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Letter to the Editor

Sodium-2-mercaptoethanesulfonate (MESNA) and Ifosfamide Nephrotoxicity

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THE ASSOCIATION of high-dose ifosfamide therapy with nephrotoxicity was first described by van Dyk *et al.* more than a decade ago [1]. Since the development of MESNA as a uroprotector (Asta-Werke AG, Bielefeld, F.R.G.), however, no further reports on kidney toxicity appeared in the literature until Stuart-Harris *et al.* [2] described renal damage in patients receiving a 24-hr infusion of high-dose ifosfamide combined with a conventional fractionated MESNA schedule. A similar case was described by Sangster *et al.* [3]: after 8 courses of 24-hr ifosfamide infusion (8 g/m^2) the patient developed adult Fanconi's syndrome with progressive glomerular failure; MESNA was given 4-hourly as bolus injection.

The experimental toxicity data on ifosfamide suggest that kidney toxicity is an infrequent side-effect in animals: in acute as well as in chronic toxicity studies increases of BUN or histological evidence for kidney damage was rarely seen and, if so, only in the highest dose ranges [4]. Furthermore, glomerular and tubular necrosis following the administration of ifosfamide in the LD_{10} range in mice was completely abrogated by concomitant MESNA treatment [5].

Although the exact mechanism of ifosfamide nephrotoxicity is not yet clear, most experimental and clinical data currently available suggest that toxic metabolites (e.g. 4-hydroxyifosfamide, chloracetaldehyde and acrolein) with a high affinity for MESNA are causatively involved in this side-effect. Since its introduction into clinical trials, ifosfamide has usually been administered in fractionated dose schedules (e.g. one dose every 24 hr for 5 days), and thus the recommended MESNA regimen (20% of ifosfamide dose every 4 hr × 3) has been entirely based on the excretion kinetics of the toxic ifosfamide metabolites into the bladder as well as on the availability of sufficient amounts of intravesical MESNA throughout the critical period following therapy. It is not surprising that this MESNA regimen is inadequate in conjunction with a 24-hr high-dose ifosfamide infusion. Since the bladder forms a depot for reactive sulfhydryl groups, hemorrhagic cystitis may still be safely prevented by intermittent MESNA. Within the tubular system, however, the concentration of sulfhydryl groups will be subjected to considerable variations with intermittent MESNA dosing; in contrast, a constant or even increasing amount of toxic metabolites is present throughout the 24 hr of ifosfamide infusion.

Continuous infusion is a new and experimental way of high-dose ifosfamide administration. Therefore the concomitant MESNA treatment has to be designed rationally taking into consideration the pharmacokinetics of the two reaction partners. An initial bolus injection of 10% of the total ifosfamide dose to be given should be followed by a continuous infusion of MESNA, containing 100% of the ifosfamide on a mg-by-mg basis. Taking into account the comparatively long plasma half-life of ifosfamide, MESNA will have to be administered for another 8–12 hr following the termination of the therapy. Ifosfamide and MESNA are compatible in aqueous solutions and both drugs can be given in the same infusion fluid. The chemical stability of the two compounds in solution is sufficient to allow for 8–12 hr-lasting infusion bottles. Although the above recommendations are at present only based on extrapolations from

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experimental data, their clinical validity is suggested by the experience of Klein *et al.* [6], who did not observe urinary tract toxicity after long-term infusion of ifosfamide employing a similar MESNA schedule.

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