Cancer Chemother Pharmacol (1993) 32: 78–81

Cancer Chemotherapy and Pharmacology

Short communication

Oral bioavailability of mesna tablets

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Received 5 August 1992/Accepted 3 December 1992

Abstract. To test the feasibility of uroprotection with sodium 2-mercaptoethane-sulfonate (mesna) in tablet form the bioavailability of mesna tablets was determined in healthy volunteers by HPLC. The area under the plasma concentration-time curve (AUC) of free mesna was significantly lower following oral (110 μmol.l^{-1}.h^{-1}; 95% CI 98–122) than following i.v. administration of 1.2 g of mesna (201 μmol.l^{-1}.h^{-1}; 95% CI 158–244). The AUC for total mesna, i.e. dimesna and mixed disulfides, however, were comparable in the two groups, with 628 (539–717) and 772 (713–831) μmol.l^{-1}.h^{-1}, respectively. The mean residence time was significantly longer following oral mesna, at 79 (76–83) min vs 239 (229–250) min. Following oral mesna 51.1% (46.2–56.0%) of the administered dose was recovered in the urine in 24 h, compared with 60.6 (53.6–67.6)% in 4 h following i.v. mesna, and the average concentration of mesna in the urine exceeded 3 mmol.l^{-1} for 8 h. The data indicate that mesna in tablet form has an adequate bioavailability for uroprotection and therefore may be preferable to liquid mesna, which has an unpleasant taste. Oral mesna has a longer mean residence time than i.v. mesna, which means that uroprotection can be achieved with longer dosing intervals.

Introduction

Mesna (sodium 2-mercaptoethane-sulfonate) is increasingly used to prevent haemorrhagic cystitis associated with chemotherapeutic regimens containing high doses of ifosfamide and cyclophosphamide [3, 5]. After entering the circulation, mesna is thought to undergo rapid oxidation to its disulfide, dimesna, which is then excreted by the kidneys. Between 30% and 50% of glomerularly filtered dimesna is reduced back to mesna in the renal tubular epithelium by glutathione reductase [8], and the resulting sulfhydryl can react with toxic oxazaphosphorine metabolites such as acrolein and 4-hydroxy-ifosfamide in the bladder [11].

Because of the short half-life of mesna [6] compared with ifosfamide and cyclophosphamide, frequent i.v. administration of the uroprotective agent is necessary. A more convenient way of administering mesna would be oral administration. Mesna in liquid form has an adequate bioavailability for uroprotection [11]. However, mesna in solution has an unpleasant foul taste, which can only partially be masked by administering the drug in fruit juice and which limits patient compliance. Patient compliance might improve if mesna could be administered orally in a taste-neutral form, such as mesna tablets. In order to test the feasibility of uroprotection by mesna in tablet form the bioavailability of mesna tablets was investigated.

Subjects and methods

The pharmacokinetics of mesna (sodium-2-mercaptoethane-sulfonate) after intravenous and oral administration were studied in eight healthy volunteers, 2 women and 6 men, 24–39 years of age, all within 10% of their ideal body weight. Informed consent was obtained from each of the participants. The protocol was approved by the ethics committee of the local medical school. The studies were performed in the morning after an overnight fast. An indwelling catheter was placed into an antecubital vein of each arm in order to obtain blood repeatedly without tourniquet.

Intravenous mesna (Asta Medica, 400 mg/ml) was infused over 2 min at a dose of 1.2 g (7.3 mmol). Blood samples were obtained 0, 5, 10, 15, 30, 60, 120, and 240 min after termination of the infusion, and urine was collected over a 4-h period.

Oral mesna was administered at a dose of 1.2 g (Asta Medica, four tablets of 300 mg each) together with 200 ml tap water a minimum of 3 days after i.v. mesna. Blood was collected after 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 h. Additional samples were obtained 10, 12 and 24 h after administration in three volunteers. Urine was collected during the following periods: 0–2, 2–4, 4–6, 6–8, and 8–24 h. Food and liquids were allowed 2 h after the administration of mesna.

