Pharmacokinetics of intravenous and oral sodium 2-mercaptoethane sulphonate (mesna) in normal subjects

C. A. JAMES, T. G. K. MANT & H. J. ROGERS

Guy's Drug Research Unit, Division of Clinical Pharmacology, United Medical and Dental Schools, London SE1 9RT

1 The pharmacokinetics of mesna (sodium 2-mercaptoethane sulphonate) and its inactive disulphide, dimesna, were investigated using high performance liquid chromatography in six normal subjects following intravenous and oral administration of 800 mg mesna.

2 The mean maximum mesna concentration after i.v. administration was 111 (s.d. $\pm$ 28.3) nmol ml⁻¹ and the mean maximum dimesna concentration was 183 (s.d. $\pm$ 41.6) nmol ml⁻¹. Following oral mesna dosing the mean peak mesna concentration was 19.6 (s.d. $\pm$ 10.2) nmol ml⁻¹ but mesna was only found in the plasma of five of the six subjects. The mean peak dimesna concentration was 22.5 (s.d. $\pm$ 12.4) nmol ml⁻¹.

3 Following i.v. mesna administration, the mean half-life of mesna was 21.8 (s.d. $\pm$ 3.1) min and total body clearance 1.23 (s.d. $\pm$ 0.31) l kg⁻¹ h⁻¹. The mean half-life of dimesna was 1.17 (s.d. $\pm$ 0.32) h. It was not possible to determine their half-lives after oral mesna administration.

4 The mean mesna concentration in the 0–4 h urine collection was 9.6 (s.d. $\pm$ 10.7; range 1.4–28.7) nmol ml⁻¹ following i.v. mesna injection. After oral mesna the highest mesna concentration occurred in either the 0–4 or 4–8 h urine collections. The mean peak mesna concentration was 2.5 (s.d. $\pm$ 1.7) μ mol ml⁻¹ (c.f. estimated uroprotective concentration of 1.7 μ mol ml⁻¹).

5 The mean 4 h urinary clearance of the uroprotective species mesna was 0.413 (s.d. $\pm$ 0.136) l kg⁻¹ h⁻¹. After both i.v. and oral mesna the urinary excretion of mesna is predominantly during the first 4 h. The urinary availability as mesna alone after oral dosing was 53.0 $\pm$ 19.5% of that following i.v. administration.

6 It should be possible to use oral mesna as a uroprotective agent in conjunction with oxazaphosphorine treatment either by giving an oral dose of 40% of the cytotoxic dose 2 h before the cytotoxic or using both i.v. (20% cytotoxic dose) and oral (40% cytotoxic dose) mesna doses with the oxazaphosphorine followed by oral mesna (40% of oxazaphosphorine dose) every 4 h.

Keywords mesna dimesna pharmacokinetics

Introduction

Until recently, a dose-limiting side effect of the oxazaphosphorine cytotoxic agents cyclophosphamide and ifosfamide has been the occurrence of urotoxic side-effects (Van Dyk *et al.*, 1972; Vahlensieck *et al.*, 1974; Stuart-Harris *et al.*, 1983). These adverse effects result from the urinary elimination of 4-hydroxy oxazaphosphorine metabolites and particularly acrolein (Brock *et al.*, 1979, 1981a; Brock & Pohl, 1983). An important advance in the clinical use of these compounds has been the use of mesna (2-mercaptoethane sulphonate sodium). This is a sulphhydryl donor which, without affecting cytotoxic efficacy, prevents or mitigates these adverse effects in experimental (Brock *et al.*, 1981b; Brock & Pohl, 1983) and clinical (Scheef *et al.*, 1979; Burkert, 1983) studies. The free sulphhydryl groups of mesna react with 4-hydroxy oxazaphosphorine metabolites to produce a non-toxic compound and with the double bond of acrolein to form a stable and harmless thio-ether.

