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LETTER TO THE EDITOR

Delayed methotrexate excretion in infants and young children with central nervous system tumors and postoperative fluid collections

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Dear Sir,

The authors are to be congratulated for examining the subject of delayed methotrexate (MTX) excretion due to fluid collections (third spacing) in infants with brain tumors and for looking for the causes of the associated toxicity [1]. They mention that craniospinal irradiation is to be avoided because of unacceptable neurotoxicity but do not discuss neurotoxicity as part of the toxicity pattern after MTX. This is understandable since infants with brain tumors are not an easy group of patients to evaluate since both the brain tumor and the surgery contribute to neurotoxicity and these data are not available in a retrospective review.

We would like to bring to the attention of the authors and readers the recent analysis of the published data that shows that the folic acid rescue doses and the time to start of rescue are critical factors in prevention of neurotoxicity [2, 3]. The infants described here started folinic acid rescue after 42 h and used a total dose of 75 mg/m^2 after 2.5 g/m^2 MTX in neonates and after 5 g/m^2 MYX in older infants.

The published data shows that although 75 mg/m^2 mg of folinic acid after 2.5 g MTX was adequate to prevent neurotoxicity, after 5 g/m^2 MTX, 105 mg/m^2 folinic acid is required to prevent neurotoxicity [2]. In adolescent osteosarcoma patients, who were without the confounding effects of brain tumors or brain surgery, it was possible to show more neuropsychological damage in 11 of 14 parameters when less than 250 mg/m^2 folinic acid was given after 12–20 g/m^2 MTX [4].

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Folinic acid rescue started 42–48 h after the start of MTX resulted in toxicity after doses of more than 1 g/m^2 MTX except when serum levels remained low at 24, 30, and 36 h [3]. The fear that 'over rescue' constitutes a problem in the clinically relevant dose range has been found to be baseless and can now be ignored as a reason to reduce folinic acid dosage [5].

These data were not available to the authors when this protocol was designed but should be taken to heart when subsequent studies are being developed. We suspect that this is even more of a problem with patients such as those studied here since it would be expected that infants will be at a greater risk than older children from inadequate rescue and that fluid collections with third spacing will increase the danger of toxicity due to the delayed MTX excretion.

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