Cisplatin-Induced Renal Toxicity: Possible Reversal by N-Acetylcysteine Treatment

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Abstract. Cisplatin administration is frequently associated with renal insufficiency and tubular dysfunction. In this article, a case of massive cisplatin overdose as a result of an accidental substitution for carboplatin is reported. The patient developed oliguric renal failure, hepatotoxicity, ototoxicity, peripheral neuropathy, blindness, and severe myelosuppression. A therapeutic trial with N-acetylcysteine to reverse renal toxicity was attempted. This article reviews the literature on cisplatin nephrotoxicity, with an emphasis on possible mechanisms involved, and suggests therapy for its modification. (J Am Soc Nephrol 8: 1640–1645, 1997)

Cisplatin (CP) is an effective anti-tumor agent widely used for diverse tumor types. The almost universal nephrotoxicity associated with CP results in significant morbidity and complications and often limits its tolerable dosage. It has been proposed that hydration and intravenous mannitol decrease the incidence of CP nephrotoxicity by decreasing the exposure of renal tubular cells to the drug (1). Currently, despite routine hydration and frequent use of mannitol before CP administration, there is still significant incidence of renal insufficiency. Furthermore, a decrease in the glomerular filtration rate has been documented after CP administration, even in the absence of creatinine elevation and despite prehydration, diuretics, and mannitol use (2–4). Prevention of CP nephrotoxicity would reduce morbidity and complications, decrease hospitalization costs, and may allow administration of higher dosage of this effective anti-tumor drug with added therapeutic potential. We hope that this case report, that of a massive CP overdose resulting from an accidental substitution of CP for carboplatin, and review of the literature will provide an insight into the mechanism of renal toxicity caused by CP and offer some therapeutic suggestions for its modification.

Case Report
A 38-year-old woman was diagnosed with large-cell lymphoma of the small intestine in 1990. She underwent segmental resection of small intestine, followed by chemotherapy. Peritonsillar abscess was clinically diagnosed in October of 1994, and a biopsy of the tonsil and peripharyngeal area revealed recurrence of lymphoma of the same type. She was electively admitted to the hospital for CP chemotherapy. Laboratory results from tests performed at the time of her hospital admission were as follows: blood urea nitrogen (BUN), 9 mg%; creatinine, 0.8 mg%; Na, 144 mmol/L; K, 4.2 mmol/L; Cl, 107 mmol/L; CO₂, 27 mmol/L; Ca, 9.8 mg%; PO₄, 3.3 mg%; albumin, 3.8 g%; total protein, 7.1 g%; alkaline phosphatase, 82 U/L; alanine aminotransferase (ALT), 44 U/L; aspartate aminotransferase (AST), 24 U/L; lactate dehydrogenase (LDH), 160 U/L; amylase, 53 U/L; and total bilirubin, 0.6 mg%. She received a total of 640 mg of CP intravenously over 4 days. One day after completion of this chemotherapeutic course, she began complaining of generalized weakness and numbness. She gradually developed decreased hearing and vision and later became deaf and near-blind. It was discovered that she had inadvertently received higher doses of CP than intended. Acute pancreatitis, hepatic and oliguric renal failure developed, and the renal service was consulted. Two days after the last CP dose, laboratory tests revealed the following results (Table 1): ALT, 766 U/L; AST, 1246 U/L; LDH, 1627 U/L; amylase, 1633 U/L; total bilirubin, 2.2 mg%; direct bilirubin, 2.1 mg%; albumin, 3 g%; total protein, 5.2 g%; creatinine, 4.1 mg%; and BUN, 50 mg%. Review of the literature suggested a potential benefit from the use of reducing agents in the reversal of CP-induced renal insufficiency. One such agent, N-acetylcysteine, has successfully been used in a Wistar rat model of CP nephrotoxicity (5) and is frequently used in humans after acetaminophen overdose. A safety profile has been established for this drug, and it is known to have no significant side effects. In an attempt to reduce renal toxicity, a trial of N-acetylcysteine was begun on the 8th day after the initial CP treatment and was given at the recommended dosage for the treatment of acetaminophen overdose (first dose of 140 mg/kg body wt, followed by 70 mg/kg every 4 h for 4 d). On the 2nd day of N-acetylcysteine therapy, the patient’s BUN and creatinine levels peaked at 103 mg% and 9.7 mg%, respectively, and then began to decline. On that same day, the patient was transferred to the medical intensive care unit in a picture of sepsis and disseminated intravascular coagulation. Four days after N-acetylcysteine was started, despite the patient’s critical condition, and while she was receiving a high dosage of pressors for blood pressure support, her urine output had in-
creased to 3 liters per day, and the following laboratory results were recorded: BUN, 71 mg/dl; creatinine, 6.4 mg/dl; ALT, 71; AST, 62 U/L; LDH, 1157 U/L; alkaline phosphatase, 28 U/L; total protein, 2.5 g%; albumin, 1.3 g%; total bilirubin, 4.5 mg%; and direct bilirubin, 3.5 mg%. However, the patient died of overwhelming sepsis, complicated by disseminated intravascular coagulation and severe leukopenia that was unresponsive to granulocyte macrophage colony-stimulating factor. The autopsy revealed acute tubular necrosis with atypical regeneration, edema, and microthrombi in the arterioles and capillary loops. Edema and microthrombi were also seen in other organs and were believed to be related to disseminated intravascular coagulation and not to a process specific to the kidneys.

