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
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 CPDG5 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?

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**REFERENCES**


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**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 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.

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**REFERENCES**


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<th>Patient No.</th>
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<th>Third Procedure</th>
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<tr>
<td>1</td>
<td>Lumbar drainage, 15 mL</td>
<td>VL perfusion, 240 mL, 3 h</td>
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<tr>
<td>2</td>
<td>Lumbar drainage†</td>
<td>Intraventricular CPDG2</td>
<td>Intralumbar CPDG3</td>
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<td>3</td>
<td>Lumbar drainage, 20 mL</td>
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<td>4</td>
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<td>VL perfusion, 250 mL</td>
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†No data available on the volume of drainage.


