comparison of CrCl rate before and after cisplatin administration was assessed. The 24-hour decrease in CrCl rate in the normal saline-alone and normal saline plus furosemide arms did not show a significant difference after the first administration of cisplatin or following completion of all cycles. There was a significant decrease in 24-hour CrCl rate in the normal saline plus mannitol group compared to the normal saline group (p = 0.02) and between the normal saline plus mannitol group and the normal saline plus furosemide group (p = 0.02) after the first administration of cisplatin. The decrease in 24-hour CrCl rate 6 days after cisplatin infusion was also significantly different between the normal saline plus mannitol arm and the normal saline arm (p = 0.04) and the normal saline plus mannitol arm and the normal saline plus furosemide arm (p = 0.01). The 24-hour CrCl rate in the normal saline plus mannitol arm also showed a cumulative decrease in renal function with subsequent cycles of cisplatin.

In this study, the addition of mannitol did not appear to be nephroprotective when compared to the other randomization arms. The study was underpowered and the number of patients needed was not reached because of premature closure of the study based on the trend of worse outcomes with concomitant mannitol. The 24-hour urine collection was measured by patients, so accurate measurements may not have always been possible. Also, patients may not have been adherent to fluid intake recommendations after cisplatin administration. Variability in fluid intake could have increased the risk of dehydration and possible acute renal injury, especially in the group receiving diuretics. Investigators also found a poor correlation between measured 24-hour CrCl compared to calculated CrCl, resulting in an overestimate of true renal function. Despite these limitations, a trend
to toward decline in renal function was still apparent in the hydration plus mannitol arm.\textsuperscript{17}

Leu et al. performed a larger retrospective trial in 2010 that aimed to determine whether forced diuresis with 12.5 g of mannitol plus normal saline loading (ie, infusion before cisplatin) or with normal saline loading alone plus optional posthydration is better for prevention of nephrotoxicity associated with cisplatin therapy.\textsuperscript{18} Ninety-two patient records, with 46 patients in each group, were reviewed to establish the incidence of nephrotoxicity, average decline in CrCl, degree of nephrotoxicity (grade 0: SCr within normal limits, grade 1: 1.5 upper limit of normal [ULN], grade 2: >1.5-3.0 × ULN, grade 3: >3.0-6.0 × ULN, grade 4: >6.0 × ULN), time to resolution, rates of hospitalization, and electrolyte abnormalities between the 2 groups. The primary outcome was the average change in CrCl between the groups. Patients were receiving cisplatin >40 mg/m\textsuperscript{2} and most of the patients were receiving treatment for lung cancer. Patients included in the analysis had normal baseline renal function, defined as CrCl 60 mL/min or greater (Cockcroft-Gault equation). The mean baseline CrCl was 89.7 ± 13.8/min (normal saline loading) and 83.5 ± 14/min (forced diuresis). The incidence of nephrotoxicity was higher in the mannitol group, but there was no statistically significant difference in average decline in CrCl between the 2 groups (p = 0.09). The average decrease in CrCl in the saline group was 33.9 mL/min (normal saline loading) and 38.9 mL/min (forced diuresis). Grade 1 and 2 nephrotoxicity was more prevalent in the forced diuresis group. A unique endpoint, time to resolution of nephrotoxicity, showed that the normal saline group’s mean time to resolution was 129.3 days compared to 23 days in the mannitol group, but was not found to be statistically significant. This endpoint also does not show that mannitol was nephroprotective. The investigators evaluated these data using random SCr values available in the charts. Treatment doses for each cancer type were also different and there was a higher incidence of lung cancer in the mannitol group versus head and neck and gynecologic malignancies in the saline group. Patients receiving mannitol were given 1 L of normal saline before and after cisplatin, whereas most patients in the saline group received 1 L of normal saline for prehydration only, likely because the patients in the mannitol group were at higher risk for dehydration and needed adequate hydration after mannitol therapy. In this trial, there was no clinically significant difference between saline prehydration and combination forced diuresis for decreasing nephrotoxicity in patients on cisplatin therapy.

