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Combined intravenous and oral mesna in outpatients treated with ifosfamide

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Abstract *Purpose*: To prevent hemorrhagic cystitis, mesna is typically injected intravenously (IV) at the time of an ifosfamide dose and 4 and 8 h later. To simplify outpatient ifosfamide therapy, we gave the second and third mesna doses orally. *Methods*: The mesna doses (400 or 600 mg/m^2) were 40% (w/w) of each ifosfamide dose (1.0 or 1.5 g/m^2), which was given daily for 5 days. We evaluated urinary mesna excretion and plasma concentrations in ten patients from the beginning of mesna infusion until the time of the second oral dose. The first oral dose was administered at hour 2 in the last six patients to allow time for absorption of mesna. *Results*: The rate and amount of mesna excretion was less variable over time and among patients after oral than after IV administration. No macrohematuria was observed in these ten patients nor in an additional 50 patients given oral mesna at hours 2 and 8 during at least two cycles of ifosfamide therapy. *Conclusion*: These pharmacokinetic and clinical efficacy data support the use of a combined regimen of IV and oral mesna to simplify outpatient ifosfamide administration.

Key words Mesna · Oral administration · Urinary excretion · Ifosfamide · Outpatient therapy

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Introduction

Hemorrhagic cystitis, a complication of ifosfamide and cyclophosphamide therapy, can be averted by concomitant administration of mesna (sodium 2-mercaptoethanesulfonate) [1]. Mesna is typically injected intravenously (IV) at 4-h intervals for at least 8 h after doses of ifosfamide. The inconvenience of this schedule for outpatients has prompted practitioners to administer the second and subsequent doses of mesna orally. The safety and efficacy of oral mesna has been documented [5], and the pharmacokinetics of single-dose oral mesna have been studied in healthy adult volunteers [2, 6–8]. We determined the urinary and plasma disposition of free-thiol mesna and its inert disulfide, dimesna, during a combined IV and oral mesna regimen in patients receiving ifosfamide. We measured the concentrations of these compounds in the urine and plasma of ten patients to characterize the absorption and to compare the rates of excretion after IV versus oral administration, and we assessed the efficacy of a combined IV and oral mesna regimen in an additional 50 patients.

Methods

Patients and drug administration

Ten patients aged 23 to 72 years with advanced disease and various tumor types and sites participated in pharmacokinetic studies (Table 1) after informed consent had been obtained. Patients 3 and 5 had retroperitoneal masses and patients 6 and 9 had diabetes mellitus. Seven patients had received earlier platinum therapy. Patient 8 had had a nephrectomy several months before the study. The creatinine clearances (range 34 to 137 ml/min) were predicted from the patients' serum creatinine concentrations (range 0.8 to 3.3 mg/dl) and their age, weight, and sex [3]. Six patients received single-agent ifosfamide (1.5 g/m^2) and three mesna doses (600 mg/m^2) daily for 5 days. The remaining four patients received 1 g/m^2 ifosfamide per day and three 400 mg/m^2 mesna doses; the combination chemotherapy administered to these patients included cisplatin in three cases. The daily hydration volume was at least 2400 ml. Ampules of mesna (Mesnex Injection, Bristol-Myers

Table 1 Patient characteristics

Patient no.	Age	Sex	Type of carcinoma	Nephrotoxic chemotherapy		Creatinine clearance[a] (ml/min)	Mesna dose (mg/m^2)
				Previous	Concurrent		
1	61	M	Hepatocellular	Cisplatin, Carboplatin	None	64	600
2	64	M	Lung	Carboplatin	None	64	600
3	72	F	Colon	None	None	50	600
4	48	M	Lung	None	None	40	600
5	23	M	Testicular	Cisplatin, Ifosfamide	Cisplatin	137	400
6	64	M	Lung	Cisplatin	None	88	400
7	62	M	Renal cell	Carboplatin, Cisplatin	None	55	600
8	58	M	Renal cell	None[b]	None	34	600
9	66	M	Lung	Carboplatin	Cisplatin	89	400
10	63	M	Lung	Carboplatin	Cisplatin	89	400

[a]Predicted creatinine clearance based on serum creatinine, age, weight, and sex [3]
[b]Nephrectomy