After injection, mesna undergoes rapid oxidation forming the inert disulphide, dimesna, which penetrates into most tissues poorly but undergoes rapid renal elimination because it is rapidly taken up by the kidney cells (Brock *et al.*, 1984). A proportion of the dimesna passing into the renal tubules is reduced back to mesna via a mechanism involving glutathione. This free mesna is then available for uroprotection. To ensure protection of the bladder and urinary tract, a sufficient concentration of free thiol must be maintained in the urine during the period of excretion of the toxic metabolites of oxazaphosphorine drugs. It is recommended that 20% of the oxazaphosphorine dose in milligrams is given as mesna simultaneously with the cytotoxic with further mesna injections at 4 and 8 h. Repeated intravenous injections are troublesome for patient and doctor, particularly if the treatment consists of daily injections of oxazaphosphorine drugs. An oral regimen for mesna administration would thus be clinically valuable since it might allow treatments to be given on an outpatient basis with consequent savings in the duration of in-patient care and thus money. The pharmacokinetics of mesna and dimesna have never been satisfactorily studied in man. This is largely because a suitable analytical method for these compounds has not been available and previous studies (Burkert *et al.*, 1984; Jones *et al.*, 1985) have had to rely upon the relatively imprecise colorimetric Ellman free thiol assay (Ellman, 1959). We have recently developed a high performance liquid chromatographic assay (James & Rogers, 1986) which has allowed a

pharmacokinetic investigation of this important adjuvant to cytotoxic chemotherapy to be carried out and we present the results of these studies below.

Methods

Subjects

Six healthy Caucasian subjects (three male, three female; ages 26–54 years; body weights 44–72 kg) gave informed consent to take part in this study, the protocol of which was approved by the Committee on Ethical Practice of Guy's Hospital and Medical School. Apart from one subject on a low oestrogen oral contraceptive none of the subjects was taking any drugs and none consumed more than 14 units of alcohol/week.

Treatments were randomised at each dosing period so that three subjects were randomly assigned to receive an intravenous dose of mesna (Uromitexan, Boehringer Ingelheim, Bracknell, Berks) of 800 mg and three to receive the same solution containing 800 mg mesna orally, diluted in approximately 200 ml orange drink immediately before ingestion. After an interval of 7 days the subjects received the alternate form of medication. Subjects reported to the Drug Research Unit at approximately 08.00 h. Each dose was administered after an overnight fast, and no oral intake other than water was allowed until 4 h after drug administration when a light meal was taken. Subjects remained at rest for the first hour of the study but subsequently were allowed to move about at will.

Specimen collection schedule and handling

(a) *Plasma* Blood samples (3 ml) were collected into heparinised tubes through an intravenous cannula kept patent with small boluses of heparinised saline (150 units/20 ml saline) at the following times: 0 (baseline), 5, 10, 15, 20, 30, 45 min, and 1, 2, 3 and 4 h after intravenous dosing and at 0, 15, 20, 30, 45 min, and 1, 1.25, 1.5, 2, 2.5, 3 and 4 h after oral dosing. After mixing, the blood was transferred to a 1.5 ml micro-centrifuge tube and spun at 15000 g for 10 s. Plasma (0.4 ml) was added to another micro-centrifuge tube containing 0.4 ml 5% sodium hexametaphosphate and 0.4 ml 0.333 M sulphuric acid. After vortex mixing the tube was centrifuged at 15000 g for 2 min. The resulting supernatant was divided into three aliquots and frozen at -20°C . This procedure was completed within 5–10 min of the sample being taken from the subject.

(b) *Urine* Urine was collected into vessels containing 2 ml 1 M HCl and 250 mg EDTA during the following periods: 0 (baseline), 0–4 and 4–8 h and into containers with 5 ml 1 M HCl and 1 g EDTA for the 8–24 h collection period. Subjects were instructed to void immediately prior to dosing and aliquots were retained for the baseline drug assay sample (blank). To assure complete urine collection, subjects were instructed to void at the conclusion of the collection period. The resulting urine volumes were measured to the nearest 2 ml and a 10 ml aliquot was placed in a plastic tube and frozen at -20°C or lower.

Estimation of mesna and dimesna (James & Rogers, 1985)

In brief, the method was as follows:

(i) *Plasma* For mesna assay the plasma supernatants were diluted 1 in 5 with water and then directly injected into the h.p.l.c.

Dimesna was measured by reducing dimesna back to mesna with borohydride and calculating dimesna concentration by subtraction of the previously estimated mesna concentration. For the reduction 0.1 ml of plasma supernatant was placed in a 1.5 ml centrifuge tube with 0.1 ml of 1% EDTA in a mixture of disodium phosphate (0.5 M, 50 ml) and sodium hydroxide (1 M, 22 ml). Sodium borohydride (0.1 ml, 4%) was added and the tubes heated to 50°C for 30 min. After cooling 0.2 ml of 9.7% acetic acid was added. The samples were left for 2–3 days in the dark before chromatography to allow the borohydride reagent to disperse completely.

