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ORIGINAL ARTICLE

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Urine mesna excretion after intravenous and oral dosing in ifosfamide-treated children

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Abstract *Purpose*: To describe mesna excretion in children. *Patients and methods*: We studied 14 children (aged 1–18 years) who received 1.8 g/m^2 of ifosfamide per day for 5 days. For uroprotection, the children were given intravenous mesna (equal to 20% of the ifosfamide dose) followed by two oral doses (each equal to 40% of the ifosfamide dose). The concentrations of mesna and the metabolite dimesna were measured in urine samples collected on treatment days 1 and 5. *Results*: Of 14 patients enrolled, 11 (aged 4–18 years) were evaluable. The profiles of mesna excretion rates were similar on days 1 and 5. Mesna excretion declined rapidly over 1–2 h after intravenous dosing. Increases in mesna excretion after oral dosing lagged by 2–4 h. About 21% of the mesna administered was excreted unchanged over 24 h on both days 1 and 5. The proportion excreted varied by severalfold between patients, but there was no association with age. *Conclusion*: The profile of mesna excretion after intravenous and oral dosing in these children was similar to that in reported studies of ifosfamide-treated adults.

Keywords Urine · Mesna · Oral administration · Children

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Introduction

Mesna is coadministered with ifosfamide to reduce the incidence of hemorrhagic cystitis [1, 3]. When given by intravenous (i.v.) injection, mesna doses are repeated every 4 h because the half-life of mesna is shorter than that of ifosfamide. Interest in an oral formulation for outpatients led to the development and regulatory approval of mesna tablets [2]. The recommended dose and schedule for oral mesna is 40% of the ifosfamide dose at 2 h and 6 h after an initial i.v. dose of 20% at the time of ifosfamide infusion [2, 8]. This regimen for oral mesna is supported by clinical and pharmacokinetic studies in adult populations [2, 7]. Oral mesna should produce a similar profile of urine excretion in children because of its limited metabolism and distribution. However, there are no pediatric data. We studied mesna excretion in children at a single institution for comparison with procedurally similar reported studies in adults [5, 7].

Patients and methods

Ifosfamide and mesna treatment

Enrolled in the study were 14 pediatric patients after providing informed consent. The study was approved by the institutional review board of A.C. Camargo Hospital, São Paolo, Brazil. Each child received single-agent ifosfamide (1.8 mg/m^2) and mesna therapy for 5 days. The mesna regimen included an i.v. dose of mesna equal to 20% of the ifosfamide dose at the time of ifosfamide infusion followed by two oral doses. Each oral mesna dose was equal to 40% of the ifosfamide dose. There were two oral mesna schedules. In the first seven patients, i.v. mesna was administered at the time of ifosfamide infusion, and then oral mesna was administered at hours 4 and 6 in lieu of i.v. doses. After review of these data, oral mesna was administered to patients

8–14 at hours 2 and 6 after the i.v. mesna dose. Mesna was supplied by the former Asta Medica (now Baxter Oncology) in ampoules at 100 mg/ml for injection. The oral doses were prepared by adding the mesna to juice. Mesna is stable in juice and other beverages for at least 24 h [4].

Urine collection

On day 1 and day 5, urine voids were collected on demand for the 2 h before infusion, at hours 1 and 2 after injection, and then at 2-h intervals between hours 2 and 12. Spontaneous urine voids were pooled between hours 12 and 22. A nadir sample was collected between hours 22 and 24. Urine voids were added to 500 ml bottles that contained 8.25 ml 6 *N* HCl and 12.5 ml 10% EDTA to preserve mesna. After the addition of urine, these containers were kept at 4°C for up to 24 h. After measuring the volumes, two 2-ml aliquots were shipped on dry ice from São Paulo, Brazil, to Memphis, Tennessee. These samples were stored at −80°C until the analysis of mesna, dimesna, and creatinine concentrations. Creatinine was measured to assess the completeness of urine collection.