Squibb, New Jersey) were used for both the oral (in at least 30 ml of a cola) and IV doses. A dose of mesna equal to 40% (w/w) of the ifosfamide dose was injected IV beginning at time 0 for 13 to 40 min. This IV dose was followed by two oral doses (each also 40% of the ifosfamide dose) at hours 4 and 8 in patients no. 1 and 2 (Table 1), at hours 3 and 8 in patients no. 3 and 4, and then at hours 2 and 8 in the remaining six patients. Microscopic hematuria was evaluated daily before the delivery of the ifosfamide dose and was considered to be positive if there were more than 50 red blood cells per high power field. The incidence of gross hematuria, nausea, vomiting, and diarrhea was assessed in 50 additional patients who received at least two cycles of ifosfamide and IV–oral mesna therapy according to the 0-, 2-, and 8-h schedule.

Specimen collection and processing

Urine was collected after the IV mesna dose for 8 h at hourly intervals. The mesna in aliquots of urine was stabilized by adding ethylene diaminetetraacetic acid (EDTA) and hydrochloric acid to final concentrations of 0.22% and 0.09 *N*, respectively. Blood samples were obtained immediately after and at 10, 20, 30, 60, and 90 min after IV mesna injection, at the time of the first oral dose, and then hourly until the second oral dose. Two parts of blood were added to one part of 5% EDTA, and the mixture was immediately centrifuged for 5 min. Two parts of the supernatant plasma were mixed with one part of perchloric acid (1 *M*) to prepare a protein-free supernate. All plasma samples were deproteinized and frozen within 26 min of collection (median 12 min). The samples were stored at −24 °C for up to 9 days (median 4 days) and shipped on dry-ice to St. Jude Children's Research Hospital, where they were stored at −70 °C (median 10 days) until analyzed. The samples were analyzed within 3 weeks except for patient no. 1 (4 weeks) and patient no. 3 (5 weeks).

Assay methods

Mesna and dimesna were separated by ion pairing reverse phase chromatography and quantitated by postcolumn sulfitolysis, reaction with 2-nitro-5-thiosulfobenzoate, and spectrophotometric detection at 412 nm [4]. All urine and blood samples from a patient were assayed together. Each assay was calibrated with aqueous standards, which produced values identical to those obtained with protein-free plasma or urine matrices in method validation assays. The lower limit of quantitation was 3.3 μ*M* for both mesna and dimesna when 100 μl urine or 600 μl protein-free plasma were injected in the validation studies. Between-run coefficients of variation for the assay at 5 μ*M*, 50 μ*M*, and 200 μ*M* were 17%, 19%, and 2.3% for mesna and 21%, 11%, and 6.9% for dimesna, respectively.

Urine validation studies

When added to preserved urine samples, mesna and dimesna were stable for at least 1 week at −24 °C and for 3 months at −70 °C.

Blood validation studies

When added to whole blood, dimesna was completely recovered when samples were deproteinized within 10 min; by contrast, only 57% to 65% of added mesna was detected. Protein-free plasma controls containing 20, 50, or 100 μ*M* dimesna showed no change in their respective concentrations when stored at −24 °C for 10 weeks or at −70 °C for 5 months. By contrast, mesna values in similar control samples stored at −24 °C decreased by 26% to 45% after 1 week and by 68% to 83% after 10 weeks. When stored at −70 °C for 5 months, protein-free plasma controls containing 20 μ*M* or 50 μ*M* mesna showed decreases of 27% and 19%, respectively. To minimize the instability of plasma mesna, the samples were analyzed within 3 weeks in all but two instances.

Plasma pharmacokinetics

The pharmacokinetic parameters of the IV mesna dose were computed by fitting the data for plasma samples obtained up to 90 min postinfusion to a one-compartment open model (PCNONLIN Version 3.0, SCI Software, Lexington, Ky.). Parameters were computed for plasma concentrations of mesna, dimesna, and the sum of the mesna concentration plus twice the dimesna concentration. To estimate a volume of distribution for the metabolite dimesna, the dose was assumed to be one-half that of the mesna dose. The adequacy of modeling was affirmed by the low overall averages of the standard errors which were 9% for the apparent volume of distribution, 13% for the half-life, 6% for the maximum concentration, and 8% for the area under the concentration-time curve (AUC); in addition, the ratio of the AUC computed by the trapezoidal method to the model-estimated AUC was 0.88 for mesna, 0.76 for dimesna, and 0.91 for the sum of mesna and twice the dimesna concentrations. A two-compartment model for IV delivery did not provide acceptable precision of fit, probably because there were too few data points. Pharmacokinetic analysis of oral mesna was limited to a determination of the AUC by the trapezoidal method between hours 2 and 8 in patients no. 5–10.

