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Methotrexate distribution within the subarachnoid space after intraventricular and intravenous administration

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Abstract *Purpose*: Intrathecal methotrexate achieves high concentrations in cerebrospinal fluid (CSF), but drug distribution throughout the subarachnoid space after an intralumbar dose is limited. The objective of this study was to quantify methotrexate distribution in CSF after intraventricular and intravenous administration and to identify factors that influence CSF distribution. *Methods*: Nonhuman primates (*Macaca mulatta*) with permanently implanted catheters in the lateral and fourth ventricles received methotrexate by bolus injection (0.5 mg) and infusion (0.05 to 0.5 mg/day over 24 to 168 h) into the lateral ventricle, as well as intravenous infusions. CSF was sampled from the lumbar space, fourth ventricle and the subarachnoid space at the vertex. Methotrexate in CSF and plasma was measured with the dihydrofolate reductase inhibition assay. *Results*: After bolus intraventricular injection, methotrexate exposure in lumbar CSF ranged from 11% to 69% of that achieved in the fourth ventricle. During continuous intraventricular infusions, methotrexate steady-state concentrations (C_{ss}) in lumbar CSF and CSF from the vertex were only 20% to 25% of the ventricular CSF C_{ss}. The dose, duration of infusion, and infusate volume did not influence drug distribution to the lumbar CSF, but probenicid increased the lumbar to ventricular C_{ss} ratio, suggesting the involvement of a probenicid-sensitive transport pump in the efflux of MTX from the CSF. During the intravenous infusions, the ventricular methotrexate C_{ss} was lower than the lumbar C_{ss} and the C_{ss} in CSF from the vertex. *Conclusion*: Methotrexate CSF distribution after intraventricular injection was uneven, and at steady-state CSF methotrexate concentrations were lower at sites that were more distant from the injection site.

Key words Methotrexate · Cerebrospinal fluid · Intrathecal · Pharmacokinetics

Abbreviations *AUC* area under the concentration-time curve · *CSF* cerebrospinal fluid · *IT* intrathecal · *i.v.* intravenous · *MTX* methotrexate · C_{ss} steady-state concentration · C_{ss}^{V} steady-state ventricular CSF concentration · C_{ss}^{L} steady-state lumbar CSF concentration

Introduction

Intrathecal (IT) administration of methotrexate (MTX) is a form of regional chemotherapy that is used in the treatment and prevention of the meningeal spread of leukemia and lymphoma. Because of the small volume of cerebrospinal fluid (CSF), MTX concentrations exceeding 100 μM can be achieved with a dose of 12 mg, resulting in a substantial pharmacokinetic advantage for this route of administration [8, 18, 20]. IT MTX will induce a remission in 80% to 90% of children with acute lymphoblastic leukemia, who experience a meningeal relapse, but few of these patients are cured with IT therapy alone [3]. As adjuvant or preventive therapy in children with newly diagnosed acute lymphoblastic leukemia, IT MTX alone or in combination with IT cytarabine or cranial radiation significantly reduces the meningeal relapse rate [13].

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A major limitation of IT drug administration is nonuniform distribution of drug throughout the subarachnoid space. After intralumbar injection of 6.25 or 12.5 mg/m^2, peak ventricular CSF MTX concentrations ranges from 0.6 to 22 μM, which is substantially lower than the 200 μM peak concentration achieved after an intraventricular dose of 6.25 mg/m^2 [20]. MTX concentration within the CSF after IT administration is dependent on the site and mode of administration, bulk CSF movement and absorption, choroidal drug uptake and clearance, and diffusion or transport of drug across the CSF-brain interface [6].

Surgically implanted ventricular access devices, such as the Ommaya reservoir, were developed to provide a convenient and reliable route of delivering drugs directly into the ventricular CSF [17]. Although there are no large, prospective comparative trials testing the efficacy of this route of administration, retrospective studies suggest that the use of these devices is more efficacious and less toxic than the traditional intralumbar route [9–11]. In addition, intraventricular MTX injection achieves higher and less variable drug concentrations in the ventricular CSF and better distribution of drug throughout the subarachnoid space [20].

In the present study, the distribution of MTX in CSF was studied in a nonhuman primate model designed to allow for simultaneous sampling of CSF from multiple sites within the subarachnoid space. Factors influencing CSF drug distribution were also investigated.