A similar incident was reported by Chu et al. (6). Despite treatment with plasmapheresis and documentation of significant lowering of plasma CP level (from 2900 to 200 ng/ml), their patient developed end-stage renal disease and went on to receive a renal transplant.

**Discussion**

CP nephrotoxicity is dose-dependent and cumulative. A significant and transient elevation of serum BUN and creatinine levels is observed in most patients after a single dose of 40 to 100 mg/m² and cumulatively after subsequent cycles (4,7). At high doses, such as 100 mg/m² given over 5 days, a prolonged elevation of BUN and creatinine levels occurs in almost all patients and can last for more than 2 years (8).

The exact mechanism by which CP produces renal damage is still unknown. After a single dose of CP, there is preferential sequestration of the drug in the kidneys, liver, intestine, and testes, with concentrations in the kidneys being as high as 37 times those of plasma (9). Renal clearance of CP is a balance of glomerular filtration, tubular secretion, and absorption (10, 11). Morphologic changes are most prominent in S3 segments of proximal tubules, where loss of brush border membrane, cell swelling, nuclear condensation, and focal areas of tubular necrosis are seen. The reasons for selective necrosis of S3 regions of proximal tubule after CP administration is unclear. It is hypothesized that CP accumulates selectively in S3 segments secondary to secretion by the adjacent pars recta. Alternatively, hemodynamic changes caused by CP may lead to decreased circulation in the vasa recta, causing damage to the most susceptible adjacent regions that include S3 segments (12). Offerman et al. (13) found that a decrease in effective renal plasma flow precedes the decrease in GFR during CP infusion, suggesting that the primary effect of the drug may be on renal hemodynamics. However, CP can induce renal tubular cystic changes in metanephric organ culture, where there is no vascularization, glomerular filtration, or tubular urine formation (14). Nephron obstruction and increased intratubular pressure cannot develop in this *in vitro* system. Thus the cystic

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**Table 1. Patients’ laboratory results, record of fluid intake, urine output, and days of N-acetylcysteine therapy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cr</th>
<th>BUN</th>
<th>SGOT</th>
<th>SGPT</th>
<th>LDH</th>
<th>Total protein</th>
<th>Albumin</th>
<th>Total bilirubin</th>
<th>Direct bilirubin</th>
<th>Amylase</th>
<th>Alk. phos.</th>
<th>PT/PIT</th>
<th>IV intake/urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of last cisplatin dose is designated as day zero. Pertinent medications, hemodynamic recordings and events are listed relative to day zero.</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>1.3</td>
<td>20</td>
<td>91</td>
<td>90</td>
<td>227</td>
<td>7.0</td>
<td>4.1</td>
<td>0.8</td>
<td>0.3</td>
<td>72</td>
<td>68</td>
<td>13.4/31.8</td>
<td>/1000</td>
</tr>
<tr>
<td>Day 1</td>
<td>3.1</td>
<td>34</td>
<td>523</td>
<td>440</td>
<td>892</td>
<td>6.8</td>
<td>4.0</td>
<td>2.2</td>
<td>1.6</td>
<td>120</td>
<td>70</td>
<td>15.8/36.8</td>
<td>/1000</td>
</tr>
<tr>
<td>Day 2</td>
<td>4.1</td>
<td>50</td>
<td>1246</td>
<td>766</td>
<td>1627</td>
<td>5.2</td>
<td>3.0</td>
<td>3.0</td>
<td>2.1</td>
<td>1633</td>
<td>69</td>
<td>20.7/1351</td>
<td>/800</td>
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<tr>
<td>Day 3</td>
<td>5.8</td>
<td>70</td>
<td>585</td>
<td>467</td>
<td>1431</td>
<td>5.8</td>
<td>2.6</td>
<td>3.5</td>
<td>2.0</td>
<td>1530</td>
<td>62</td>
<td>1743/36.8</td>
<td>/900/400</td>
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<tr>
<td>Day 4</td>
<td>8.7</td>
<td>97</td>
<td>236</td>
<td>280</td>
<td>1304</td>
<td>1.3</td>
<td>2.4</td>
<td>3.5</td>
<td>3.5</td>
<td>2188</td>
<td>63</td>
<td>4.0/71/31.8</td>
<td>?/300</td>
</tr>
<tr>
<td>Day 5</td>
<td>9.7</td>
<td>103</td>
<td>183</td>
<td>280</td>
<td>1404</td>
<td>2.2</td>
<td>2.3</td>
<td>4.3</td>
<td>2.9</td>
<td>1743</td>
<td>63</td>
<td>4.3/174</td>
<td>2017/1351</td>
</tr>
<tr>
<td>Day 6</td>
<td>8.6</td>
<td>85</td>
<td>150</td>
<td>196</td>
<td>8569</td>
<td>3.9</td>
<td>2.3</td>
<td>4.3</td>
<td>2.9</td>
<td>2200</td>
<td>55</td>
<td>4.5/280</td>
<td>4921/2300</td>
</tr>
<tr>
<td>Day 7</td>
<td>6.4</td>
<td>71</td>
<td>130</td>
<td>174</td>
<td>1157</td>
<td>3.2</td>
<td>1.5</td>
<td>4.3</td>
<td>3.2</td>
<td>1360</td>
<td>27</td>
<td>3.5/280</td>
<td>6800/3000</td>
</tr>
</tbody>
</table>