Results

Urinary excretion

Figure 1A shows the rate of excretion of free-thiol mesna for the six patients who received oral mesna at 2

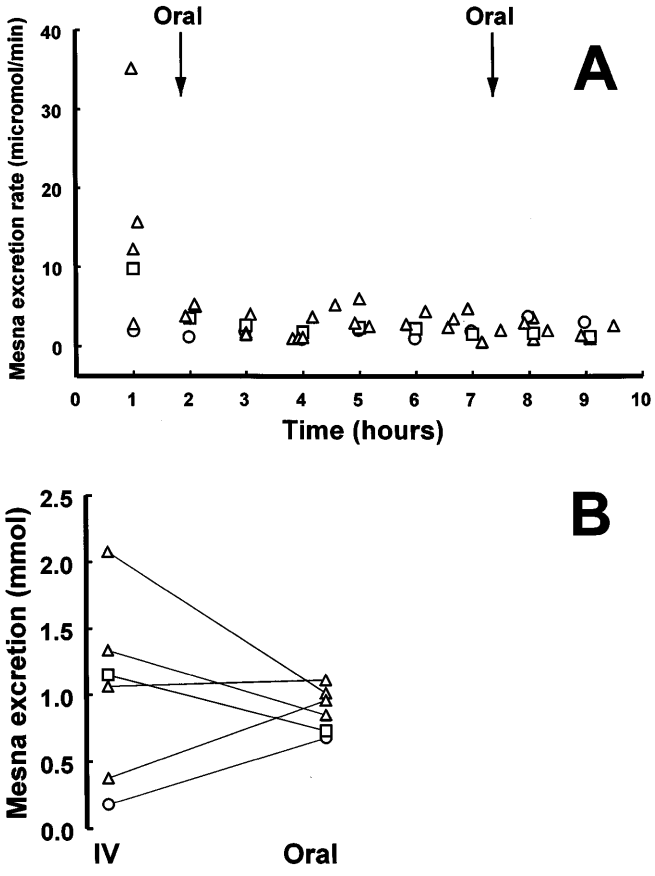

Fig. 1A,B Urinary excretion of mesna in the six patients given an IV dose of mesna with ifosfamide at time 0, followed by an equivalent oral dose 2 h later: **A** rate of mesna excretion; **B** cumulative amount of mesna excreted during the 2 h after the IV dose and during the 6 h after the oral dose (*triangles* patients who received 400 mg/m^2 mesna, *circles* a patient who received 600 mg/m^2 mesna, *squares* a patient with a unilateral nephrectomy who received 600 mg/m^2 mesna)

and 8 h. Although adjusted for urine output, the excretion rate varied from 2 to 35 μmol/min during the first hour after IV administration. After oral doses, the excretion rate varied over a narrower range (1 to 6 μmol/min) and remained constant between hour 2 and hour 8. Figure 1B shows that the amount of mesna excreted after the IV dose (mean ± SD, 1.03 ± 0.69 mmol) was similar to that excreted after the first oral dose (0.89 ± 0.17 mmol); again, the range was narrower after oral administration. Patient no. 7 excreted the least mesna after IV delivery despite receiving the larger dose (600 mg/m^2) and having a substantial urine flow (850 ml in 2 h). In the patient (no. 8) with a single kidney and the lowest creatinine clearance rate, mesna excretion was nevertheless similar to that of the other patients. The cumulative mesna excretion through hour 8 for the six patients ranged from 6% to 29% (mean 18%) of the administered IV plus first oral mesna dose, showing more than fourfold interpatient variation that was associated mostly with the IV dose (Fig. 1B). Mesna excretion was not complete by the time of the second oral dose at 8 h. The mesna as a percentage of the sum of mesna and dimesna in the urine samples after IV delivery (20% to 56%, mean 41%) did not differ from that after oral administration (17% to 62%, mean 37%), suggesting that the proportion of excreted mesna that is available for uroprotection is not affected by the route of administration.