Materials and methods

Drugs and chemicals

MTX without preservative was kindly provided by Lederle Laboratories. For intraventricular bolus injection or infusion, MTX was diluted in Elliott's B Solution (Pharmaceutical Resources Branch, CTEP, NCI). Leucovorin, which was administered to animals after completion of CSF sampling to prevent systemic toxicity, was also provided by Lederle. Inulin, probenicid, and chemicals used in the MTX assay were obtained from Sigma Chemical Co. (St. Louis, Mo.). For IT administration, inulin and probenicid were diluted in Elliott's B Solution and sterilized by filtration through 0.22 μm filters (Millipore).

Animals

Seven adult male rhesus monkeys (*Macaca mulatta*) ranging in weight from 6.0 to 11.7 kg were used in these experiments. The animals were fed Purina Monkey Chow twice daily and were group-housed in accordance with the Guide for the Care and Use of Laboratory Animals [16]. Each animal had a lateral ventricular catheter attached to a subcutaneous access port for drug administration and a fourth ventricular catheter attached to an Ommaya reservoir for CSF sampling as previously described (Fig. 1) [14]. Lumbar CSF was obtained from a temporary lumbar catheter and CSF from the subarachnoid space at the vertex was sampled through a burr hole in the skull as previously described [2]. Blood samples following intravenous (i.v.) infusion of MTX were drawn from a central venous catheter placed in either the femoral or the saphenous vein contralateral to the site of drug infusion.

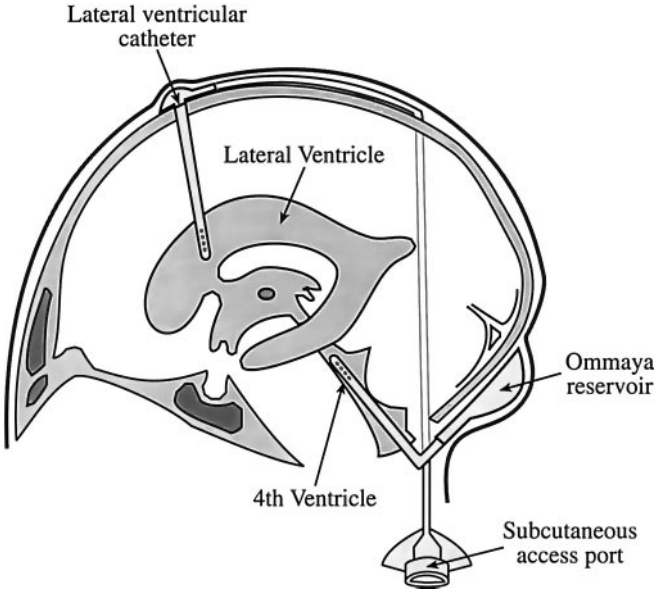

Fig. 1 Diagram of nonhuman primate model. CSF samples were obtained from the fourth ventricular catheter that is attached to a subcutaneous Ommaya reservoir, and MTX was administered intraventricularly through the access port that is attached to the lateral ventricular catheter

Experiments

CSF was obtained at frequent intervals from the fourth ventricular Ommaya reservoir and the lumbar space after a bolus intraventricular dose of 0.5 mg MTX ($n = 3$) and after continuous intraventricular infusions of 0.050 mg/day ($n = 3$), 0.2 mg/day ($n = 4$) and 0.5 mg/day ($n = 4$) of MTX infused over 24 to 168 h. The CSF volume in rhesus monkeys (13 to 15 ml, derived by calculating the CSF volume of distribution of inulin) is approximately one-tenth of that in humans, so that the 0.5-mg dose in the animal model is equivalent to a 5-mg dose in humans. The effect of the volume of infusate on the distribution of MTX within the subarachnoid space was studied by comparing fourth ventricular CSF and lumbar CSF MTX concentrations after a continuous infusion of 0.2 mg/day of drug in a volume of either 5 ml/day or 48 ml/day ($n = 2$). The effect of probenicid, which has previously been shown to inhibit the efflux of MTX from CSF [21], on the CSF distribution of MTX was evaluated in two animals. Fourth ventricular CSF and lumbar CSF MTX concentrations were measured at steady-state (C_{ss}) during a continuous intraventricular infusion of 0.2 mg/day of MTX without probenicid for the first 24 h (0 to 24 h) and then with 24 mg/day of probenicid in the infusate for the second 24 h (24 to 48 h).

