Cisplatin’s role in chemotherapy is crucial, as it is commonly used to treat multiple malignancies. However, one of the most concerning toxicities associated with its use is nephrotoxicity.

Following treatment with cisplatin, glomerular filtration rate (GFR) begins to decline, and is progressive with each additional treatment.1,2 Though the exact mechanism of toxicity is unknown, adequate hydration may reduce the risk of this serious and potentially irreversible adverse effect.

The theory behind using a diuretic, such as mannitol, along with saline is a logical one. By increasing diuresis one would assume the result would be decreased concentrations of cisplatin in the kidneys and therefore less nephrotoxicity. However, research shows mannitol, in addition to saline hydration, may actually produce significantly greater nephrotoxicity when compared to normal saline (NS) alone, or saline/furosemide hydration.

An article published in a 2003 edition of Cancer Chemotherapy Pharmacology, detailed a randomized trial conducted at the University of Texas by Santos, J.T., et al.2 The objective of the trial was to determine which hydration method was associated with the least cisplatin-associated nephrotoxicity. The trial included 49 women, whose chemotherapy regimen included cisplatin. Patients were randomized into one of the following three hydration treatment arms; saline, saline/furosemide (40 mg given 30 minutes prior to cisplatin), or saline/mannitol (50 grams mixed with cisplatin dose). All hydration regimens included 500 mL of NS infused over 2 hours prior to cisplatin therapy, 1000 mL of NS mixed with cisplatin dose, and 500 mL infused over 2 hours after cisplatin therapy.

Twenty-four-hour creatinine clearance (CrCl) was measured before each chemotherapy treatment and 6 days after the last treatment. The primary outcomes of interest were change in 24 hour CrCl from baseline (before the first dose) after the first dose and 6 days after completion of entire regimen. Those data are listed in Table 1 (mean +/- SD).

The results after the first dose of cisplatin revealed no significant difference in 24 hour CrCl between the saline and saline/furosemide group. However, the CrCl decrease in the saline/mannitol group was statistically significant in comparison. The data collected 6 days after the completion of the entire cisplatin regimen were analyzed and produced similar results. The differences in 24 hour CrCl between the saline and saline/furosemide groups were not significant. Significant decreases were observed in the saline/mannitol group when compared to the saline and the saline/furosemide groups.2

### ESCP Cisplatin Hydration Guidelines

<table>
<thead>
<tr>
<th>Hydration</th>
<th>NS @ 100 mL/h beginning at least 12 hours prior to cisplatin administration. Maintain adequate IV or oral hydration for at least 3 days after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Flow</td>
<td>3-4 times per hour the day prior to administration and 2-3 days after</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Do not use furosemide or mannitol</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>Monitoring between days 3 &amp; 5 after course completion may be most beneficial</td>
</tr>
</tbody>
</table>

### WHAT ABOUT CLINICAL GUIDELINES?

The most current guidelines pertaining to prevention of cisplatin nephrotoxicity are from the European Society of Clinical Pharmacy (ESCP) and were published in 2008. A portion of these guidelines has been provided for convenience in Table 2.

Obviously, the recommendation regarding a 12 hour pre-hydration may not always be feasible. It does, however, emphasize the importance placed on adequate hydration prior to cisplatin administration. The authors reason that this aggressive hydration regimen will induce sufficient diuresis and will cause the excess electrolyte loss associated with diuretic use.1 Evidence in favor of diuretic use to decrease cisplatin-induced nephrotoxicity is insufficient. Current ESCP guidelines recommend against using both mannitol and furosemide.2 Until benefits can be proven, perhaps the use of diuretics should be avoided in an attempt to prevent unintentional harm.
Those with great deal of experience will no doubt question the aforementioned study presented on page 1.

Notably, 50 grams of mannitol is a high dose, higher than many practitioners routinely use when trying to prevent nephrotoxicity associated with cisplatin.

Perhaps a more reasonable dose of mannitol would have been 12.5 grams, which seems to be used more commonly in practice.

In addition to this study, another important study by Al-Sarraf and colleagues is cited in the European Society of Clinical Pharmacy Interest Group on Cancer Care guidelines.

Al-Sarraf and colleagues compared hydration, hydration + furosemide, and hydration + mannitol in a randomized fashion to prevent cisplatin induced nephrotoxicity.

No significant difference was found on subsequent cycles between either group, although the mannitol group initially showed a protective effect after cycle 1. However, this benefit was lost in subsequent cycles.

These two studies by Santosos and Al-Sarraf comprise the best evidence we have to compare cisplatin-induced nephrotoxicity prevention strategies in a prospective and randomized fashion.

Unfortunately, a clear answer is not available. Therefore, practitioners must carefully weigh the risks and benefits of either treatment option.

This study nicely represents the difficulties in evaluating this evidence. While there are numerous design flaws with this study, it echoes what previous studies have shown:

1. Mannitol provides no consistent benefit over sodium chloride hydration alone.
2. Mannitol MAY be do more harm than good.

Overall, no significant difference in creatinine clearance reduction was found between the mannitol group (~38.8 mL/min) and the sodium chloride alone group (~33.9 mL/min).

However, more patients in the mannitol group had lung cancer, while more patients in the sodium chloride group alone and head and neck cancer.

Obvious study weaknesses include retrospective nature and lack of information on baseline demographics.

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