*Day of last cisplatin dose is designated as day zero. Pertinent medications, hemodynamic recordings and events are listed relative to day zero. Day zero: last cisplatin dose; day 1: hearing, vision, and balance problems; day 3: renal consult suggests the use of N-acetylcysteine—no diuretic response to repeated doses of furosemide given intravenously; day 4: N-acetylcysteine was started—transfer to MICU in respiratory failure (ARDS)—thickened gallbladder wall and gallstones are observed on abdominal ultrasound study; day 5: patient is treated with dopamine, dobutamine, and levophed—PAWP 14, CVP 8, BP 91/51, MAP 63, PAP 34/20, Cl 3.1; day 6: blood pressure is 80 to 90/40 to 50, patient is lethargic, moves extremities spontaneously and withdraws to painful stimuli—dopamine, dobutamine, and levophed treatment is continued; day 7: blood pressure is 103/40, temperature is 99°, pulse is 124, CVP 161—patient is poorly responsive and dies later in the day.

Cr, creatinine; BUN, blood urea nitrogen; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; LDH, lactate dehydrogenase; Alk. phos., alkaline phosphatase; PT/PTT, prothrombin time/partial thromboplastin time.

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**N-Acetylcysteine Improves Cysplatin Nephrotoxicity**

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changes are probably a result of a direct effect of the drug on the tubular cells or supporting wall. Furthermore, functional studies show that CP nephropathy is not limited to S3 segments but, rather, involves the entire nephron. In a study of ten patients receiving CP, urine evaluation for immunoglobulin G (IgG) and albumin as parameters of glomerular function, α1-microglobulin, and N-acetyl-β-glucosaminidase (NAG) for proximal tubule function, and Tam Horsefall-protein (THF) for distal tubule function, CP led to an increase in urinary albumin, IgG, NAG, and THF when more than one course of CP was given (15). These findings suggest that CP causes changes in the function and/or structure of the entire nephron. It is evident that these changes occur rapidly, because β2-microglobulin is found in the urine as early as 12 hours after the administration of CP (16) in almost all subjects studied and persists for as long as 6 weeks after the last CP dose (17).

CP is heavily bound to plasma and cellular proteins, which accounts for the difficulty involved in clearing it from the circulation and tissue. It binds irreversibly to sulfhydryl groups of low- and high-molecular-weight molecules (18). This correlates with a fall in the concentration of renal sulfhydryl moieties, with the greatest decline occurring in the mitochondrial and cytosolic fractions (19). This binding inhibits a number of sulfhydryl-containing enzymes, including ATPases, thymidylate synthetase, gyceraldehyde-3-phosphate dehydrogenase, glucose-6-phosphate dehydrogenase, gamma-glutamylcysteine synthetase, and ribonucleotide reductase (20). Small molecules-bound CP can traverse cell membranes, is filterable, and can be excreted in the urine, whereas large molecules-bound CP is not (21). Hence, in addition to conventional therapy, beneficial anti-nephrotoxic modalities will likely be aimed at (1) competing with CP binding to large molecules (mostly proteins), (2) shifting the binding from large to small molecules, thus increasing the filterable fraction, and (3) replenishing the antioxidant pool, because CP appears to have an affinity for sulfhydryl groups in this pool.