The distribution of the large molecular weight marker compound, inulin, was also studied in the model by measuring fourth ventricular CSF and lumbar CSF C_{ss} after a continuous intraventricular infusion of 24 mg/day ($n = 2$) for 24 h.

The distribution of MTX over the cerebral cortices was studied during continuous intraventricular (0.2 mg/day for 24 h) and continuous i.v. (loading dose, 300 mg/m^2 over 1 h; infusion rate, 60 mg/m^2 per h) infusions of MTX in three animals. CSF was sampled from fourth ventricular CSF, lumbar CSF, and the subarachnoid space at the vertex at steady-state as previously described [2]. During the i.v. infusion, plasma samples were obtained simultaneously with the CSF samples.

Sample analysis

MTX concentration in CSF and plasma was measured with the dihydrofolate reductase inhibition assay [1]. Inulin concentration

was measured spectrophotometrically following reaction with indole-3-acetic acid [4].

Pharmacokinetic analysis

For the bolus intraventricular dose of MTX, the area under the CSF concentration-time curve (AUC) was estimated using the trapezoidal method. The CSF clearance was derived from the $\frac{Dose}{AUC}$ and the ratio of MTX concentrations in lumbar CSF to fourth ventricular CSF was derived from the ratio of the AUCs ($\frac{AUC_{Lumbar\ CSF}}{AUC_{Ventricular\ CSF}}$). For the continuous intraventricular infusions the clearance was derived from $\frac{Infusion\ rate}{C_{ss}}$ and the ratio of MTX concentrations in lumbar or subarachnoid CSF from the vertex to the concentration in fourth ventricular CSF was derived from the ratios of the C_{ss}.

Results

Bolus intraventricular injection

Fourth ventricular CSF and lumbar CSF MTX concentrations after a 0.5-mg bolus dose into the lateral ventricle are shown in Fig. 2A. The 1-h postdose fourth ventricular CSF MTX concentration ranged from 107 to 150 μM and the mean (range) AUC in fourth ventricular CSF was 411 $\mu M \cdot$ h (391 to 428 $\mu M \cdot$ h). The mean (range) terminal half-life of MTX in fourth ventricular CSF was 3.6 h (3.0 to 4.4 h) and the mean (range) clearance was 0.045 ml/min (0.043 to 0.047 ml/min).

Lumbar CSF MTX concentrations after the lateral ventricular bolus dose were more variable than fourth ventricular CSF drug concentrations. Peak lumbar CSF MTX concentrations ranged from 14 to 61 μM and the AUC ranged from 45 to 268 $\mu M \cdot$ h (mean, 151 $\mu M \cdot$ h). The mean (range) ratio of lumbar CSF to fourth ventricular CSF MTX concentration (AUC ratio) was 0.38 (0.11 to 0.69). The mean (range) apparent clearance of MTX derived from the lumbar CSF AUC was 0.20 ml/min (0.068 to 0.41 ml/min).

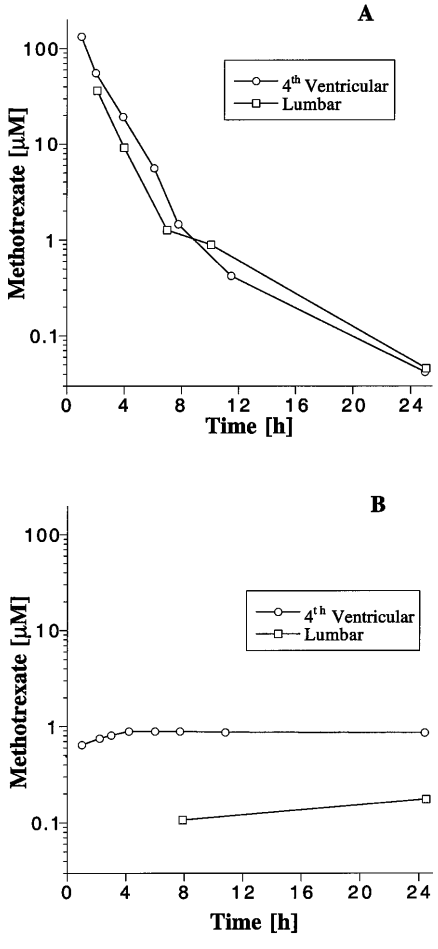

Fig. 2A,B CSF concentration-time profile of MTX in fourth ventricular CSF (○) and lumbar CSF (□) after a bolus dose of 0.5 mg (**A**) and an infusion of 0.05 mg/day (**B**) into the lateral ventricle. Points represent means from three animals