The h.p.l.c. system comprised a Kratos Spectroflow 400 h.p.l.c. pump, a Coulochem Model 5100A electrochemical detector with Model 5011 analytical cell, and a Rheodyne 7125 injection valve with 20 μl sample loop. Detector 2 of the electrochemical detector was run at -200 mV . Separation was performed on a Hypersil ODS 3 column (10 cm $\times$ 4.6 mm).

The solvent system consisted of 0.1 M phosphate buffer pH 7.0 containing 0.005 M tetrabutylammonium hydroxide and 5% acetonitrile delivered at a flow rate of 1.2 ml min^{-1} .

Calibration curves were prepared by spiking blank plasma with mesna 122–1220 nmol ml^{-1} and taking this through the complete procedure. The response of the detector was standardised by bracketing injections of patient samples and plasma standards with injections of 20 μl of 12.2 nmol ml^{-1} aqueous solution of mesna. A calibration curve was prepared by dividing the peak

height for the plasma standard with the mean of the two bracketing aqueous standards.

(ii) *Urine* Urine samples were measured under similar conditions to plasma. Calibration was effected with dilutions of mesna in water between 3.0–24.4 nmol ml^{-1} . Urine samples were diluted between 1:50 to 1:400 before injection.

The response of the detector was linear between 30–600 pmol injected on column and samples were diluted to remain within this range. With appropriate dilution linear calibration curves were obtained up to 1830 nmol ml^{-1} of mesna in plasma. The limit of detection was 6.1 nmol ml^{-1} in both plasma and urine.

Pharmacokinetic analysis

Elimination rate constants (k) were determined by linear regression of log concentration–time plots to obtain the maximum correlation coefficient and the half-life ($t_{1/2}$) determined from $0.693/k$. The apparent volume of distribution following i.v. mesna administration was found from $V = \text{Dose}/C_0$ where C_0 was the extrapolated plasma concentration at time 0. The total body clearance was found from $\text{CL} = kV$. The renal clearance was determined from $\text{CL}_R = \text{Amount excreted in urine}/\text{AUC}$ where AUC was the area under the plasma concentration, time curve over the corresponding time period which was estimated by the linear trapezoidal approximation.

Results

Figures 1 and 2 give specimen plasma concentration–time profiles of mesna and dimesna following oral and i.v. administration of mesna. Table 1 details the pharmacokinetic parameters of mesna derived following i.v. administration. The mean ($\pm$ s.d.) maximum concentration of mesna was $111 \pm 28.3\text{ nmol ml}^{-1}$ and of dimesna was $183 \pm 41.6\text{ nmol ml}^{-1}$. The mean half-life was 21.8 min. Table 2 gives the corresponding data for the dimesna produced: the mean half-life of this compound was longer at 1.17 h. Following oral administration of mesna the lag time before appearance of mesna in the plasma varied from 0.33 to 2.5 h and for dimesna from 0.25 (in a subject where mesna was not detected until 2.5 h) to 0.5 h. Peak concentrations of mesna and dimesna occurred late in the sampling period and in some cases even limited pharmacokinetic analysis was not possible. Table 3 shows the results of these calculations. The mean maximum concentration of mesna (five subjects) was $19.6 \pm 10.2\text{ nmol ml}^{-1}$ and in one subject it was

Figure 1 Plasma mesna and dimesna concentrations following intravenous administration of 800 mg mesna to subject 3.

Figure 2 Plasma mesna and dimesna concentrations following oral administration of 800 mg mesna to subject 3.

not detectable. Mean peak plasma concentrations of dimesna were $22.5 \pm 12.4 \text{ nmol ml}^{-1}$.

Table 1 Pharmacokinetic parameters derived from i.v. administration of mesna

Subject	C0 (nmol ml^{-1})	k (h^{-1})	$t_{1/2}$ (h)	V (l kg^{-1})	CL ($\text{l kg}^{-1} \text{ h}^{-1}$)	AUC_{iv} ($\text{nmol ml}^{-1} \text{ h}$)	CL_R 4 h renal clearance ($\text{l kg}^{-1} \text{ h}^{-1}$)
1	157	1.95	0.356 (21.3 min)	0.425	0.829	70.5	0.288
2	106	1.80	0.385 (23.1 min)	0.648	1.17	52.6	0.513
3	145	2.43	0.285 (17.1 min)	0.533	1.30	51.2	0.351
4	164	1.85	0.375 (22.5 min)	0.675	1.25	73.5	0.621
5	151	2.06	0.337 (20.2 min)	0.520	1.07	64.8	0.431
6	73.4	1.58	0.439 (26.4 min)	1.11	1.75	43.5	0.273
Mean	133	1.95	(0.363) (21.8 min)	0.652	1.23	59.4	0.413
s.d.	35.5	0.287	0.0514 (3.1 min)	0.242	0.305	12.0	0.136