**Discussion**

Cisplatin is a highly effective antineoplastic agent that is used for a variety of malignancies. Its survival benefits outweigh the risk of nephrotoxicity and it remains one of the most prescribed chemotherapeutic agents. Based on the available data, it is not clear whether the use of mannitol with hydration will reduce the severity of nephrotoxicity associated with cisplatin therapy.

Studies comparing hydration versus hydration plus forced diuresis have shown conflicting results. Some have suggested that mannitol decreases cisplatin toxicity, while others have shown that the use of mannitol may have no effect in reducing cisplatin toxicity. There are no guidelines that provide standard dosing for hydration or forced diuresis; therefore, the amount of hydration or mannitol and duration of therapy were variable across studies and may explain the conflicting results between studies. If patients are not adequately hydrated, forced diuresis, causing volume contraction and decreased volume status, could perpetuate acute kidney injury, contributing to increased renal damage associated with mannitol use. Greater nephrotoxicity may also be seen in the studies that preceded current standard antiemetic regimens for patients receiving highly emetogenic therapy. These patients endured more nausea and vomiting associated with chemotherapy and, as a result, were possibly more dehydrated. Also, depending on the tumor type, renal toxicity was evaluated for doses ranging from 40 mg/m\textsuperscript{2} to more than 120 mg/m\textsuperscript{2}. Cisplatin nephrotoxicity is known to be dose dependent, so the extent of renal damage can be variable based on diagnosis, doses used for treatment, and number of cycles received.

The strongest data available suggest that standard practices of prehydration followed by infusion of mannitol with cisplatin may have no additional benefits over hydration alone.\textsuperscript{17,18} These trials show an increase in SCr and worsening renal function after cisplatin therapy. The differences in CrCl increase among the various preventative methods were minimal. Santoso et al. showed that mannitol had the least nephroprotective effects when compared to hydration alone or hydration plus furosemide.\textsuperscript{17} The investigators also used a higher dose of mannitol than seen in previous trials, which may have contributed to the decline in renal function, bringing up the question of whether larger doses of mannitol can actually decrease the nephroprotective effects of forced diuresis. The retrospective trial conducted by Leu and Baribeault determined that there was no difference in the decrease of renal function between hydration and hydration plus mannitol.\textsuperscript{18} They did show a difference in time to resolution of renal symptoms, which in the mannitol group was much less compared to the hydration group (23 days vs 129.3 days, respectively). However, recovery of renal function between the groups does not assess the prevention of nephrotoxicity and is not clinically meaningful.

Many patients will experience cisplatin-induced nephrotoxicity, and efforts to reduce the damage only mildly alleviate toxicity after cisplatin therapy. From the data available, pre- and posthydration provide nephroprotection, and yet the use of mannitol has become standard practice at many institutions without strong data to support its use. At this time, there is no convincing evidence that diuretics...
may attenuate cisplatin nephrotoxicity. Strategies need to be implemented that affect cisplatin’s direct molecular damage. Multiple alternatives have been considered that can inhibit renal damage from the molecular level by decreasing entry of cisplatin into the renal cells, reducing signal transduction, reducing oxidative stress, and reducing inflammation leading to toxicity.\textsuperscript{18}

**Summary**

Based on data gathered by 3 clinical trials and 1 retrospective trial, nephrotoxicity in patients receiving cisplatin is mildly alleviated but unavoidable when using the current techniques of hydration and forced diuresis. When compared directly, no studies have shown overwhelming evidence that the use of mannitol significantly reduces the risk of nephrotoxicity over hydration alone. In addition, mannitol administration has been associated with increased rates of nephrotoxicity in some trials. Given this information and the quality of the data, a definitive recommendation for or against mannitol as a nephroprotective agent cannot be provided at this time for patients receiving cisplatin therapy. Additional studies are needed to confirm the magnitude of benefit, if any, achieved when mannitol is administered with cisplatin therapy as compared with hydration methods alone. No guidelines are available to provide recommendations on this issue; however, the European Society of Clinical Pharmacy Special Interest Group on Cancer Care does not recommend the use of forced diuresis for the prevention of cisplatin-induced nephrotoxicity.\textsuperscript{19} New strategies need to be employed that directly affect the molecular changes in the renal epithelium if risk to renal function associated with cisplatin continues to be a dose-limiting factor in this patient population. These strategies are not yet validated. Therefore, the most appropriate current method to reduce cisplatin-associated renal complications consists of using the appropriate dose of cisplatin, avoiding concomitant nephrotoxic medications, and properly hydrating the patient.