Intraventricular infusions

Fourth ventricular CSF and lumbar CSF MTX concentrations during a 24-h infusion of 0.05 mg into the lateral ventricle are shown in Fig. 2B. Fourth ventricular CSF MTX concentrations rapidly reach a steady state and the mean (range) C_{ss}^{V} was 0.85 μM (0.53 to 1.2 μM). Clearance of MTX from fourth ventricular CSF during the infusion ranged from 0.063 to 0.14 ml/min (mean, 0.10 ml/min). Lumbar CSF MTX concentrations were substantially lower than fourth ventricular CSF concentrations at the end of the infusion. The mean (range) C_{ss}^{L} was 0.22 μM (0.15 to 0.29 μM) and the C_{ss}^{L} to C_{ss}^{V} ratio ranged from 0.24 to 0.29.

Increasing the infusion dose rate to 0.5 mg over 24 h resulted in a mean (range) C_{ss}^{V} of 6.1 μM (4.5 to 7.1 μM) and a mean C_{ss}^{L} of 1.6 μM (range, 1.4 to 3.0 μM) for a mean C_{ss}^{V} to C_{ss}^{V} ratio of 0.27 (range, 0.20 to 0.49). The mean clearances of MTX derived from the C_{ss} in fourth ventricular CSF and lumbar CSF at this dose were 0.13 ml/min and 0.42 ml/min, respectively.

Intraventricular MTX infusions at a dose of 0.2 mg/day were performed for 72 h, 120 h, and 168 h, and fourth ventricular CSF and lumbar CSF were sampled daily. The mean (range) C_{ss}^{V} was 4.3 μM (2.8 to 5.1 μM) and the mean (range) clearance was 0.075 ml/min (0.060 to 0.11 ml/min). Even at infusion durations of up to 168 h, the gradient between fourth ventricular CSF and lumbar CSF MTX concentrations persisted. The mean (range) C_{ss}^{L} was 0.88 μM (0.63 to 1.3 μM) and the C_{ss}^{L} to C_{ss}^{V} ratio ranged from 0.14 to 0.30.

Inulin is a large molecular weight, inert compound that is restricted from readily diffusing out of the CSF because of its size. It has frequently been used as a marker compound to measure the CSF bulk flow rate. Continuous intraventricular infusion of inulin at a dose of 24 mg/day resulted in a mean C_{ss}^{V} of 373 μg/ml, a mean C_{ss}^{L} of 320 μg/ml and a C_{ss}^{L} to C_{ss}^{V} ratio of 0.87. The mean clearance of inulin from fourth ventricular CSF was 0.048 ml/min.

Infusate volume

An infusion dose rate of 0.2 mg/day was administered in a volume of either 5 ml/day or 48 ml/day to determine if increasing the infusate volume improves drug distribution. The latter rate was designed to be approximately equal to the CSF bulk flow rate. The mean C_{ss}^{V} at the 5 ml/day rate was 4.3 μM and at the 48 ml/day rate was 2.6 μM. The mean C_{ss}^{L} at the high and low infusate rates were 0.82 μM and 0.88 μM, respectively. Although the C_{ss}^{L} to C_{ss}^{V} ratio was higher with the higher infusate rate (0.38) compared with the lower infusate rate (0.22); this was due primarily to the dilution of the fourth ventricular CSF concentration, rather than improved delivery of drug to the lumbar CSF.

Probenicid

When probenicid (24 mg/day) was added to the infusate in two animals receiving 0.2 mg/day of MTX into the lateral ventricle, the mean C_{ss}^{V} increased from 5.1 μM to 6.4 μM, and the C_{ss}^{L} increased from 1.9 μM to 4.8 μM. The C_{ss}^{L} to C_{ss}^{V} ratio with probenicid was 0.83.