Plasma concentrations and pharmacokinetic parameters

Plasma concentrations of mesna and dimesna were evaluated after IV and oral doses to complement the analysis of urinary excretion. Figure 2 shows the pharmacokinetic parameters for the IV dose in each of the ten patients. The means of the volumes of distribution for mesna (mean ± SD, 30 ± 8.3 l) and dimesna (36 ± 13 l) were higher than the mean of those for the mesna–dimesna sum (21 ± 5.5 l). The sum may better reflect the volume of distribution of the drug by accounting for intravascular oxidation of mesna to dimesna. The mesna AUC was higher than that for dimesna in three patients, which might be explained by a capacity to maintain mesna in its reduced form by these individuals, or by preanalytical instability of mesna in samples from the other patients. The mesna AUC values for patients no. 1 and 3 whose samples were analyzed after 4 and 5 weeks of storage, respectively, were nevertheless close to the median value.

The predicted creatinine clearance was significantly correlated both to the half-life ($r = -0.62$, $P = 0.03$)

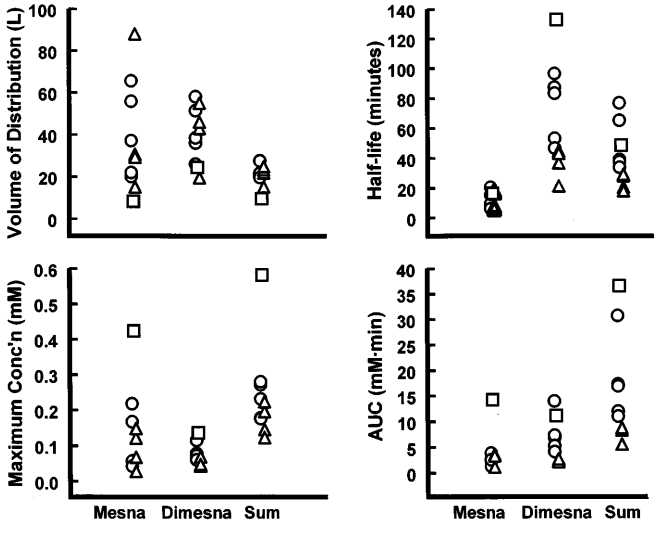

Fig. 2 Plasma pharmacokinetic parameters for the IV mesna dose in all ten patients. The volume of distribution, half-life, and maximum concentration were estimated by a one-compartment open model. Areas under the concentration-time curves (AUC) were determined by the trapezoidal method (*Sum* parameters for the sum of mesna plus twice the dimesna concentration, *triangles* patients who received 400 mg/m^2 mesna, *circles* patients who received 600 mg/m^2 mesna, *squares* a patient with a unilateral nephrectomy who received 600 mg/m^2 mesna)

and to the AUC ($r = -0.59$, $P = 0.04$) of plasma dimesna. The four patients (no. 5, 6, 9, 10) who had the highest predicted creatinine clearance values (Table 1) showed the shortest half-lives for dimesna and for the mesna–dimesna sum (Fig. 2). The patient (no. 8) who had only one kidney and the lowest creatinine clearance showed the longest dimesna half-life, and the highest maximum concentration and AUC for both mesna and the mesna–dimesna sum. These plasma data support glomerular filtration as the principle mode of elimination.

The absorption of mesna required several hours; plasma mesna concentrations peaked at 2 to 4 h after the first oral dose (data not shown). In the six patients dosed at hour 2, the AUC of the mesna–dimesna sum during the 6 h after the first oral dose was 86% (mean) of the sum excreted during the 2 h after the IV dose (data not shown). These data further demonstrate sustained absorption and excretion of the oral mesna dose.

Efficacy

Adverse effects of the IV–oral mesna regimen were negligible. One of the ten patients in the pharmacokinetic study developed gross hematuria associated with a urinary drainage catheter. None of the remaining nine patients in that group had microscopic hematuria, and none of the additional 50 patients had gross hematuria. One patient refused a single oral mesna dose because of nausea after ifosfamide and cisplatin. He did not develop hematuria and successfully completed the remainder of the IV–oral mesna regimen.

Discussion

Oral administration of mesna can facilitate ifosfamide therapy in an outpatient setting. The goal of our study was to begin developing guidelines for administration of oral mesna based on measurements of the drug in the blood and urine. Appropriate scheduling depends on the length of time required for absorption of mesna from the gastrointestinal tract. To establish the size of the dose, one needs to know how much mesna is excreted into the urine in its active form after equivalent IV and oral doses. Finally, oral mesna administration must be as effective as IV administration in the prevention of hemorrhagic cystitis.