Drug measurements

Mesna and dimesna in urine were separated by reverse-phase ion-pairing chromatography (Hewlett-Packard HP1090 high-performance liquid chromatographic system) and measured by postcolumn sulfitolysis and reaction with 2-nitro-5-thiosulfobenzoate, an agent that reacts specifically with thiols and disulfides, releasing a chromophore for detection at 412 nm [5, 6]. Each assay was calibrated with eight nonzero standards (range 5–1500 μ*M*). The calibration curve characteristics were computed by weighted (1/concentration^2) linear regression. Three pairs of control samples for each analyte (12.5, 125, and 1000 μ*M*) were evenly spaced throughout each analytical run. Validation studies verified no interference from endogenous urine components and acceptable performance (< 15% change) in mesna and dimesna measurements for accuracy, within- and between-run precision, two freeze-thaw cycles, and sample stability (24 h at 4°C and 1 year at −80°C).

Computations

The amounts of mesna and dimesna excreted during each urine collection period were computed from the concentrations and volumes. To adjust for differences in dosing among patients, these amounts were expressed as a percentage of the patient's daily mesna dose (the sum of the i.v. and two oral mesna doses). Excretion rates were computed from the dose-adjusted amounts excreted during each collection period divided by the number of hours in that period. Cumulative excretion was computed by summing the dose-adjusted amounts for periods up to 24 h. No adjustment was made on day 5 for any carry-over; however, baseline excretion during the preceding 2-h nadir period was negligible.

Results

Patient characteristics

Review of the case record forms indicated that mesna administration and urine collection were acceptable per protocol for 11 of the 14 children. The characteristics of these patients are shown in Table 1. Two of these patients received earlier nephrotoxic chemotherapy (patient 02, 240 mg/m^2 cisplatin; and patient 04, 600 mg/m^2 carboplatin).

Urine collection was incomplete in 3 of the 14 patients. Samples from patient 01 were discarded. We analyzed the partial sample sets of urine collected using adhesive plastic bags from two toddlers with retinoblastoma, patients 07 and 08, aged 29 and 14 months, respectively. Mesna excretion after their i.v. dose on day 5 mirrored that of the older children. Incomplete collection after oral doses precluded quantitation.

Excretion rates

Administration of the first oral dose at hour 2 rather than hour 4 produced steadier mesna excretion rates

Table 1 Patient characteristics

Patient number	Age (years)	Sex	Weight (kg)	Serum creatinine (mg/dl)	Tumor
02	15	M	40	0.7	Osteosarcoma
03	5	M	16	0.3	Ewing's sarcoma
04	7	M	23	0.3	Brain
05	18	F	55	0.4	Ewing's sarcoma
06	9	F	29	0.7	Ewing's sarcoma
09	4	M	14	0.4	Retinoblastoma
10	13	F	45	0.5	Osteogenic sarcoma
11	10	M	31	0.5	Rhabdomyosarcoma
12	14	M	58	0.5	Ewing's sarcoma
13	4	M	15	0.5	Retinoblastoma
14	15	F	70	0.7	Osteosarcoma