CSF from the vertex

The CSF MTX C_{ss} values from the fourth ventricle, lumbar space and vertex during i.v. and intraventricular infusions are listed in Table 1. C_{ss}^{V} during the i.v. infusion appeared to be lower than C_{ss}^{L} and the C_{ss} at the vertex. The mean CSF to plasma ratios (ratio of C_{ss} in CSF to that in plasma) during the i.v. infusion were 0.010 in fourth ventricular CSF, 0.044 in lumbar CSF and 0.019 at the vertex. During the intraventricular infusion the C_{ss} at the vertex (1.9 to 2.1 μM) was comparable to C_{ss}^{L} (1.1 to 1.5 μM).

Discussion

Although high concentrations of MTX can be achieved in the CSF after IT administration, the efficacy of this form of regional chemotherapy may be limited by nonuniform distribution of the drug in the subarachnoid space. The distribution of MTX within the CSF compartment is dependent on CSF bulk flow (0.4 ml/min in humans) and choroidal and arterial pulsations [6]. Although flow from the ventricles to the cistern is rapid, the flow rate from the cistern to the lumbar sac is only 0.035 ml/min in humans (equivalent to 0.0035 ml/min in our nonhuman primate model) [6]. As the CSF slowly circulates, MTX is eliminated from the CSF presumably by diffusion and transport across the CSF-brain interface (Fig. 3). In our model, the CSF MTX C_{ss} was dependent on the proximity of the sampling site to the site of drug administration, and clearance estimates derived from the C_{ss}^{L} were substantially higher than estimates derived from the C_{ss}^{V}.

After the bolus dose of intraventricular MTX, CSF MTX concentrations in the fourth ventricular CSF of primates were similar to concentrations reported in humans [7, 20]. Lumbar CSF concentrations were lower and more variable than fourth ventricular CSF after the intraventricular bolus dose. However, the distribution of MTX to the lumbar sac in these bolus experiments was probably affected by the five lumbar CSF samples required to calculate the AUC. The 1.5 to 2.0 ml of CSF removed over the 8 to 10 h after the dose would be

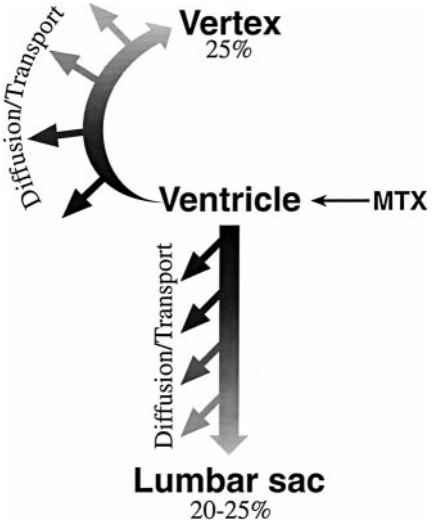

Fig. 3 Model depicting the disposition of MTX in the CSF after intraventricular administration. The clearance of MTX from CSF exceeds the CSF bulk flow rate and the flow rate from the cistern to the lumbar sac. As MTX slowly circulates to the vertex or lumbar sac it diffuses out or is transported out of the CSF through the meninges. As a result, the CSF concentration of MTX decreases as a function of the distance from the injection site, and the concentration at the vertex and in the lumbar sac is 20–25% of the concentration in ventricular CSF at steady-state

Table 1 Methotrexate distribution in the subarachnoid space at steady-state during continuous i.v. infusion (loading dose, 300 mg/m^2 over 1 h; infusion rate, 60 mg/m^2 per h) and continuous intraventricular infusion (intraventricular, 0.2 mg/day). Values are the means (ranges) from three animals

Route	Methotrexate C_{ss} (μM)			
	Plasma	Fourth ventricular CSF	Lumbar CSF	Vertex CSF
Intravenous	13.1 (12.1–15.3)	0.11 (0.096–0.17)	0.55 (0.25–0.78)	0.24 (0.15–0.35)
Intraventricular		5.8 (1.8–6.1)	1.2 (1.1–1.5)	1.5 (1.9–2.1)

predicted to almost double the flow rate of CSF into the lumbar sac, and this increase in the flow rate may have resulted in an over-estimation of the lumbar CSF MTX concentration. For the experiments in which MTX was administered by intraventricular infusion, the lumbar CSF was sampled at steady-state (8 and 24 h), and the lumbar to ventricular MTX concentration ratio was lower.

