Adverse Effects of Intrathecal Methotrexate in Children With Acute Leukemia in Remission

By Clementina F. Geiser, Yvonne Bishop, Norman Jaffe, Lorrie Furman, Demetrius Traggis, and Emil Frei, III

A toxic syndrome characterized by fever, headache, and vomiting, lasting 2–5 days, occurred in 61% of 39 children with acute leukemia in complete remission, receiving central nervous system prophylaxis with intrathecal methotrexate, and in 14% of 34 children receiving the same plus cranial radiation. The syndrome was accompanied by pleocytosis with lymphocytes, monocytoid cells, and neutrophils. There was evidence of cumulative Mtx toxicity, since the toxic syndrome occurred mostly after the third and fourth dose and did not recur with longer intervals between doses. The incidence of the syndrome was significantly reduced by the use of Elliott's B solution as Mtx diluent, rather than water or normal saline. The occurrence of pleocytosis and toxic clinical syndrome was also significantly reduced in patients receiving concomitant cranial irradiation, probably due to the lympholytic action of radiotherapy and the depressed cellular response of irradiated tissues. The use of Elliott's B solution as diluent for IT Mtx and an appropriate interval between Mtx doses are suggested for prevention of this toxic syndrome.

SINCE THE DEMONSTRATION that aminopterin administered intrathecally decreased the number of blasts in the cerebrospinal fluid (CSF) of patients with meningeal leukemia,1 the antifolates have been widely employed for therapy and prophylaxis of this complication. Various neurologic complications have been described following the repeated use of intrathecal methotrexate (IT MTX) for therapy of meningeal leukemia and brain tumors. The present report describes our experience in 57 children receiving IT MTX for "prophylaxis" of meningeal leukemia, that is, for the eradication of possible occult disease. Since these patients presumably have an intact central nervous system, other variables such as abnormal CSF dynamics due to leukemic involvement or to other pathology should not complicate interpretation of IT MTX effects.

MATERIALS AND METHODS

Fifty-seven children, aged 2–16 yr, 47 with acute lymphatic leukemia (ALL) in complete remission, seven with inactive lymphosarcoma, and three with inactive reticulum cell sarcoma, received "prophylactic" courses of IT MTX consisting of 12.5 mg/sq m every 3–4 days for a total of five doses. Of these patients, 18 received, in addition, concomitant cranial irradiation (2400 R).

Sixteen of the patients who received central nervous system (CNS) prophylaxis with IT MTX...
alone received a second course of CNS prophylaxis with both IT MTX and cranial irradiation at a later date, while still in complete remission. The interval from the previous prophylaxis was 2 wk-9 mo, with a median of 4 mo. There were, therefore, a total of 73 prophylactic courses in 57 patients.

Lumbar punctures were performed with a 22-gauge needle, in the lateral position. Approximately half of the patients received local procaine anesthetic, while the other half received brief general anesthesia with nitrous oxide-halothane. CSF was withdrawn for chamber cell count, cytocentrifuge examination, and for protein, sugar, and culture studies.

The commercial methotrexate solution of 25 mg/ml, which contained 0.08% of methyl paraben and 0.02% of propylparaben as preservatives, was diluted to a methotrexate concentration of 1 mg/ml with artificial CSF (Elliott's B solution, Baxter Travenol Laboratories, Morton Grove, Ill.) and then injected through a Millipore filter by isovolumetric exchange with spinal fluid. In 13 courses, MTX solution of 10 mg/ml was used; in these cases the total volume injected was smaller, and it was introduced with barbotage. During a 6-mo period, Elliott's B solution was unavailable, and either saline without preservative or water without preservative was used as the vehicle. This provided an opportunity to evaluate the role of various diluents in the production of toxic manifestations.

Symptoms following lumbar puncture were classified as minor or major. Minor symptoms included transient pain in the back of the legs and occasional headache and vomiting which were not incapacitating and did not last more than 1 day. Major symptoms consisted of vomiting, headache, and fever between 38° and 39°C, occasionally reaching 40°C, lasting 2-5 days. Only cases with major symptoms will be evaluated in this report.