Table 2 Terminal constant of elimination, half-life and AUC calculated from plasma dimesna data following i.v. mesna

<i>Subject</i>	k (h^{-1})	$t_{1/2}$ (h)	<i>AUC</i> ($nmol\ ml^{-1}\ h$)
1	0.631	1.10	167
2	0.608	1.14	177
3	0.697	0.994	103
4	0.807	0.859	152
5	0.387	1.79	153
6	0.611	1.13	108
Mean	0.624	1.17	143
s.d.	0.138	0.322	30.8

Following intravenous administration of mesna, maximum concentrations of mesna occurred in the 0–4 h urine collection, the mean being $9.6 \pm 12.7 \mu\text{mol ml}^{-1}$. The mean peak dimesna concentration in urine was $4.3 \pm 28 \mu\text{mol ml}^{-1}$. After oral mesna the maximum mesna concentration occurred in either the 0–4 h or 4–8 h urine sample, the mean being $2.5 \pm 1.7 \mu\text{mol ml}^{-1}$ and for dimesna being $1.8 \pm 1.5 \mu\text{mol ml}^{-1}$. These concentrations may be considered in the context of the minimum effective uroprotective concentration of $1.7 \mu\text{mol ml}^{-1}$ proposed by Burkert *et al.* (1984).

Table 4 summarises the excretion of mesna and dimesna in the urine as a percentage of dose. The 4 h renal clearance of mesna is shown in Table 1. The urinary bioavailability of the oral dose estimated as total drug excreted and as mesna (the active species) alone is shown in Table 5.

No subject suffered significant adverse effects due to participation in this study and there were no adverse sequelae following its completion.

Discussion

Plasma concentrations of mesna following i.v. injection were found to be adequately described by a one compartment open pharmacokinetic model and yielded values for plasma half-life of approximately 22 min. A study by Pohl *et al.* (1981) using a colorimetric assay for free sulphhydryl groups based upon Ellman's reaction found their data following 60 mg kg⁻¹ mesna given intravenously to be better fitted to a two-compartment model and determined a mean first order elimination rate constant of 2.31 h⁻¹ giving a half-life of 0.3 h (18 min) which is consistent with the present study results.

Following oral administration of mesna, wide intersubject variability of plasma concentrations

Table 3 Estimations of constant of elimination, half-life and AUC for mesna and dimesna following oral administration of mesna. Calculation of k and $t_{1/2}$ was not possible in all cases

Subject	Mesna						Dimesna					
	k (h ⁻¹)	t _{1/2} (h)	C _{max} (nmol ml ⁻¹)	t _{max} (h)	AUC (nmol ml ⁻¹ h)		k (h ⁻¹)	t _{1/2} (h)	C _{max} (nmol ml ⁻¹)	t _{max} (h)	AUC (nmol ml ⁻¹ h)	
1	—	—	12.0	4.0	30.2		—	—	18.0	2.5	48.0	
2	1.29	0.54	26.5	1.0	46.6		0.897	0.773	45.5	2.0	97.4	
3	—	—	27.7	2.5	57.8		0.303	2.28	22.6	2.0	52.6	
4	—	—	5.5	3.0	7.0		—	—	19.7	3.0	46.7	
5	—	—	26.2	3.0	55.9		0.399	1.74	20.7	2.5	43.1	
6	—	—	—	—	—		—	—	—	—	20.5	

Table 4 Percentage of dose excreted in urine as mesna or dimesna over 4 h and 24 h collection periods