During continuous infusion of MTX into the lateral ventricle in the nonhuman primate model, CSF MTX C_{ss}^{L} values were only 20 to 25% of simultaneous C_{ss}^{V} values. In a single patient with recurrent meningeal leukemia treated at the NCI with continuous intraventricular infusions of 1 to 5 mg/day of MTX, the mean C_{ss}^{L} to C_{ss}^{V} was 0.26, suggesting that the nonhuman primate model may be predictive of MTX distribution in humans. A similar concentration gradient between fourth ventricular CSF and lumbar CSF was not observed with the large molecular weight marker compound, inulin, indicating that the lower lumbar CSF MTX concentrations were not the result of a dilutional effect resulting from CSF secretion by the spinal subarachnoid tissues, confirming previous reports [12].

This nonuniform distribution of MTX within the CSF compartment was not affected by the MTX dose, duration of infusion, or the infusate volume. The coadministration of probenicid resulted in an increase in the lumbar CSF MTX concentration relative to the fourth ventricular CSF concentration. MTX is taken up by choroid plexus in vitro by a probenicid-sensitive transport system [19]. However, our in vivo data suggest that this transport pump may be more widely distributed in the CNS, and that the concurrent administration of probenicid may improve the distribution of MTX within the CSF compartment. The mean clearance of MTX in fourth ventricular CSF after the bolus dose (0.045 ± 0.002 ml/min) was lower than mean clearance during the infusions (0.10 ± 0.03 ml/min), which is also consistent with the presence of a capacity-limited elimination mechanism (e.g. transport system) that is saturated at the high CSF MTX concentrations achieved after bolus administration. In experiments in primates in which MTX clearance was measured during ventriculolumbar perfusions, Blasberg and colleagues found evidence of a contribution from choroid uptake and diffusion of MTX into brain as mechanisms of drug elimination from CSF [6].

The vertex is the site of CSF absorption into the blood via the arachnoid villi. CSF MTX concentration at the vertex was equivalent to the concentration of drug in the lumbar CSF. Therefore, monitoring the MTX concentration in the lumbar CSF after an intraventricular dose may be a more accurate reflection of the minimal drug exposure achieved throughout the subarachnoid space than monitoring concentrations at the site of injection. During the i.v. infusion, the concentration gradient appeared to be reversed (fourth ventricular CSF MTX concentrations were lower than the lumbar CSF concentrations). We have observed this pattern with other agents administered i.v., such as the antiretroviral drug, lamivudine [5]. For MTX this disparity could be the result of a greater number of the probenicid-sensitive transport pumps in the choroid plexus than in the lumbar region. Although higher i.v. MTX doses and the resultant higher CSF MTX concentrations may overcome this disparity by saturating the pump capacity, for i.v. doses, fourth ventricular CSF appears to represent the site of minimum MTX exposure.

Current concepts of pharmacokinetics are derived primarily from drug disposition in plasma after parenteral or oral administration. After i.v. drug administration, mixing within the plasma compartment is nearly instantaneous because the circulation time $\left(\frac{Blood\ volume}{Cardiac\ output}\right)$ is <1 min, and, except for chemically reactive agents, drug is eliminated from plasma only when it circulates through excretory organs (liver or kidney). Therefore, within minutes of administering a drug i.v., the drug concentration in plasma obtained from any peripheral vein will be equivalent. The physiology of CSF accounts for the differences in the pharmacokinetic behavior of IT-administered drugs in the CSF when compared to plasma drug disposition after i.v. administration. The CSF circulation time $(\frac{CSF\ volume}{CSF\ bulk\ flow\ rate})$ is 6 to 8 h, and diffusion or transport of a drug from the CSF can apparently occur at any site in the CSF compartment. As a result, even under steady-state conditions the drug concentration in CSF is a function not only of the dose, but also of the distance from the site of drug injection (Fig. 3). In the presence of tumor infiltration of the meninges, CSF flow and MTX elimination are delayed [8, 15], and this could accentuate the incomplete distribution of the drug. These aspects of MTX disposition in CSF must be considered when interpreting CSF MTX concentrations and CSF pharmacokinetic studies.

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