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Morgan Corbin

John B. Bossaer
East Tennessee State University, bossaer@etsu.edu

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Mannitol Prescribing Practices With Cisplatin Before and After an Educational Newsletter Intervention

Morgan Corbin[1] and John B. Bossaer[2]

Abstract

Background: Mannitol has been used in the past for the prevention of cisplatin-induced nephrotoxicity. Studies on its efficacy have conflicting results. An educational newsletter was designed for local oncologists on the conflicting data of mannitol use in preventing cisplatin-induced nephrotoxicity. **Purpose:** The purpose of this study was to determine whether a pharmacist-created newsletter intervention led to changes in the mannitol prescribing practices of local oncologists. **Methods:** A newsletter describing the paucity of evidence to support mannitol use to prevent cisplatin-induced nephrotoxicity was distributed via e-mail to local oncologists in October 2010. Mannitol prescribing rates were retrospectively evaluated before and after newsletter distribution. The Mann-Whitney *U* test was used to compare nonparametric continuous data. The chi-square test was used for nominal data. Descriptive statistics were performed for baseline demographics, and odds ratios were calculated for possible risk factors for acute kidney injury (AKI). The primary endpoint was a change in mean mannitol dose before and after the newsletter intervention. The secondary endpoint was the difference in the rate of AKI before and after the intervention. Data were collected for 67 patients with various malignancies. **Results:** There was a difference in the average mannitol dose before and after newsletter intervention ($P = .02$). The rates of AKI before and after newsletter were similar. **Conclusion:** A pharmacist-led newsletter intervention was associated with significantly decreased rates of mannitol usage after intervention.

Keywords

cisplatin, mannitol, prescriber education, prescribing habits

Cisplatin was the first platinum agent discovered to have oncological activities, and it is used in the treatment of many malignancies including testicular, head and neck, lung, gynecologic, and other cancers. Cisplatin causes significant toxicities such as nausea, vomiting, ototoxicity, electrolyte abnormalities, and nephrotoxicity. Nephrotoxicity was cisplatin's major dose-limiting adverse effect until pretreatment and posttreatment hydration became a standard preventive measure.[1] Despite this, nephrotoxicity may still occur, leading to dose delays and treatment cessation. Cisplatin's package insert states that 28% to 36% of patients treated with a single dose of cisplatin (50 mg/m^2) can experience nephrotoxicity, which is manifested as elevations in blood urea nitrogen and serum creatinine (SCr).[2] In addition to hydration, forced diuresis with mannitol has been used to minimize cisplatin-induced nephrotoxicity.

Mannitol is an osmotic diuretic that is indicated for the promotion of diuresis; it is a logical choice for reduction of cisplatin-induced nephrotoxicity as it is nontoxic and could reduce the half-life of cisplatin in the kidney.[3] However, studies have not demonstrated a clearly consistent benefit of mannitol use in preventing cisplatin-induced nephrotoxicity.[4-6] Readers are referred to a thorough review of this topic for more in-depth information, which concluded, "There are no compelling data that the addition of mannitol is more nephroprotective than the use of hydration alone."[7] In reflection of this, an educational newsletter was prepared and e-mailed to oncologists on the lack of data to support mannitol's use for preventing cisplatin-induced nephrotoxicity with the hope of decreasing mannitol prescribing. The objective of this study was to determine whether a pharmacist-created newsletter intervention led to changes in the mannitol prescribing practices of local oncologists.

[1]University Health, Shreveport, LA, USA
[2]East Tennessee State University, Johnson City, TN, USA

Supplemental material is available in the online version of the article.

Corresponding Author:
John B. Bossaer, Associate Professor of Pharmacy Practice, Bill Gatton College of Pharmacy, East Tennessee State University, Box 70657, Johnson City, TN 37614, USA.
Email: bossaer@etsu.edu

Methods

Study Design

Educational newsletters were developed monthly by Advanced Pharmacy Practice Experience (APPE) students. Topics were selected by the APPE preceptor (J.B.B.) who edited the newsletter after the revision process. Topics focused on supportive care of oncology patients and techniques to minimize toxicity from chemotherapy. To encourage readability, the newsletters were short (1-2 pages) and included figures or tables to easily communicate information. In October 2010, an educational newsletter (eAppendix) was delivered electronically to all institutional oncologists, oncology nurses, and oncology pharmacists that described the state of evidence at that time for using mannitol to prevent cisplatin-induced nephrotoxicity.

To determine whether the newsletter changed prescribing practices, a retrospective chart review of patients treated for the first time with cisplatin at Johnson City Medical Center (JCMC) and the Regional Cancer Center (RCC) was conducted. Patients were identified by pharmacy billing records for cisplatin followed by a review of electronic medical records. This study was approved by East Tennessee State University Institutional Review Board.