Analytical methods. Blood (5 ml) was collected into heparinized tubes and centrifuged at 3000 *g* for 2 min. Within 3 min of collection 50 μl of

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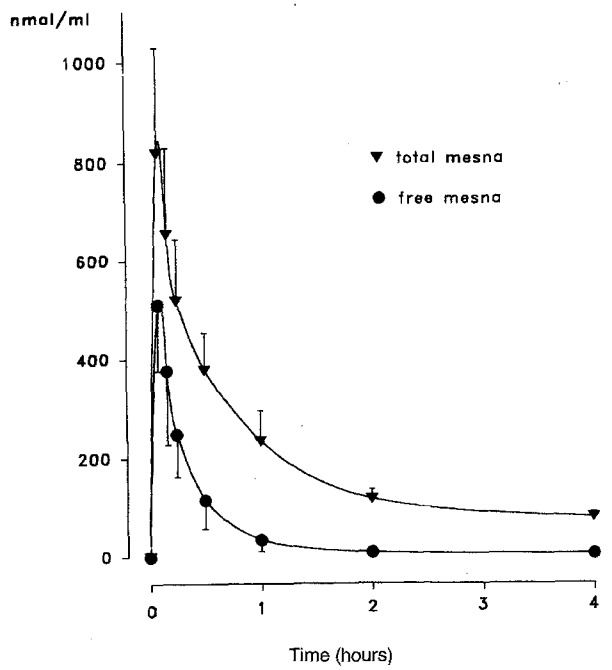

Fig. 1. Plasma concentrations of free mesna (*circles*) and total mesna (*triangles*) following the intravenous infusion of 1.2 g mesna (mean + 95% CI, $n = 8$)

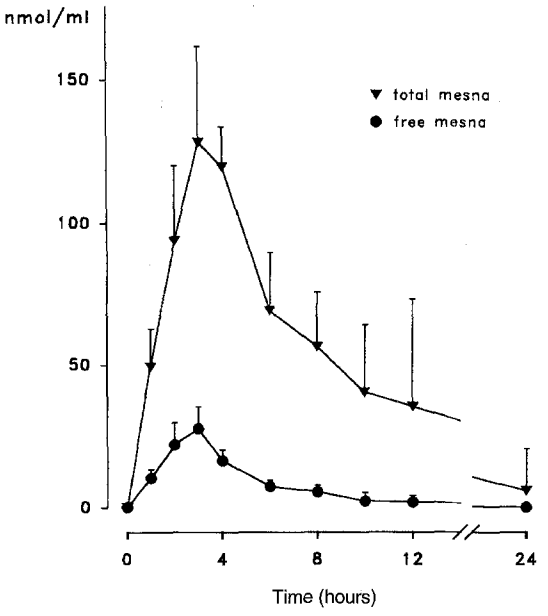

Fig. 2. Plasma concentrations of free mesna (*circles*) and total mesna (*triangles*) after oral administration of 1.2 g mesna (mean + 95% CI, $n = 8$)

the supernatant plasma was removed and derivatized with monobromobimane (10 µl of a solution of 25 mmol/l in acetonitrile; Thiolite reagent, Calbiochem, La Jolla, Calif.) after addition of penicillamine as internal standard. After 5 min at room temperature 20 µl of perchloric acid (20%) were added to precipitate the proteins and to stabilize the sulfhydryl-monombromobimane adducts. The derivatized samples were stored at –20° C until analysis by HPLC. Calibration curves were established daily by adding known amounts of mesna [1].

Total mesna, i.e. the thiol disulfide and small molecular and protein mixed disulfides, were measured after reduction of disulfides with dithiothreitol. Samples of 50 µl of plasma were reduced by addition of 100 µl dithiothreitol (20 mmol/l in 0.2 M Tris/HCl buffer, pH = 8.5). The samples were incubated for 40 min at room temperature [1]. Fifty microliters of sulfosalicylic acid (15%) were added and the samples were then centrifuged. Two hundred microliters of the clear supernatant were extracted three times with ethylacetate to remove excess dithiothreitol. To 60 µl of the acqueous phase 300 µl 0.2 M Tris/HCl buffer (pH = 8.5) and 10 µl monobromobimane (15 mmol/l in acetonitrile) were added. After 5 min at room temperature, 20 µl of perchloric acid (20%) were added and the samples were kept at –20° C until analysis. For HPLC analysis penicillamine, derivatized with monobromobimane, was added as external standard. Calibration curves were determined by adding known amounts of mesna to plasma and were linear up to 800 µmol/l. Total mesna and cysteine in urine were measured following the same protocol as for disulfides in plasma.

