
Re: Treatment of Accidental Intrathecal Methotrexate Overdose

Widemann et al. (1) presented data on the use of cerebrospinal fluid (CSF) exchange to remove methotrexate before carboxypeptidase G₂ (CPDG₂) administration among patients who had an accidental intrathecal methotrexate overdose. They reported that CSF drainage removed 32%–58% of the methotrexate dose. Although they showed the percent decreases in CSF methotrexate concentration before and after CPDG₂ administration, they did not show the CSF

methotrexate concentrations before CSF exchange. The absence of this information raises questions about the effectiveness of CSF drainage compared with CPDG₂ administration and about whether the combination of procedures removes more methotrexate than either procedure alone. We are also curious about what method was used to determine the total amount of drug removed with CSF exchange. Calculating the amount extracted by using the difference in CSF methotrexate concentrations is complicated by ongoing movement of methotrexate out of the CSF. The most accurate method would be to measure the total amount of methotrexate in the CSF collected from the exchange.

In another recent report (2) that described the use of CSF exchange for accidental intrathecal methotrexate overdose, CSF exchange was performed over a 48-hour period. The graph of CSF methotrexate concentration versus time did not show a rapid drop in CSF methotrexate concentration, suggesting that the exchange had minimal effect on CSF methotrexate elimination. It is unclear how the exchange was done in the Widemann et al. study because the method used was not described in detail.

We conducted an informal survey among medical oncology and hematology units in New South Wales and the Australian Capital Territory (Australia) to find out whether any had protocols to treat accidental intrathecal methotrexate overdose (Table 1). It proved difficult to reach a consultant on call at the different hospitals; nevertheless, the health care

Table 1. Responses by New South Wales physicians to questions about treatment of intrathecal methotrexate (MTX) overdose*

Hospital	Responder (specialty)	Response to overdose	Presence of protocol	CSF exchange	Carboxypeptidase G ₂
Hospital 1	Consultant (Oncology)	IV leucovorin	No	Would never do	Heard of but never used
	Advanced Trainee (Oncology)	IV leucovorin	No	Never heard of	Never heard of
	Pharmacist	IV leucovorin	No	Never heard of	Never heard of
	Consultant (Hematology)	IV leucovorin	Yes	Never heard of but would not do	Never heard of
Hospital 2	Consultant (Oncology)	IV leucovorin	Yes for IV	Never heard of	Never heard of
	Consultant (Hematology)	Stop MTX, administer folinic acid 50 mg q4h, check MTX levels	Probably	Never heard of	Heard of but never used
	Pharmacist	Unknown	No	Never heard of	Never heard of
	Nurse (Oncology)	Call consultant	No	Never heard of	Never heard of
Hospital 3	Advanced Trainee (Oncology)	Call consultant	No	Never heard of	Never heard of
	Consultant (Hematology)	IV leucovorin	Yes	Never heard of	Never heard of
Hospital 4	Advanced Trainee (Oncology)	IV leucovorin	No	Heard of but never used	Heard of but never used
	Advanced Trainee (Hematology)	Protocol	Yes	No set protocol	Using
Hospital 5	Consultant (Hematology)	IV leucovorin	Yes	Never heard of	Never heard of
	Consultant (Oncology)	Clinical circumstances	IV leucovorin protocol	Never heard of	Never heard of
Hospital 6	Consultant (Oncology)	IV leucovorin	Yes	Heard of but never used	Never heard of
	Consultant (Hematology)	IV leucovorin	No	No	Heard of but never used
Hospital 7	Consultant (Hematology)	Folinic acid, dialysis	Not sure	Never heard of	Never heard of
	Nurse (Oncology)	Call consultant	No	N/A	Heard of but never used
Hospital 8	Consultant (Hematology)	Uncontactable	Yes	Heard of but never used	Heard of but never used
	Consultant (Oncology)	IV leucovorin	No	Never heard of	Never heard of
Hospital 9	Nurse (Oncology)	Call PCC	No	Never heard of	Never heard of
	Consultant (Oncology)	Uncontactable			
Hospital 10	Consultant (Hematology)	Call PCC	No	Never heard of	Never heard of
	Consultant (Oncology)	uncontactable			
Hospital 11	Registrar (Oncology)	IV leucovorin-; call PCC	Not sure	Never heard of	Never heard of
	Registrar (Hematology)	IV leucovorin, NaHCO ₃ ; call PCC	Would adapt the leucovorin protocol used for IV MTX overdose	Never heard of	Never heard of
Hospital 12	Consultant (Hematology)	Folinic acid rescue	Yes	Never heard of	Never heard of
	Consultant (Oncology)	Uncontactable			
Hospital 13	Hematology-Oncology	Uncontactable			
	Consultant (Oncology)	Folinic acid rescue. Would PCC be helpful?	Protocol for standard dose	Never heard of	Heard of but never used
	Consultant (Hematology)	Uncontactable			