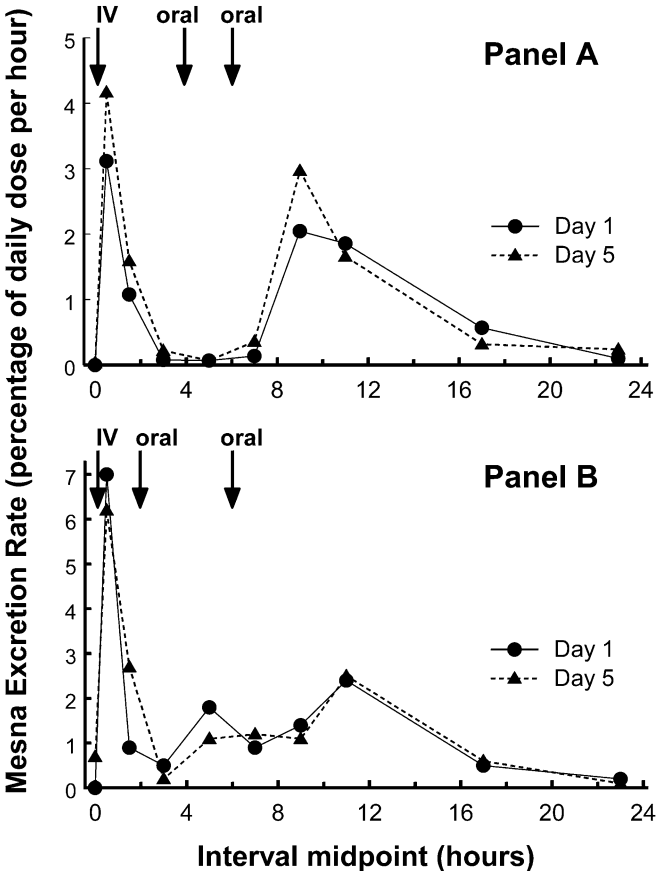

Fig. 1a, b Rates of mesna excretion on day 1 and day 5. Oral and i.v. mesna were administered at the times indicated by the *arrows*. The amount of mesna in urine samples was divided by the total daily dose to adjust for differences between patients. The amounts excreted per hour are plotted at the midpoint of the urine collection intervals. **a** Mean values for the five children (patients 02–06) who received oral doses at 4 and 6 h. **b** Mean values for the six children (patients 09–14) who received oral doses at 2 and 6 h

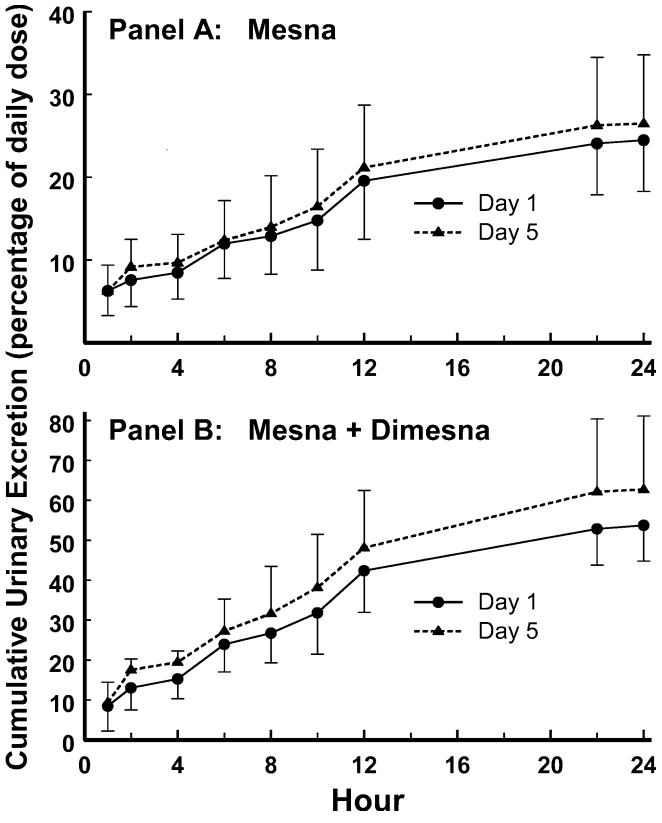

Fig. 2 Cumulative urinary excretion for the six children given oral mesna doses at 2 and 6 h after their i.v. mesna dose. The mean values and standard deviations are plotted at the end of the collection intervals

(Fig. 1). In children who received the first oral dose at hour 4 (Fig. 1a), mesna excretion was low for several hours between the i.v. and the oral dose. Mesna excretion lagged by 2–4 h after the first oral dose. There was a single broad peak of excretion centered near hour 10 after the second oral mesna dose. By contrast, oral mesna doses administered at hours 2 and 6 (Fig. 1b) were followed by separate peaks of mesna excretion 3–5 h after each dose, and the nadir after the initial i.v. injection was blunted. The profile of mesna excretion rates was similar on day 1 and day 5.