Separation of the sulfhydryls was performed on a Machery-Nagel Nucleosil RP-18 column, 150 × 4.6 mm, 7 µm particle size. The column was used at ambient temperature and at a flow rate of 1.4 ml/min. The elution solvent A was acetonitrile, solvent B consisted of 1 g/l of octanesulfonic acid and 1% acetic acid in water. The elution profile which was generated by a Waters gradient controller was as follows: 0–2 min 5–8% A slow gradient, 2–15 min 8–10% A convex gradient, 15–35 min 10–30% A convex gradient, 35–41 min 30% A isocratic, 41–50 min 5% A isocratic. The sulphydryl adducts were quantitated by means of a fluorescence spectrophotometer.

Taking a blood sample five times through the procedure for free and total mesna the coefficient of variation was found to be 8.5% and 9.8% for free and total mesna, respectively. The recovery of mesna from drug-free blood samples spiked with known amounts of mesna was 102 ± 10% ($n = 5$). With concentrations of mesna of 10 µM the peak to noise ratio exceeded 4.

Data analysis. The area under the plasma concentration-time curves (AUC) was calculated by the trapezoidal rule. The mean residence time (MRT) was calculated by dividing AUC by AUMC, the area under the first moment curve. The systemic clearance was calculated by dividing the administered dose by the appropriate AUC. The results are given as mean and 95% confidence interval.

Results

No volunteers experienced any side effects during the administration of intravenous or oral mesna. The mesna tablets were considered taste-neutral and were well accepted by the volunteers.

The plasma concentrations of free and total mesna following intravenous and oral administration are shown in Figs. 1 and 2. Peak plasma concentrations of 511 (95% CI 404–617) µmol/l free mesna and 820 (652–988) µmol/l of total mesna were achieved following the infusion, indicating that mesna rapidly forms disulfides, either with itself or with other circulating thiols. With oral application of mesna the maximal concentration of free and total mesna were substantially lower with 33 (26–40) µmol/l and 139 (117–161) µmol/l, respectively. Following oral administration peak concentrations of mesna and total mesna were achieved between 1.5 and 4 h and 3 and 7 h, respectively. In some cases total mesna was detectable in plasma up to 24 h.

The areas under the plasma concentration time curves (AUC) of free and total mesna are shown in Table 1. The ratio of free to total mesna averaged 0.26 and 0.18 follow-

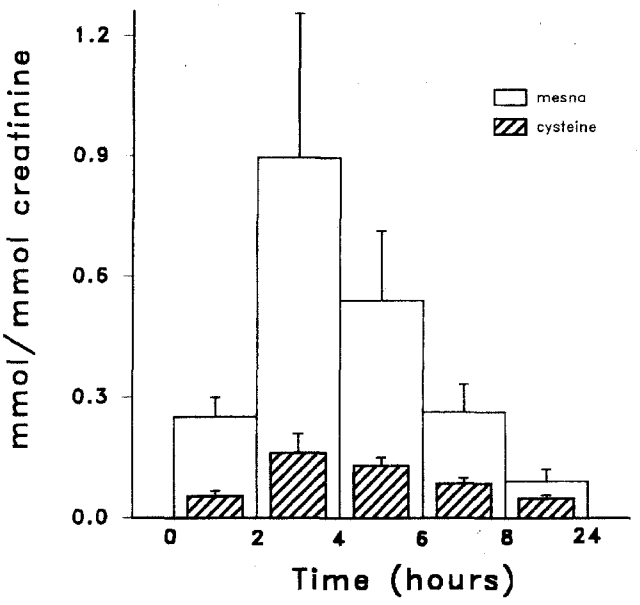

Fig. 3. Excretion of mesna (*empty bars*) and cysteine (*hatched bars*) in urine following the oral administration of 1.2 g mesna (mean + 95% CI, $n = 8$)