Subject	Mesna excretion over 4 h		Mesna excretion over 24 h		Dimesna excretion over 4 h		Dimesna excretion over 24 h	
	i.v.	oral	i.v.	oral	i.v.	oral	i.v.	oral
1	30.4	11.6	31.3	25.5	32.8	18.4	39.4	39.4
2	39.3	19.5	41.2	22.6	26.6	19.6	31.6	30.7
3	23.2	11.7	23.2	12.8	30.8	8.7	38.5	26.6
4	41.2	15.6	43.2	27.9	26.9	18.6	29.9	37.3
5	35.5	5.6	37.0	12.5	26.9	11.1	31.7	22.8
6	14.6	0.054	14.8	4.3	26.2	5.1	28.5	33.3
Mean	30.7	10.7	31.8	17.6	28.4	13.6	33.3	31.7
s.d.	10.2	7.0	11.0	9.2	2.7	6.1	4.6	6.3

Table 5 Total urinary excretion (mesna plus dimesna) expressed as % of dose excreted over 4 h and 24 h. Urinary availability calculated as amount of mesna recovered as both mesna and dimesna and as mesna alone in urine over 24 h following oral administration—expressed as % of similar recovery following i.v. dose

Subject	% excretion over 4 h		% excretion over 24 h		% urinary availability of total drug administered	% urinary availability as mesna alone
	i.v.	oral	i.v.	oral		
1	63.2	30.0	70.7	64.9	91.8	81.4
2	65.9	39.1	72.8	53.3	73.2	54.7
3	54.0	20.4	61.7	39.4	63.9	55.0
4	68.1	34.2	73.1	65.2	89.2	64.4
5	62.4	16.7	68.7	35.3	51.4	33.8
6	40.8	5.2	43.3	37.6	86.8	28.8
Mean	59.1	24.3	65.1	49.3	76.1	53.0
s.d.	10.2	12.5	11.4	13.7	16.1	19.5

of mesna was observed. In particular subjects 4 and 6 showed very little evidence of free mesna in the plasma after oral drug administration although both of these subjects clearly absorbed the drug since appreciable concentrations of dimesna were detected in their plasma presumably resulting from pre-systemic metabolism. Following intravenous injection of mesna, high plasma concentrations of dimesna were found even in the earliest samples analysed (Figure 1). This is consistent with the finding of relatively higher total thiol concentrations than of free thiol concentrations in early blood samples following intravenous administration of mesna to dogs and man. This was explained by the investigators as resulting from the rapid auto-oxidation of mesna in plasma (Pohl, 1981; Pohl *et al.*, 1981). Analysis of ampoules of mesna shows that dimesna is not present as a contaminant prior to injection and mesna is stabilised by EDTA which is present in the injection solution. Plasma dimesna kinetics

following intravenous mesna administration in some cases showed inflexion on the log concentration-time plots. The mean terminal half-life of dimesna under these conditions was 1.17 h. This suggests that the elimination of dimesna from plasma is disposition rate limited rather than dependent upon its rate of formation from mesna. The assay employed in this study relies upon reduction of the disulphide bond to produce free mesna which can then be assayed by h.p.l.c. This is more specific than Ellman's (1959) method but it could not distinguish, for example, between a mesna-cysteine adduct and dimesna. However, dimesna is believed to be the sole metabolite of mesna (Pohl, 1981; Pohl *et al.*, 1981; Brock *et al.*, 1982) and within a few minutes of administration to the dog over 90% of the administered dose of mesna is found in the blood as dimesna (Brock & Pohl, 1983). Gobert *et al.* (1971) using radio-labelled mesna were unable to demonstrate any formation of adduct compounds of this type in

hydrolysed human plasma protein using electrophoresis and Sephadex gel filtration techniques. Their isotope label study also failed to reveal any urinary metabolites other than dimesna. A more recent study by Duran *et al.* (1981) using mass spectrometry, however, has detected 2-mercaptoethane-sulphate-cysteine disulphide in the urine of four patients receiving mesna as a mucolytic. Thus it is likely that a large part, if not all, of the material that we have identified as dimesna in this paper is mesna disulphide.

Following oral mesna the plasma kinetics of dimesna show a slower rise than after intravenous mesna which presumably reflects both rate of mesna absorption and its first pass transformation to dimesna. Under these circumstances the estimation of half-life of dimesna was not possible in all subjects studied. This was partially an effect of the blood sampling scheme adopted and in future studies it would be important for later samples to be taken for dimesna estimation.