In agreement with this analysis, it was found that sulfur nucleophile (sodium thiosulfate, sodium diethyldithiocarbamate, glutathione (GSH), sodium N-methyl-d-glucamine diethiocarbamate, and S-2-3-aminopropylamino-ethylphospho-orthio acid)—containing drugs offer the best protection against CP-induced renal damage in animal models and abrogate the hypomagnesemia and urine losses of Mg++, Na+, K+, and Ca++ that are associated with CP administration (22-24) (Table 2). Analysis of the comparative effectiveness of these different agents in the Sprague-Dawley rat model of CP nephrotoxicity suggests that GSH may be the most protective (22).

GSH is a non-protein sulfurl compound with numerous biological functions that include inactivation of peroxides and free radicals, protection of sulfhydryl groups of proteins, and detoxification of foreign substances (10). Administration of GSH increases the content of non-protein sulfhydryls in the kidney and protects against CP nephrotoxicity (20). Protection may be in part related to "sequestration" of CP in a small molecule-bound pool, where an estimated 30% of CP in the cytosolic fraction is bound to GSH (25). Thiosulfates bind to CP covalently, resulting in the production of complexes that are neither nephrotoxic nor cytotoxic (26). Moreover, this sequestration prevents interaction between CP and "critical cellular sites" and supports cell viability (10). On the other hand, depletion of the glutathione pool by use of buthionine sulfoximine, a selective inhibitor of γ-glutamylcysteine synthetase (the enzyme responsible for glutathione synthesis), increases the lethal toxicity of CP (20). Thus sulfhydryl groups are "consumed" by CP, and the concentration of free renal sulfhydrys correlates with the degree of protection from CP nephrotoxicity. Consistent with that, in a clinical study with escalating dosage of CP, the concurrent administration of sodium thiosulfate permitted a twofold increase in dose and total exposure to CP (26). Notably, no reduction of CP anti-tumor activity was found with GSH use (27).

Along the principles outlined earlier, selenium (sodium selenite) also offers protection from CP nephrotoxicity by binding to CP. Selenium is converted to methyl- and glutathionylelselenol, a bioactivation that is glutathione-dependent. Methylselenol forms complexes in vitro with CP, and it is believed that complex formation takes place in vivo and that the complexed CP is not nephrotoxic. Here too, reducing agents such as glutathione work in synergy with selenium, and the protection from platinum toxicity correlates with the higher level of selenium and glutathione in the kidney, compared with that of the tumor. However, the clinical application of sodium selenite remains limited because of its toxicity (28).

Table 2. Agents reported to have protective effects against cisplatin-induced nephrotoxicity, and their proposed mechanism(s) of action.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Proposed Mechanism of Action</th>
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<tbody>
<tr>
<td>Diuretics</td>
<td>Force intratubular debris and restore tubular patency</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Force intratubular debris and increase renal blood flow, thus increasing glomerular filtration rate</td>
</tr>
<tr>
<td>GSH—Glutathione and other reducing agents</td>
<td>Replenish sulfhydryl groups</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Binds and sequesters cisplatin in a nontoxic form</td>
</tr>
<tr>
<td>Selenium</td>
<td>Forms nontoxic complexes with cisplatin</td>
</tr>
<tr>
<td>Glycine</td>
<td>Unclear</td>
</tr>
<tr>
<td>Urinastatin</td>
<td>Inhibits lysosomal enzymes, which are released by cisplatin-induced tissue injury</td>
</tr>
<tr>
<td>CaCl$_2$</td>
<td>Protection of membrane enzymes and transporters and restores Ca stores</td>
</tr>
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</table>
N-acetylcysteine, a sulfhydryl compound donor that acts by replenishing glutathione, was shown to "completely abolish the nephrotoxic effects of CP" (5). Pretreatment of Wistar rats with N-acetylcysteine enhances CP excretion and decreases its renal tissue concentration, with a concomitant increase in urinary CP excretion and decreases its renal concentrations. Consistent with these findings, calcium channel blockers were reported to enhance CP-induced nephrotoxicity in the rat (30). Similar protection is obtained with a glycine infusion given concomitantly with CP (31), or with urinastatin, a Kunitz-type proteinase inhibitor that is proposed to decrease the effects of lysosomal enzymes released by CP-induced tissue injury (32).