RESULTS

Of the 73 prophylactic courses, 29 (40%) were associated with major symptoms, and 24 of these were in patients receiving IT MTX alone. The incidence of major symptoms was significantly higher (p < 0.01) in the patients receiving IT MTX alone than in those receiving concomitant cranial radiation (Table 1). This was also true in the 16 patients who first received a course of CNS prophylaxis with IT MTX and subsequently received reprophylaxis with IT MTX and cranial radiation: nine of them developed symptoms during the first course and only one patient had symptoms during both courses of prophylaxis (0.02 > p > 0.01, extended McNemar test).

Cumulative toxicity tended to occur during the five-dose course of CNS prophylaxis (Table 1). Major symptoms occurred during 29 of the 73 courses, on 40 different occasions. In the absence of cumulative toxicity, eight episodes would be expected after each dose, but significantly more occurred after doses III and IV (Trend test, 0.05 > p > 0.2). Patients who manifested symptoms after any dose were not given the next dose within the normal 3-4 days but were delayed up to 11 days. The number of such prolonged intervals increased for later doses in a course. This explains the reduction in incidence of major

<table>
<thead>
<tr>
<th>Type of Prophylaxis</th>
<th>Courses of Prophylaxis</th>
<th>MTX Doses in ALL Courses</th>
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<tbody>
<tr>
<td></td>
<td>Symptomatic/Total</td>
<td>Dose I</td>
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<tr>
<td>MTX + x-ray</td>
<td>5/34</td>
<td>1/34</td>
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<tr>
<td>Total</td>
<td>29/73</td>
<td>3/73</td>
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symptoms following the fourth and fifth dose. In no instance did severe symp-
toms occur when the interval from the preceding dose was more than 5 days.

With two exceptions, the same diluent was used throughout a course of pro-
phylaxis. For the 71 consistent courses the incidence of major symptoms
was 61.1% and 51.7% for normal saline and water, respectively, compared with
12.5% for Elliott’s B (Table 2). The reduced number of major symptoms for
Elliott’s B was not a function of whether cranial irradiation was administered
(test for three-factor effect, \( p > 0.05 \)) and was a significant finding
(\( p < 0.05 \)).

Pleocytosis above 10 cells/cu mm was observed in 40 of the 71 courses,
(median, 32 and range, 11–350 cells/cu mm). On stained cytocentrifuge pre-
paration, the cells consisted of variable numbers of lymphocytes and mono-
cytoi d cells with occasional polymorphs, except in one-fourth of the cases where
polymorphs predominated. Pleocytosis occurred in 27 of 29 symptomatic and
in 13 of 42 asymptomatic courses. It occurred in 31 (80%) of the courses with
IT MTX alone and in nine (28%) of the courses with concomitant cranial ir-
radiation.

Log-linear models were fitted to the four variables, type of prophylaxis,
diluent, symptoms, and pleocytosis. With four variables there are six possible
two-way interactions. A model that only included four of these was found to
fit well (\( \chi^2 = 14.39 \), 12 degrees of freedom). One of the interactions included
was type of prophylaxis and vehicle. Inclusion of this interaction was a method
of adjusting for the uneven distribution of the diluents: most of the patients
who received MTX alone had water, most of those who were irradiated had
Elliott’s B solution. Three other interactions, which were significant at the 5% level,
were included in the model: (a) pleocytosis and type of prophylaxis, (b)
pleocytosis and symptoms, (c) symptoms and vehicle. The interactions that
were excluded because they were not significant at the 5% level are: (d) pleo-
cytosis and vehicle, (e) symptoms and type of prophylaxis.