In clinical practice, however, it is the urinary excretion of sulphhydryl groups which is important for uroprotection. We found that after intravenous mesna most of the urinary mesna excretion occurs in the first 4 h after drug administration. After oral dosing mesna excretion is prolonged over the first 8 h although in general the 0–4 h urine sample contains the larger amount of mesna. The excretion pattern of dimesna follows that of mesna. The results of the present study do not agree well with the conclusions of Burkert *et al.* (1984) who, using a colorimetric assay, found that 48.7% of 20 mg kg⁻¹ i.v.; 52.5% of 20 mg kg⁻¹ p.o. and 52.6% of 40 mg kg⁻¹ p.o. was excreted as free thiol (mesna) in the urine. Our results give a lower mean (31.8%) after intravenous and 17.6% after oral administration with a significantly lower ($P < 0.01$) excretion of mesna following oral administration of mesna. Our lower results for urinary excretion are quantitatively similar to those of Ikeuchi & Amano (1985) who, using a specific isotachopheresis method, found $35.9 \pm 1.7\%$ of the dose of mesna in the urine following intravenous injections of 800 mg day⁻¹ for 3 days. They also found $57.6 \pm 2.8\%$ of the dose as dimesna thus accounting for $93.5 \pm 3.5\%$ of the dose in all. This result suggests that very little mesna, if any, is excreted in the urine as a mesna adduct with other sulphhydryl compounds such as cysteine. Jones *et al.* (1985) found a mean of 24.2 (s.d. 9.0)% of an oral dose of 400 mg mesna to be excreted as free sulphhydryl groups by three subjects (two subjects studied twice).

Urinary excretion of dimesna was quantitatively important (Table 4) and similar to that of mesna itself. The urinary availability as mesna alone was $53.0 \pm 19.5\%$ with a wide variability (coefficient of variation = 35.5%). Assuming that the only route of mesna elimination is renal and that the only species eliminated are mesna and dimesna, the total availability of mesna given by the oral route based on urinary excretion is $76.1 \pm 16.1\%$.

The results of this investigation may be summarised as follows: (1) Compared with i.v. administration of mesna, overall availability of mesna in urine after oral administration is approximately 50%. (2) Deviations in drug disposition seem to be of similar magnitude both after intravenous and oral administration, e.g. in subject 6. (3) The onset of significant plasma levels of mesna/dimesna following oral administration is delayed approximately 1 h. (4) The onset of urinary excretion of mesna after oral administration is delayed and more prolonged, perhaps due to sustained absorption from the gastrointestinal tract.

The practical implications of these findings are threefold. Firstly, oral doses of mesna should be twice as high as i.v. doses. According to current practice this would result in a dosage recommendation of 40% of the ifosfamide dose per unit administration. Secondly, the sustained absorption of oral mesna requires a start of mesna medication approximately 2 h prior to administration of the oxazaphosphorine. A suitable regime might be oral mesna at a dosage of 40% of the respective oxazaphosphorine dose given 2 h before the cytotoxic then simultaneously and 4 and 8 h after oxazaphosphorine administration. Alternatively, an initial intravenous dose (20% of the respective oxazaphosphorine dose) could be given with the cytotoxic accompanied by a simultaneous oral dose of mesna (40% of oxazaphosphorine dose). Additional oral mesna (40%) would be administered at 4 and 8 h after the cytotoxic agent.

Finally, a dosage schedule of repeat oral mesna administrations every 4 h should be sufficient to yield reliable uroprotection, corresponding to the clinically effective i.v. schedule which has been found presently effective in clinical practice.

We are grateful to Asta-Werke Degussa Pharma Gruppe, the Cancer Research Campaign and the Friends of Guy's Hospital for financial support, and to Drs J. Pohl, M. Peukert and H. Sindermann for helpful discussion.