*CSF = cerebrospinal fluid; IV = intravenous; q4h = every 4 hours; N/A = not applicable; PCC = poison control center; MTX = methotrexate.

provider responsible for administering the drug in most institutions (a nurse, pharmacist, or advanced trainee) was not aware of any protocols to that effect. Only eight individuals were aware that CPDG₂ is a potential rescue therapy, and only one individual had heard of CSF exchange. None of the individuals interviewed said they would consider using CSF exchange as a treatment.

Many consultants interviewed expressed concerns about how such an overdose might occur. They noted that their institutions had introduced numerous steps to check methotrexate dosages. They also noted that the volume limitation inherent to intrathecal administration would limit the amount of methotrexate inadvertently given via this route. Widemann et al. (1) do not discuss how these unfortunate incidents occurred, but such knowledge would also be useful in understanding the steps that might need to be implemented to prevent their occurrence.

Our survey results suggest that more information on these treatment modalities is required so that chemotherapy units can design protocols for rescue treatment of patients who receive an accidental overdose and to provide information for clinical toxicologists or pharmacologists who might be required to give advice if faced with this unfortunate situation. Specifically, what is the maximum amount of CSF that can be withdrawn at one time? How much fluid can be infused back into the thecal space?

SOPHIE GOSSELIN
GEOFFREY K. ISBISTER

REFERENCES

- (1) Widemann BC, Balis FM, Shalabi A, Boron M, O'Brien M, Cole DE, et al. Treatment of accidental intrathecal methotrexate overdose with intrathecal carboxypeptidase G₂. *J Natl Cancer Inst* 2004;96:1557-9.
- (2) Finkelstein Y, Zevin S, Heyd J, Bentur Y, Zigelman Y, Hersch M. Emergency treatment

of life-threatening intrathecal methotrexate overdose. *Neurotoxicology* 2004;25:407-10.

NOTES

Affiliation of authors: Department of Pharmacology and Clinical Toxicology, Newcastle Mater Misericordiae Hospital, Newcastle, New South Wales, Australia.

Correspondence to: Dr. Sophie Gosselin, Department of Clinical Pharmacology and Toxicology, Newcastle Mater Misericordiae Hospital, Level 5 Clinical Sciences Building, Waratah, NSW 2298, Australia (e-mail: sophie.gosselin@mcgill.ca).

DOI: 10.1093/jnci/dji108

RESPONSE

We thank Drs. Gosselin and Isbister for their letter and welcome the opportunity to provide additional information. The causes of the accidental intrathecal methotrexate overdoses in our report are similar to those previously reported (1,2). There were two main causes of the accidental intrathecal methotrexate overdoses

reported in our study. Three of the patients in our study were scheduled to receive methotrexate intravenously as a bolus dose and as an intrathecal injection on the same day. Accidental intrathecal administration of the higher intravenous dose, which was prepared in a small volume, resulted in the overdose. The other four overdoses were due to preparation errors; for three overdoses, the wrong-sized vial of methotrexate (1 g instead of 20 mg) was reconstituted. For one patient no details regarding the preparation error were available.

We calculated the amount of methotrexate that was removed by lumbar drainage by multiplying the volume of cerebrospinal fluid (CSF) removed by the concentration of methotrexate measured in an aliquot of the CSF drainage. Table 1 shows the sequence of rescue interventions undertaken for each patient in our study. Six of seven patients underwent ventriculolumbar perfusion or ventricular or lumbar exchange. However, we had an aliquot from the entire volume exchanged for only one of those patients (patient 4), in whom 20% of the administered methotrexate dose was removed by lumbar exchange.