This analysis shows that pleocytosis occurs more frequently when MTX
alone is administered than when patients are also irradiated (interaction a);
this is true regardless of vehicle (interaction d). Symptoms rarely occur in the
absence of pleocytosis (interaction b); in the presence of pleocytosis they occur
less frequently with Elliott’s B solution than when saline or water are used as

<table>
<thead>
<tr>
<th>Type of Prophylaxis</th>
<th>Diluent</th>
<th>Total Courses</th>
<th>Courses with Major Symptoms</th>
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<tr>
<td></td>
<td></td>
<td>Number</td>
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<td>1</td>
</tr>
<tr>
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<td>Normal saline</td>
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vehicle (interaction c). The apparent relationship between symptoms and type of prophylaxis is explained by the decreased occurrence of pleocytosis when irradiation is given, and thus is not a direct relationship (interaction e).

No significant difference in frequency of symptoms occurred between the courses using a MTX solution of 1 mg/ml (25/60, or 41%) or 10 mg/ml (4/13, or 30%).

The type of anesthesia used during the lumbar punctures did not influence the occurrence of symptoms. Thirty-nine patients consistently had the same anesthesia for the five lumbar punctures of each course: 11 of the 19 patients who had general anesthesia and 13 of the 20 who had local anesthesia developed major symptoms.

As expected, the CSF opening pressure was significantly elevated under nitrous oxide–halothane anesthesia ($p < 0.01$), with a range of 110–500 mm H$_2$O. However, for each group with or without general anesthesia, there was no significant difference in CSF opening pressure of asymptomatic patients and patients during symptomatic episodes.

The CSF glucose level did not correlate with the presence of pleocytosis or with the type of cells in the CSF, but rather with the fasting status of the patient. In the fasting patients the CSF glucose showed a range of 19–64 mg/100 ml with a mean of 40, in the nonfasting patients a range of 43–75, with a mean of 58. In the 12 lumbar punctures with pleocytosis above 40 cells/cu mm the mean glucose content was 49 mg/100 ml.

**DISCUSSION**

During the 73 courses of CNS prophylaxis, there were no cases of paralysis, dementia, or death, as reported in the literature for patients receiving intensive IT MTX for CNS leukemia, brain tumors, or brain metastases.$^4$–$^7$ The presence of CNS disease prior to IT MTX appears to be a prerequisite to such severe neurologic complications. Pain and weakness in the legs were present prior to IT MTX in two of the 12 reported patients who developed palsies,$^{11,12}$ and transient weakness and paraplegia following MTX recurred after Ara C in two more patients, suggesting causes independent of the MTX.$^6,^7$ Of the eight cases examined at autopsy, there was residual CNS leukemia associated with myelomalacia of the thoracic segment in a case of paraplegia$^4$ and leukemia associated with petechiae in a case of quadriplegia.$^{12}$ However, residual CNS leukemia was not present in the other patients who showed: hyalination of meningeal vessels and demyelination of spinal cord and lumbosacral spinal roots on the right in a case of paralysis of the right leg,$^8$ necrosis of the walls of blood vessels with cerebral focal infarcts in a case of dementia,$^{10}$ and chronic ependymitis with mild hydrocephalus and periventricular white matter necrosis in three patients who received intraventricular instillations of MTX for treatment of brain tumors.$^9$

Toxic palsies and death following IT MTX in patients with CNS leukemia were associated with an abnormally high concentration and a prolonged half-life of MTX in the CSF.$^{12}$ This finding suggests that the severe neurotoxicity reported in patients with pre-existing leukemic meningitis or brain tumors may
be related to alterations in the CNS vascularity and the cerebrospinal fluid pathways, which favor a delayed egress of MTX from the CSF.

Chemical arachnoiditis with symptoms similar to those in our patients has been reported in a small percentage of children receiving IT MTX for meningeal leukemia,\textsuperscript{13,14} and a nonbacterial meningitis with granulocytic pleocytosis was reported in one of nine patients after ventricular-spinal perfusion with MTX.\textsuperscript{15}

There have been also reports of toxicity characterized by fever, headache, dizziness, and vomiting in ALL patients receiving “prophylactic” IT MTX while in complete remission.\textsuperscript{12,16-20}

The post-IT MTX syndrome in our patients suggested a chemical meningitis, manifesting with fever, headache, and vomiting, lasting 2–5 days, often requiring hospitalization. Meningeal signs, if present, were very mild. Pleocytosis was closely related to the toxic syndrome, since it was present in 93\% of the patients who developed symptoms and was only rarely found in clinically asymptomatic patients. Hyperemia of the meninges, with migration of lymphocytes, neutrophils, and monocytoid cells into the CSF, are probably the earliest response of the meninges to IT MTX.