References

- Brock, N. & Pohl, J. (1983). The development of mesna for regional detoxification. *Cancer Treat. Rev.*, **10** (Suppl. A) 33–44.
- Brock, N., Hilgard, P., Pohl, J., Ormstad, J. & Orrenius, S. (1984). Pharmacokinetics and mechanism of action of detoxifying low-molecular weight thiols. *J. Cancer Res. clin. Oncol.*, **108**, 87–97.
- Brock, N., Pohl, J. & Stekar, J. (1981a). Studies on the urotoxicity of oxazaphosphorine cytostatics and its prevention. I. Experimental studies on the urotoxicity of alkylating compounds. *Eur. J. Cancer. clin. Oncol.*, **17**, 596–607.
- Brock, N., Pohl, J., Stekar, J. & Scheef, W. (1982). Studies on the urotoxicity of oxazaphosphorine cytostatics and its prevention. III. Profile of action of sodium 2-mercaptoethane sulphonate (Mesna). *Eur. J. Cancer clin. Oncol.*, **18**, 1377–1387.
- Brock, N., Pohl, J. & Stekar, J. (1981b). Studies on the urotoxicity of oxazaphosphorine cytostatics and its prevention. II. Comparative study on the uroprotective efficacy of thiols and other sulphur compounds. *Eur. J. Cancer clin. Oncol.*, **17**, 1155–1163.
- Brock, N., Stekar, J., Pohl, J., Niemeyer, U. & Schefler, G. (1979). Acrolein, the causative factor of urotoxic side-effects of cyclophosphamide, ifosfamide, trofosfamide and sufosfamide. *Arzneimittelforschung*, **29**, 659–661.
- Burkert, H. (1983). Clinical overview of mesna. *Cancer Treat. Rep.*, **10** (Suppl. A) 175–181.
- Burkert, H., Lucker, P. W., Wetzelsberger, N. & Bruel, H. P. (1984). Bioavailability of orally administered mesna. *Arzneimittel-Forschung*, **34**, 1597–1600.
- Duran, M., Aarsen, G., Fokkens, R. H., Nibbering, N. M. M., Cats, B. P., de Bree, P. K. & Wadman, S. K. (1981). 2-mercaptoethane sulphonate-cysteine disulfide excretion following the administration of 2-mercaptoethanesulphonate—a pitfall in the diagnosis of sulfite oxidase deficiency. *Clin. Chim. Acta*, **111**, 47–53.
- Ellman, G. L. (1959). Tissue sulphhydryl groups. *Arch. Biochem. Biophys.*, **82**, 70–77.
- Gobert, J., Risack, L. & Close, J. (1971). Etudes biochimiques, metaboliques et pharmacologiques d'un mucolytic: le Mistabron. *Acta Anaes. Belg.*, **22**, 85–114.
- Ikeuchi, I. & Amano, T. (1985). Simultaneous determination of 2-mercaptoethanesulfonate and its disulphide in human urine by isotachopheresis. *Chem. Pharm. Bull.*, **33**, 3016–3019.
- James, C. A. & Rogers, H. J. (1986). Estimation of mesna and dimesna in plasma and urine by high performance liquid chromatography with electrochemical detection. *J. Chromatogr.*, **382**, 394–398.
- Jones, M. S., Murrell, R. D. & Shaw, I. C. (1985). Excretion of sodium 2-mercaptoethanesulphonate (MESNA) in the urine of volunteers after oral dosing. *Eur. J. Cancer clin. Oncol.*, **21**, 553–555.
- Pohl, J. (1981). Toxikologie, Pharmakokinetik und Interaktionen von Uromitexan®. In *Neue Erfahrungen mit Oxazaphosphorinen unter besonderer Berücksichtigung des Uroprotektors Uromitexan®*, eds Burkert, H. & Nagel, G. A., pp. 12–20. Basel: S. Karger.
- Pohl, J., Brock, N., Schneider, B. & Wetzelsberger, K. (1981). Zur Pharmacokinetik von Uromitexan®. *Meth. Find. exp. Clin. Pharmac.*, **3** (Suppl. 1), 955–1015.
- Scheef, W., Klein, H. O., Burkert, H., Gunther, V., Hoefer-Janker, H., Mitrenga, D., Schnittser, J. & Voigtmann, R. (1979). Controlled clinical studies with an antidote against the urotoxicity of oxazaphosphorines: preliminary results. *Cancer Treat. Rep.*, **63**, 501–505.
- Stuart-Harris, R., Harper, P. G., Kaye, S. B. & Wiltshaw, E. (1983). High dose ifosfamide by infusion with mesna in advanced soft tissue sarcoma. *Cancer Treat. Rev.*, **10** (Suppl. A), 163–164.
- Vahlensieck, W., Hoefer-Janker, H., Bruhl, P. & Scheef, W. (1974). Zur Rathogenese, Klinik und Prophylaxe der sogenannten Cyclophosphamid-Zystitis. *Munch. med. Wochenschr.*, **116**, 1889–1894.
- Van Dyk, J. J., Falkson, H. C., van der Merwe, A. M. & Falkson, G. (1972). Unexpected toxicity in patients treated with iphosphamide. *Cancer Res.*, **32**, 921–924.

(Received 20 August 1986,
accepted 10 December 1986)