Although we would like to believe that the improvement in renal function seen during therapy in this patient was related to the use of N-acetylcysteine, we cannot be certain that this is true, because of the patient's severe illness and death a short time after treatment was begun. In support of the potential benefit from N-acetylcysteine, we offer the following explanations: First, there was a temporal relationship between the recovery of urine output, the decline in BUN and creatinine levels, and N-acetylcysteine therapy (Figure 1). Second, there has been no report in the literature to suggest any recovery of renal function after such a dose, and irreversible renal damage has been reported with even modest CP dosages (33). In addition, the recovery of renal function that follows modest CP dosages normally occurs after a 2-week delay (4). Because the CP nephrotoxicity is dose-dependent, this time lag would likely be even longer, and the recovery of renal function would not be immediate, as was seen in this case. Last, the recovery of urine output was not facilitated by the use of diuretics and occurred in parallel with a deterioration in the hemodynamics that otherwise would produce the opposite outcome, that is, a decline in urine output. Hence, we would have anticipated a further decline in BUN and creatinine levels and an improvement in renal function if sepsis and death had not occurred. If we were to speculate on a possible mechanism for the improvement in renal function in this particular case, it would likely be related to the reductive capacity of N-acetylcysteine. Most of the administered CP is normally excreted in the urine within the first few hours, and the remainder is irreversibly bound to tissue proteins. Because no measurements of urine CP were made during the patient's illness, it would be difficult to determine whether N-acetylcysteine had any effect on the removal of CP from tissues and clearance in the urine. Additionally, N-acetylcysteine was administered at a stage when CP toxicity had already been established. Therefore, if it had any efficacy, it is likely to be related to the replenishment of glutathione and non-protein sulfhydryl stores, leading to diminished formation of free oxygen radicals and the maintenance of cellular reparative functions. It is interesting to note that some improvement in liver function tests occurred after N-acetylcysteine administration. In part, this improvement may be related to N-acetylcysteine; however, the occurrence of pancreatitis and, possibly, concomitant cholecystitis in this patient makes the interpretation of these findings difficult. Exploring the potential usefulness of N-acetylcysteine as an adjunct therapy in the management of CP nephrotoxicity, or in its prevention, may be worthwhile because decreasing nephrotoxicity may allow the administration of larger dosages of CP, with potential added anti-tumor benefits when myelosuppression is not a limiting factor. It remains to be seen how concomitant administration of N-acetylcysteine, which in theory should increase the renal clearance of CP, will affect its pharmacokinetics and anti-tumor effectiveness.

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Nephrology Training Program at Baylor College of Medicine–Renal Division

This program is designed to train fellows in the practice of clinical nephrology as well as to prepare future faculty members for careers in academic medicine by encouraging the pursuit of scientific endeavors at both the clinical and basic science levels. Two-year clinical or research tracks, or a three-year combined research and clinical track, are offered.

The clinical experience covers all aspects of clinical nephrology, including transplant service, inpatient consultation, outpatient clinic, peritoneal and hemodialysis, vascular access, hypertension, and fluid and electrolytes disturbances. Fellows rotate through the Methodist, Houston VA, and Ben Taub General hospitals and see patients in an outpatient dialysis facility. To encourage the individual pursuit of knowledge, to stimulate interests, and to expand exposure to new topics and information, the training program presents six to seven weekly didactic conferences, in addition to other Baylor departments’ and adjacent institutions’ vigorous seminar programs.

Members of the division are currently pursuing questions of potassium and calcium metabolism in bone and kidney cells, using state-of-the-art molecular biology techniques with the hope that the knowledge gained from these studies will provide insight into hypertension and bone disease in renal failure. Additionally, the division is investigating ion transport properties along the nephron, the role of adhesion molecules in obstructive uropathy, the treatment of dysnatremias and their complications, cell volume regulation, the molecular physiology of organic osmolyte transport, and gene regulation pertinent to the adaptation of kidney cells to osmotic stress. The laboratory is equipped for a wide range of techniques, including whole-animal physiology; isolated perfused tubule cell culture; enzyme-linked immunosorbent and receptor assays; radioimmunoassays; Western, Northern, and Southern analyses; in situ hybridization; immunoprecipitation; polymerase chain reactions; cloning; and the study of MAPK transduction pathways. Ongoing clinical research programs include the study of hypertension in renal disease, dialyzer membrane biocompatibility, and the effects of uremic toxins on myocyte function.