**References**


SELECCIÓN DE ESTUDIOS Y EXTRAICIÓN DE DATOS: La búsqueda se limitó a estudios realizados en humanos. Se evaluaron todos los estudios identificados en los que se utilizó manitol para forzar la diuresis en terapias con cisplatino.

SÍNTESIS DE LOS DATOS: La terapia con cisplatino puede producir daño renal transitorio o permanente. Se producen cambios a nivel molecular e histológico en los túbulos renales que contribuyen a la nefrotoxicidad. El perfil de reacciones adversas de cisplatino está bien documentado, pero las estrategias de prevención para aliviar el daño renal debido al tratamiento se conocen menos. Durante años se ha utilizado manitol junto a hidratación para aliviar la toxicidad asociada a la terapia con cisplatino. Sin embargo, los datos sobre la administración de manitol no han demostrado ser convincentes. Cuando se compara directamente el uso de manitol e hidratación frente a hidratación sola, no se encuentran beneficios con el uso de manitol. En algunos pacientes, manitol no solo no resulta beneficioso, sino que se ha asociado con un empeoramiento de la función renal.

CONCLUSIONES: Aunque se emplea manitol más hidratación para disminuir la nefrotoxicidad inducida por cisplatino, no hay datos que sugieran que la adición de manitol sea más nefroprotectora que la hidratación sola. Según los datos disponibles, manitol no ha demostrado reducir la nefrotoxicidad cuando se compara con hidratación sola en pacientes que reciben terapia con cisplatino. Una apropiada hidratación sigue siendo la estrategia más razonable para reducir la incidencia de nefrotoxicidad inducida por cisplatino.

Traducido por Juan del Arco

Le Rôle du Mannitol Comme Protecteur de la Fonction Rénale chez les Patients Recevant du Cisplatine

KP Morgan, LW Buie, et SW Savage

RÉSUMÉ

OBJECTIF: Revoir l’efficacité et l’innocuité du manitol à réduire l’incidence de néphrotoxicité associée au cisplatine.


SÉLECTION DES DONNÉES: La recherche a été limitée aux études effectuées chez l’humain. Toutes les études où le manitol était utilisé pour provoquer une diurèse forcée en présence d’une thérapie au cisplatine ont été évaluées.

RÉSUMÉ: L’utilisation du cisplatine peut entraîner une diminution transitoire ou permanente de la fonction rénale. Des modifications moléculaires et histologiques surviennent au niveau des tubules rénaux, contribuant ainsi à la néphrotoxicité. Le profil d’innocuité du cisplatine est bien documenté, mais les stratégies d’intervention permettant de réduire la toxicité rénale sont moins bien comprises. L’utilisation de manitol associée à une hydratation est utilisée depuis plusieurs années dans le but de réduire la toxicité du cisplatine, mais les résultats des études cliniques ne sont pas convainquants. Lorsque comparé à l’hydratation seule, l’administration de manitol en supplément de l’hydratation ne présente aucun bénéfice additionnel.Dans quelques cas, l’administration de manitol a même augmenté la détérioration de la fonction rénale.

CONCLUSIONS: Bien que le manitol combiné à l’hydratation soit utilisé en pratique pour diminuer la toxicité rénale du cisplatine, les données des études cliniques actuellement disponibles ne supportent pas cette pratique. Compte tenu de ceci, l’hydratation demeure la stratégie la plus raisonnable pour réduire l’incidence de néphrotoxicité associée au cisplatine.

Traduit par Suzanne Laplante