The survey performed by Drs. Gosselin and Isbister showed a surprising lack of awareness of treatment options, such as CSF exchange and carboxypeptidase G₂ (CPDG₂), for accidental intrathecal methotrexate overdoses considering the fact that recommendations on potential treatment options for such overdoses based on the pharmacokinetics of methotrexate in CSF have been previously published (3–6). Within 1 hour of lumbar injection of a radiolabeled tracer, radioactivity can be detected in the basal cisterns (7), implying that removal of an intrathecally injected drug such as methotrexate via lumbar drainage can only be successful if it occurs within a short time period after intrathecal injection. In 1981, Addiego et al. (3) developed a pharmacokinetic model that predicted the amount of methotrexate that can be removed by lumbar puncture and drainage by gravity at various time points after intrathecal methotrexate overdoses. They concluded that lumbar CSF drainage alone is unlikely to rescue patients who receive more than 10-fold the intended dose of methotrexate unless large volumes of CSF are removed within 15 minutes of the overdose, and they recommended emergency ventriculostomy placement and

Table 1. Sequence of rescue procedures for accidental intrathecal methotrexate overdoses and details regarding the duration of and the volume of cerebrospinal drainage, exchange, or perfusion*

Patient No.	Sequence of rescue interventions		
	First	Second	Third
1	Lumbar drainage, 15 mL	VL perfusion, 240 mL, 3 h	Intraventricular and intralumbar CPDG ₂
2	Lumbar drainage†	Intraventricular CPDG ₂	VL perfusion, 250 mL, 4 h
3	Lumbar drainage, 20 mL	Intraventricular CPDG ₂	VL perfusion, 130 mL, 1.5 h
4	Lumbar drainage, 70 mL	Lumbar exchange, 250 mL, 2 h	Intralumbar CPDG ₂
5	Lumbar drainage, 29 mL	Lumbar drainage, 30 mL	Intralumbar CPDG ₂
6	Ventricular exchange, 250 mL	VL perfusion, 250 mL	Intraventricular CPDG ₂
7	Ventricular exchange, 80 mL, 3 h	Intraventricular CPDG ₂	None

*VL = ventriculolumbar; CPDG₂ = carboxypeptidase G₂.

†No data available on the volume of drainage.

ventriculolumbar perfusion as a cornerstone of treatment.

The availability of CPDG₂ allows us to modify these recommendations. In cases of accidental intrathecal methotrexate overdose, we recommend immediate lumbar drainage to remove CSF followed by intrathecal administration of CPDG₂. Preparation for ventriculolumbar perfusion should be made in case the patient's clinical condition deteriorates. Meanwhile, systemic corticosteroids and leucovorin should be administered to minimize chemical meningitis and the risks of systemic toxicity, respectively. The rapid action of CPDG₂ may improve the outcome of patients and, in some cases, might obviate the need for the more invasive and less readily available procedure of ventriculolumbar perfusion.

Although procedures to prevent the inadvertent administration of an overdose of intrathecal methotrexate are critical, institutions should have a plan to treat an intrathecal methotrexate overdose should it occur.

BRIGITTE C. WIDEMANN
FRANK M. BALIS
PETER C. ADAMSON

REFERENCES

- (1) Spiegel RJ, Cooper PR, Blum RH, Speyer JL, McBride D, Mangiardi J. Treatment of massive intrathecal methotrexate overdose by ventriculolumbar perfusion. *N Engl J Med* 1984;311:386–8.
- (2) Ettinger LJ. Pharmacokinetics and biochemical effects of a fatal intrathecal methotrexate overdose. *Cancer* 1982;50:444–50.

- (3) Addiego JE, Ridgway D, Bleyer WA. The acute management of intrathecal methotrexate overdose: pharmacologic rationale and guidelines. *J Pediatr* 1981;98:825–8.
- (4) Balis F, Holcenberg J, Blaney S. General principles of chemotherapy. In: Pizzo P, Poplack D, editors. *Principles and practice of pediatric oncology*. Philadelphia (PA): Lippincott Williams & Wilkins; 2002. p. 237–308.
- (5) Poplack D. Massive intrathecal overdose: "check the label twice." *N Engl J Med* 1984;311:400–1.
- (6) Thomas LL, Mertens MJ, von dem Borne AE, van Bostel CJ, Veenhof CH, Veies EP. Clinical management of cytotoxic drug overdose. *Med Toxicol Adverse Drug Exp* 1988;3:253–63.
- (7) Di Chiro G. Movement of cerebrospinal fluid in human beings. *Nature* 1964;204:290–1.

NOTES

Affiliations of authors: Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD (BCW, FMB); Children's Hospital of Philadelphia, Philadelphia, PA (PCA).

Correspondence to: Brigitte C. Widemann, MD, Pediatric Oncology Branch, National Cancer Institute, 10 Center Drive, Bldg. 10 CRC Room 1–5750 MSC 1101, Bethesda, MD 20892 (e-mail: bw42y@nih.gov).

DOI: 10.1093/jnci/dji109