Cumulative urinary excretion

Figure 2 shows the 24-h profile of cumulative urinary excretion for the six evaluable children given oral mesna at hours 2 and 6. Mean mesna values of 19% (day 1) and 21% (day 5) were excreted by hour 12 (Fig. 2a). By hour 24, they had excreted an additional 6% (day 1, 25%; day 5, 27%). Dimesna excretion as a percentage of

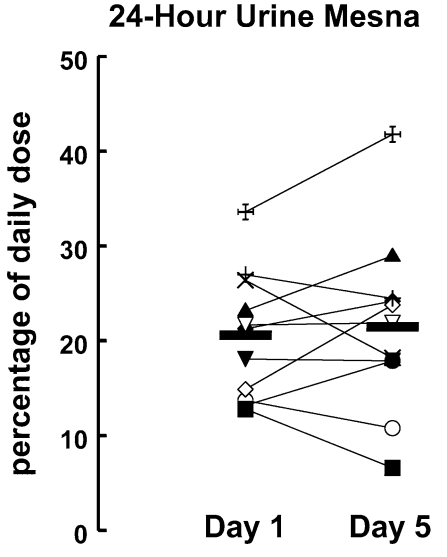

Fig. 3 The percentage of mesna excreted unchanged on day 1 and day 5 for the 11 children (bar, mean and median)

dose (data not shown) paralleled and slightly exceeded that of mesna. So, the cumulative sum of mesna and dimesna excretion (Fig. 2b) totaled 54% by the end of day 1 and 63% by the end of day 5.

Figure 3 shows all 24-h urine mesna values for the 11 evaluable children on both oral mesna schedules. There was more variability between patients than between days 1 and 5. On day 1, 13–34% (mean and median, 21%) of the administered mesna was recovered in the urine as the unchanged uroprotective free thiol. There was no particular trend for the paired values on day 5 (mean and median 22%, range 7–42%).

The completeness of urine collection was assessed by comparing the amount of creatinine excreted on day 1 with that on day 5. The 24-h creatinine excretion in individual patients did not vary by more than 20% between day 1 and day 5 with two exceptions (patient 06, 79%; patient 12, 36%). These two patients showed nearly identical mesna excretion on days 1 and 5 despite the differences in creatinine excretion. So, any incomplete urine collections may have occurred during the 14–24 h night-time period when mesna excretion was low.

Excretion after oral doses

Mesna excretion after oral dosing was estimated from urine collected between hours 2 and 24, which included mesna from the two oral doses but only negligible amounts from the i.v. dose. The mean percentage of the oral doses excreted as mesna (on both day 1 and day 5) was 18% for the 11 children.

Discussion

Our results suggest that the disposition of mesna is similar in children and adults. The profile of mesna excretion rates in the children we studied (Fig. 1) was similar to that reported for ifosfamide-treated adults [5]. Mesna excretion reduced rapidly after i.v. dosing, and mesna absorption and excretion after oral dosing lagged by 2–3 h. Although the children received their mesna in juice, whereas tablets were used in the adult study, the bioavailability is the same [6].

The proportion of mesna recovered unchanged in the urine of the children for the combined i.v.-oral regimen (mean values of 19–21%, as shown in Figs. 2 and 3) is similar to the mean values of 18–26% reported in studies of ifosfamide-treated adults [5, 7]. Also, the proportion of the two oral doses recovered in the urine between hours 2 and 24 in the children (mean 18%) was similar to that reported for adults (19%) [5].

There was no detectable age-related effect on mesna excretion in children aged 1–18 years after i.v. dosing or on mesna absorption and excretion after oral dosing in children aged 4–18 years. We obtained no quantitative data after oral dosing in toddlers because of incomplete urine collection.

Hematuria was not detected in any child in our study. This can be explained by the small number of children studied, their treatment as inpatients with 3 l/day hydration, and the low incidence of ifosfamide-induced hematuria when mesna is administered.

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