Study Population and Data Collection

JCMC is a 445-bed community hospital and a member of the Mountain States Health Alliance (MSHA). The MSHA RCC includes a 21-bed outpatient infusion suite and physician clinics. Patients receiving their first dose of cisplatin at JCMC or RCC during the study period were included. The study period included prenewsletter (January 1, 2010, to June 30, 2010) and postnewsletter (January 1, 2011, to December 31, 2011) cohorts around the time of newsletter publication (October 2010) with a 6-month gap to allow for diffusion of information. Patients younger than 18 years, those who initiated cisplatin treatment outside the study periods, and those with incomplete medical records were excluded.

Information regarding each patient's cancer diagnosis and stage, nephroprotective strategy for cisplatin (including mannitol use and dose), demographics, diabetes or hypertension history, treatment regimen (monotherapy or in combination with either chemotherapy or radiation therapy), the use of concomitant nephrotoxins, prescriber, use of feeding tube, cisplatin dose and number of doses, baseline SCr and creatinine clearance (CrCl) (including peak SCr and CrCl), and acute kidney injury (AKI) incidence, grade, and time to AKI were recorded. In the case of AKI, a grade of 0 to 5 was assigned based upon the Common Terminology Criteria for Adverse Events version 4.0.[8]

Statistical Analysis

The Mann-Whitney *U* test was used to compare nonparametric continuous data. The chi-square test was used for nominal data. Descriptive statistics were performed for baseline demographics, and a univariate analysis was performed with odds ratios calculated for possible risk factors for cisplatin-induced nephrotoxicity (cisplatin dose, mannitol use, hypertension, diabetes, female gender, feeding tube, radiation therapy, and concomitant nephrotoxin use). All statistical analyses were calculated using PASW Statistics 18 (SPSS, Chicago, Illinois).

The primary endpoint was the change in mean mannitol dose prescribed before and after the newsletter intervention. Secondary endpoints included rate of AKI before and after the newsletter intervention and possible risk factors for AKI.

Results

A total of 85 patients were identified via the pharmacy database; 18 were excluded, leaving a total of 67 patients for statistical analysis. Reasons for exclusion included being previously treated with cisplatin (14 patients), incomplete medical records for assessment (1 patient), and age younger than 18 years (3 patients). Thirty patients were included in the prenewsletter cohort, and 37 patients were included in the postnewsletter cohort.

Demographics

The patients' demographic data for both the prenewsletter and postnewsletter cohorts are summarized in Table 1. Patients were almost entirely Caucasian, and there was an approximately equal gender distribution. The median age of the prenewsletter cohort was 59 years (range, 33-74 years), and the median age of the postnewsletter cohort was 57 years (range, 40-76 years). Patient characteristics were similar between the prenewsletter and postnewsletter cohorts with the exception of primary tumor sites. In the prenewsletter cohort, more patients had lung cancer or other as the primary tumor site, whereas in the postnewsletter cohort, more patients had head/neck as the primary tumor site. Most patients in the prenewsletter cohort were receiving radiation (66.67%) and other chemotherapy (76.67%). The majority of patients in the postnewsletter cohort were also receiving radiation (81.08%) and other chemotherapy (83.78%). Patients in both cohorts were likely to be on concomitant nephrotoxins: 83.3% in the prenewsletter cohort and 97.3% in the postnewsletter cohort. Mean baseline renal function was normal in both cohorts.

The average dose of mannitol (Table 2) in the prenewsletter cohort was 12.75 g, with the average dose of mannitol in the postnewsletter cohort decreasing to 4.14 g ($P = .02$). The average cisplatin dose in the prenewsletter group was 59.4 mg versus 54.9 mg in the postnewsletter group ($P = .34$).

Table 1. Patient Characteristics (N = 67).

Characteristic	Prenewsletter cohort (n = 30)	Postnewsletter cohort (n = 37)
Age, y		
Median	59	57
Range	33-74	40-76
Sex		
Male	15 (50)	20 (54.1)
Race, n (%)		
Caucasian	28 (93.3)	35 (94.6)
African American	1 (3.3)	0 (0)
Other	1 (3.3)	2 (5.4)
Primary tumor site, n (%)		
Head/neck	6 (20)	32 (86.5)
Lung	17 (56.7)	5 (13.5)
Other	7 (23.3)	0 (0)
Stage, n (%)		
Locally advanced	16 (53.3)	18 (48.6)
Metastatic	14 (46.7)	19 (51.4)
Comorbidities, n (%)		
Diabetes	6 (20)	5 (13.51)
Hypertension	16 (53.33)	21 (56.76)
Feeding tube, n (%)		
Yes	4 (13.33)	8 (21.62)
Radiation, n (%)		
Yes	20 (66.67)	30 (81.08)
Chemotherapy, n (%)		
Combination	23 (76.67)	31 (83.78)
Concomitant nephrotoxin	25 (83.3)	36 (97.3)
NSAID	8 (26.7)	8 (21.6)
ACE/ARB	12 (40)	11 (29.8)
Diuretic	8 (26.7)	9 (24.3)
Other (eg, IV contrast)	18 (60)	35 (94.6)
Baseline renal function		
SCr, mg/dL	0.81	0.76
CrCl, mL/min	109.9	112.5