ing intravenous and oral administration, respectively. The AUC of free mesna after oral administration amounted to 58 (45–71)% of the AUC following intravenous administration. In contrast, the AUC of total mesna after oral was 89 (74–104)% of the AUC following intravenous administration owing to the much longer mean residence time of oral mesna. This is also reflected by the urinary excretion of mesna. During the 4 h following the intravenous administration of mesna the urinary excretion of mesna amounted to 4.42 (3.94–4.90) mmol corresponding to 60.6 (53.6–67.6)% of the administered dose. Following oral mesna 3.73 (3.38–4.09) mmol mesna corresponding to 51.1 (46.2–56.0)% of the administered dose were recovered in urine over 24 h. The average concentration of mesna in urine following oral administration exceeded 3 mmol/l for 8 h after dosing whereby half of the recovered mesna was excreted within 278 (252–304) min. As shown in Fig. 3, mesna resulted in a marked increase in the urinary excretion of cysteine.

Discussion

The pharmacokinetics of intravenous, subcutaneous and oral mesna in solution have been well characterized [2, 6, 7, 9–11]. The pharmacokinetics and urinary excretion of mesna tablets reported here are similar to those described in the literature for liquid mesna administered orally. Mesna in tablet form thus has a similar bioavailability and urinary availability as oral mesna in liquid form.

The mean residence time of orally administered mesna is much longer than the residence time of intravenous mesna. This may in part be due to delayed absorption. Moreover, the fraction of free circulating mesna was lower after oral than after intravenous administration, indicating that more disulfides are formed following oral administration. The renal clearance of disulfides, which may in part be protein-mixed disulfides of mesna [4], could be lower than the clearance of free mesna. As a consequence of the longer residence time of oral mesna the urinary concentration of mesna remains elevated for a prolonged period of time compared to intravenous mesna. In the present study the concentration of mesna in urine exceeded 0.6 mmol/l, which is considered the minimal protective concentration [2] for at least 8 h. Since circulating free mesna can interact with active metabolites of ifosfamide, oral mesna, which results in much lower plasma concentrations of free mesna but comparable uroprotection, may be preferable to intravenous mesna.

Although the excretion of cysteine following the administration of mesna has been documented its quantitative importance is not known [4, 7, 12]. The present data show that the administration of mesna results in a marked increase in the urinary excretion of cysteine (Fig. 3), and following oral administration of mesna the urinary excretion of cysteine amounted to approximately 25% of the urinary excretion of mesna. Thus, assays based on the determination of sulfhydryl groups rather than specific chromatographic methods may overestimate the excretion of mesna. More importantly, the mesna-induced excretion of cysteine may contribute substantially to the detoxification of reactive metabolites of oxazaphosphorines in urine.

In conclusion, the present data indicate that comparable amounts of mesna will appear in urine after intravenous and oral administration and that the bioavailability of mesna tablets is comparable to the liquid oral form of mesna. Compared to intravenous mesna uroprotection of longer duration can be achieved with oral mesna. Because of superior palatability mesna tablets may be preferable to oral mesna in solution.

Table 1. Area under the plasma concentration-time curve (AUC), mean residence time (MRT), and clearance (Cl) of mesna following oral and intravenous administration. Mean (95% confidence interval)

	Oral mesna		Intravenous mesna	
	Free	Total	Free	Total
AUC ($\mu mol/l^{-1}.h^{-1}$)	110 (98–122)	628 (539–717)	201 (158–244)	772 (713–831)
MRT (min)	221 (204–238)	239 (229–250)	38 (34–42)	79 (76–83)
Cl (l/min)	1.13 (0.95–1.31)	0.17 (0.14–0.20)	0.67 (0.57–0.77)	0.16 (0.15–0.17)

Acknowledgements. Supported by grant no. 32–29943.90 from the Swiss National Foundation for Scientific Research and ASTA Medica.

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