The approved schedule for IV administration of mesna includes injections equivalent to 20% (w/w) of the ifosfamide dose at 0, 4, and 8 h. In our study, we set the oral doses to 40% of the ifosfamide dose because mesna bioavailability is reported to be about 50% [6]. The IV mesna dose was increased to 40% to enable direct comparison of the excretion after IV and oral doses, and to ensure adequate urinary concentrations throughout the absorption phase of the first oral dose. We subsequently changed the time of the first oral dose from 4 h to 3 h, and then to 2 h to compensate for the time required for absorption. Our regimen of administering mesna at hours 0, 2, and 8 was well tolerated despite chemotherapy that included nausea-inducing drugs, and it prevented ifosfamide-induced hemorrhagic cystitis. Some of our patients excreted only a small proportion of their mesna doses as free thiol; however, they still showed no microhematuria. Subsequent clinical studies have shown that an IV mesna dose equal to 20% of the ifosfamide dose is sufficient for the first dose of the IV–oral regimen [5].

The proportion of the oral mesna dose that was excreted as free thiol over 6 h in our study (mean ± SD, 8% ± 3.2%; $n = 6$) was similar to that excreted over 4 h as reported by James et al. (10.7% ± 7.0%; $n = 6$) [6], but lower than that excreted in other studies over 4.5 h (24.2% ± 9.0%; $n = 5$) [7] and over 23 h (53%; $n = 8$) [2]. These results may differ because we and James et al. used a more specific analytical method. In addition, we studied patients receiving ifosfamide; the subjects in the other three studies were healthy volunteers who received mesna only. Ifosfamide metabolites may bind to and reduce mesna concentrations.

Excluding the patient with a nephrectomy, the maximum plasma mesna concentrations (range 42 to 218 μM; mean 108 μM) after IV doses of 600 mg/m^2 (800 to 1200 mg/dose) in our patients were similar to those (73 to 164 μM) in six volunteers who each received 800 mg IV mesna doses as reported by James et al. [6]. The half-lives for mesna (6 to 21 min) and dimesna (47 to 96 min) in our patients also were similar to those reported for those same volunteers (17 to 26 min and 52 to 107 min, respectively). Stofer-Vogel et al. [8] reported higher values for the maximum mesna concentration (mean 511 μM) and half-life (38 min) in eight volunteers who received 1200 mg mesna IV, which might be explained in part by the more rapid infusion of mesna in 2 min.

The brief half-life of free-thiol mesna is explained in part by its oxidation to dimesna. Dimesna, which has a longer half-life, appears to act as a reservoir; upon passing through the kidney dimesna is reduced to the active free thiol mesna which is excreted into the bladder, neutralizing toxic metabolites of ifosfamide in the urine. Pharmacokinetic parameters for the sum of mesna and dimesna in the plasma may more accurately reflect the disposition of the drug than for either form alone because both forms lead to uroprotection.

It appears that renal clearance is not the only mode of elimination of mesna and dimesna in patients. If mesna and dimesna do not penetrate tissues and do not bind to other compounds, the theoretical volume of distribution would be close to that of plasma water (approximately 3 l). Our estimated volume of distribution based on the sum of mesna and dimesna in the plasma is 21 l. The reaction of mesna with other thiols, disulfides, aldehydes and other compounds in plasma as well as extravascular losses may account for the difference between this theoretical and the computed volumes of distribution.

The patient who had a single kidney showed the lowest volumes of distribution for mesna and for the mesna–dimesna sum, the highest values for the maximum concentrations and AUCs (second highest for dimesna), and the longest dimesna half-life. Other patients who had low predicted creatinine clearances also showed long half-lives. In spite of these findings, we do not recommend dose adjustments based on the creatinine clearance because the mesna excretion rates in these patients were similar to those in patients with normal renal function.

These pharmacokinetic and clinical efficacy data support the use of a combined regimen of IV and oral mesna to simplify outpatient ifosfamide administration. Urinary mesna excretion was not complete by 6 h after the first oral dose, suggesting that oral administration provides a therapeutic advantage of sustained bioavailability. The optimal dosage and scheduling remain to be defined. Mesna scheduling for children or for patients receiving more intense ifosfamide regimens may also require further consideration.

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