Note. NSAID = nonsteroidal anti-inflammatory drug; ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; SCr = serum creatinine; CrCl = creatinine clearance; IV = intravenous.

Table 2. Results Before and After Newsletter Implementation.

	Before newsletter (n = 30)	After newsletter (n = 37)	*P* value
Cisplatin dose, average	59.4 mg	54.9 mg	.34[a]
Mannitol dose, average	12.75 g	4.14 g	.02[a]
Rate of AKI	40%	43%	.79[b]
AKI grade, median	1	1	.985[c]

Note. AKI = acute kidney injury.
[a]Mann-Whitney *U* test.
[b]Chi-square test.
[c]Independent-samples median test.

Table 3. Univariate Analysis of Acute Kidney Injury.

	Odds ratio	95% CI
Feeding tube	2.27	0.67-8.07
Radiation therapy	2.04	0.63-6.67
Hypertension	1.89	0.70-5.13
Cisplatin dose >75 mg/m^2	1.55	0.58-4.16
Nephrotoxin	1.49	0.25-8.74
Mannitol use	1.46	0.53-4.03
Diabetes mellitus	1.19	0.326-4.39
Female gender	0.71	0.57-1.89

Note. CI = confidence interval.

Of the 67 patients, 12 (40%) in the prenewsletter group experienced any grade AKI, whereas 16 (43%) in the postnewsletter group experienced any grade AKI ($P = .79$; Table 2). No risk factors were identified for AKI (Table 3).

Discussion

A newsletter as part of a comprehensive pharmacist-led education program has been shown to influence prescribing behavior.[9] Our 2-page newsletter appeared to change prescriber behavior as well but, as with any retrospective study, uncontrolled confounders may exist. One factor that may have affected mannitol prescribing was education regarding cisplatin nephroprotection strategies on inpatient rounds. After the newsletter was distributed, the clinical pharmacist on the inpatient rounding service began reviewing the data presented in the newsletter on a patient-specific basis when cisplatin was prescribed. The influence of this face-to-face education on the results was likely mitigated by allowing a 6-month gap between cohorts for diffusion of information.

Given that higher doses (>75 mg/m^2) of cisplatin were not associated with nephrotoxicity, the study population may have been underpowered due to its small sample size (N = 67). In addition, there may be confounding differences in baseline demographics. The prenewsletter group consisted primarily of lung cancer patients (56.7%), whereas the postnewsletter group consisted primarily of head and neck cancer patients (86.5%). As different chemotherapy regimens are used for different malignancies, this could have affected the results. However, the similar mean cisplatin dose in both cohorts argues against this. Our study also suffers from the inherent limitations of retrospective studies.

Mannitol's role as a nephroprotective agent remains unclear. Morgan et al[10] published data from a quasi-experiment recently that differed from previous studies; they presented evidence that mannitol does decrease cisplatin-induced nephrotoxicity. There were methodological differences between the study by Morgan et al and our study, including stricter inclusion criteria as patients could only have received cisplatin monotherapy for

any nongynecological solid tumor. The study also had a larger patient population (N = 143) than our study, with 3 different cisplatin dosing groups assessed. Another key difference was a standard mannitol regimen in which all doses were the same compared with community-based dosing dependent on physician preference. Unfortunately, our study focused primarily on mannitol prescribing practices and therefore could not control the many confounders affecting cisplatin-induced AKI.

Despite several retrospective studies and limited randomized studies, the effect of mannitol on preventing cisplatin-induced nephrotoxicity remains unclear. Given cisplatin's widespread utility in the oncology world, reliable evidence-based guidelines for preventing cisplatin-induced nephrotoxicity are needed. Prospective research should be considered a top priority to better address this concern.

Conclusion

A pharmacist-led newsletter intervention to educate prescribers appeared to change prescribing practices of mannitol. No risk factors were identified, including mannitol use, for cisplatin-induced nephrotoxicity. Randomized trials are needed to truly assess any benefit from mannitol use in patients receiving cisplatin.

Declaration of Conflicting Interests

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