The concomitant use of cranial radiation significantly reduced the incidence of the toxic syndrome and pleocytosis. The mechanism of this phenomenon remains obscure, but it may be related to the lympholytic action of radiation therapy and the depressed cellular response of irradiated tissues.

The diluent used as vehicle for the IT MTX influenced the occurrence of symptoms. Elliott’s B solution was associated with significantly less cases of chemical meningitis than water or saline. It is known that the ionic content, osmolarity, and pH of the solutions injected intrathecally affect toxicity, as demonstrated by the comparison of normal saline and Elliott Jasper solution in the infusion test.\textsuperscript{21} The latter solution is a bicarbonate-containing medium that maintains a physiologic pH of about 7.4 on contact with the brain.\textsuperscript{22} Comparison of the ionic content and osmolarity of CSF with those of MTX in Elliott’s B solution, in normal saline, and in water shows that MTX in Elliott’s B solution results in more physiologic values (Table 3).

The MTX used during the period of these studies contained the same paraben preservatives which have been previously suspected of playing a role in the development of post-MTX palsies in patients with CNS leukemia. However, the recent report of the occurrence of the meningeal syndrome with preservative-free MTX\textsuperscript{12} indicates that factors other than the parabens are important in causing the syndrome.

| Table 3. Ionic Content and Osmolarity of Methotrexate Solutions Used for CNS Prophylaxis and Cerebrospinal Fluid |
|----------------|------------------|-----------------|-------------|-----------|-----------|-----------|-----------|
|                | Concentration (mg/ml) | Na (meq/liter) | K (meq/liter) | Cl (meq/liter) | Ca (mg/100 ml) | Mg (mg/100 ml) | Osmolarity (milliosmols/kg) |
| MTX in Elliott’s B | 1                  | 149             | 3.8          | 137          | 5.5         | 2.8         | 295         |
| MTX in Elliott’s B | 10                 | 173             | 2.2          | 118          | 3.3         | 1.7         | 323         |
| MTX in normal saline\* | 1                 | 158             | 0            | 162          | 0           | 0           | 298         |
| MTX in normal saline\* | 10                | 201             | 0            | 166          | 0           | 0           | 349         |
| MTX in water\*    | 1                  | 11              | 0            | 7            | 0           | 0           | 76          |
| CSF (mean, 14 cases) |                  | 141             | 2.6          | 126          | 4.3         | 2.6         | 285         |

\*Without preservative.
The frequency of the toxic syndrome was similar, whether IT MTX was given in a 1 mg/ml concentration or in a smaller bolus containing 10 mg/ml injected with barbotage. Considering that the average volume of CSF in children 5–13 yr of age is 92 ml with a daily formation rate of 500 ml, most of our patients received less than one-tenth of their CSF volume in the 1 mg/ml MTX solution and probably about the same volume was exchanged by barbotage with the 10 mg/ml MTX solution. The occurrence of systemic symptoms like fever, vomiting, and headache suggests that this type of MTX toxicity occurs at the level of the medulla and tentorium and that the relatively small volume of MTX solution is rapidly circulated with the CSF.

The volume and formation rate of CSF have not been studied in children below 5 yr of age, but it is known that the head completes 70% of its postnatal growth within 2 yr and reaches almost adult size by 6 yr. As the dose of IT MTX is based on body surface, the cranial dose of MTX for older children would be relatively greater. An analysis of our patients for age-related toxicity shows that symptoms occurred in ten of 33 patients below 6 yr of age and in 18 of 40 above 6, which is not a significant difference ($\chi^2 = 0.744$), but shows a trend which is in accordance with the direct relationship of toxicity to CSF concentration of methotrexate.

ACKNOWLEDGMENT

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