INTRATHECAL METHOTREXATE NEUROTOXICITY:

CLINICAL CORRELATES AND ANTIDOTAL TREATMENT

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Abstract

The neurotoxicity of methotrexate (MTX) is more severe when administered intrathecally (IT) than by the oral and intravenous (IV) routes, and has been reported also with administration of therapeutic doses of 12 or 15 mg. Prompt recognition and treatment are essential to improve the outcome after IT-MTX overdose. Treatment options include CSF drainage or CSF exchange, ventriculolumbar perfusion, IT corticosteroids to reduce CSF inflammation and IV leucovorin to reduce systemic toxicity. Toxicity resulting from IT injection of leucovorin is controversial. CSF drainage and exchange are particularly effective if performed soon after the overdose. In this paper we propose a protocol of treatment for severe cases of IT-MTX overdose in excess of 100mg. CSF exchange is the mainstay of treatment combined with specific antidotal therapy consisting of high-dose IV leucovorin and IT dexamethasone followed by low-dose IT leucovorin. These measures constitute an effective treatment protocol for extremely high IT-MTX overdoses.

Key words:

intrathecal methotrexate, overdose, neurotoxicity, leucovorin, CSF exchange, intrathecal dexamethasone

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Due to the scarcity of reported cases there are no well-defined guidelines for treatment of excessively high IT overdoses of methotrexate. Survey of the literature shows that intrathecal doses of less than 100 mg were associated with little or mild toxicity; doses in excess of 100 mg, and mainly in excess of 500 mg, can cause severe morbidity and mortality. Prompt recognition and treatment are essential to improve the outcome of accidental overdoses. The mechanism of methotrexate (MTX) neurotoxicity is not fully elucidated, but more than one biochemical pathway is involved. Specific clinical manifestations of MTX neurotoxicity may be correlated to different biochemical mechanisms. The effect of MTX on the central nervous system (CNS) is immediate, dictating prompt intervention. This paper presents a brief survey of IT-MTX overdoses in excess of 100 mg reported in the literature.

Methods and Results

A computerized review of the medical literature published between 1966 and 2003 was performed. All case reports of IT-MTX overdose exceeding 100mg, eight times the therapeutic dose, were included. These cases include one patient treated recently by the authors of this paper (Finkelstein et al., 2003).

Table 1 summarizes the data of 9 patients who suffered from major intrathecal methotrexate overdose and compares the various treatments implemented as rescue procedures as soon as the overdose was recognized.

TABLE 1: Major intrathecal methotrexate (IT-MTX) overdoses

ent ler/age)	e (mg) IT-X	ical picture	atment	come	erence
		mptomatic	bar exchange, IV ovorin , DXM		bson, 1992
1		mptomatic	bar exchange, IV ovorin		bson, 1992
		ures	eucovorin, DXM	bvery	1997
		vulsions	eucovorin, DXM	bvery	1997
		nse pain, rtonia	eucovorin, DXM	bvery	, 1999
		te toxic ephalopathy	drainage triculolumbar usion, CPG2	bvery	Iarcaigh, 6
6		te toxic ephalopathy	perfusion, IV ovorin, nidine	bvery	gel, 1984
		te toxic ephalopathy	exchange, IV ovorin, DXM	th after bnth	nger, 1982
4	0	re low back , seizures	eucovorin, CSF nange, IT ovorin, DXM	bvery	telstein, 3

Abbreviations: DXM: dexamethasone; CSF: cerebrospinal fluid; CPG2: carboxypeptidase 2

Discussion

Neurotoxicity

The main target of MTX is the enzyme dihydrofolate reductase. MTX inhibits this enzyme (Fig.1). This results in a deficiency of reduced folate, a key intracellular compound, and thereby to decreased synthesis of both purines and pyrimidines (Erbe et al., 1975; Quinn and Kamen, 1996). MTX also interferes with transmethylation reactions which are crucial for the synthesis of proteins, lipids and myelin, presumably leading to demyelination (Fig. 1) (Harila-Saare et al., 1998).

Focal tissue necrosis was observed around the tip of a misplaced intraventricular catheter used to administer MTX (Packer et al., 1981). In another case, immediate monoparesis was observed in a child who moved forcefully during IT injection of MTX. The cord, which was directly exposed to MTX, was irreversibly damaged (Shuper et al., 2000).

Following IT administration of MTX, the CSF levels of methionine, S-adenosyl-homocysteine and homocysteine increased (Fig.1). Elevated levels of blood homocysteine are associated with endothelial cell injury and cerebrovascular infarcts. These structural lesions in brain tissue may account for the clinical focal neurological deficits and seizures as vascular-related phenomena of MTX neurotoxicity (Hankey and Eikelboom, 2001).

The inhibition of transmethylation reactions by MTX also affects catecholamine synthesis. Additional effects of MTX are increased levels of adenosine and decreased synthesis of

biogenic amine neurotransmitters. These effects might be relevant to MTX-induced seizures (Peyriere et al., 2001) (Fig.1).

The neurotoxicity of MTX is both route- and dose-dependent. When administered orally, MTX is mildly toxic to CNS. Relatively low CSF levels of MTX are obtained after a single IV dose. The water-soluble ionized compound given in single IV injections does not readily penetrate the blood-CSF barrier (Shapiro, Young and Mehta, 1975). In the treatment of CNS malignancies MTX is routinely injected intrathecally by lumbar puncture.

Clinical Correlates

IT administration of MTX was reported to cause acute leukoencephalopathy within 24-48 hours, manifested by generalized seizures, stupor and coma (Ettinger, Freeman and Creaven, 1982; Spiegel et al., 1984; O'Marcaigh et al., 1996). However, signs and symptoms of encephalopathy can be manifested subacutely days or weeks after administration. MTX-induced subacute encephalopathy is characterized by stroke-like episodes resulting in multifocal CNS deficits such as hemiparesis or dysphasia. These episodes are followed by an altered state of consciousness (usually stupor). Subacute encephalopathy typically occurs a few days after the second weekly IV dose of MTX and spontaneously resolves within 48-72 hours (Martino et al., 1984; Walker et al., 1986).
A 21 year old male patient diagnosed with T-cell acute lymphoblastic leukemia was treated with 12 mg IT-MTX at intervals up to day 102; complete remission was achieved by day 28 (Shore, Barnett and Phillips, 1990). Forty eight hours after the last MTX dose (on day

104) massive cerebral edema, herniation and brain death occurred. This is a case of progressive leukoencephalopathy on the basis of cumulative doses of IT- MTX.

The volume of MTX injected intrathecally into the lumbar sac is an important factor in its distribution within the cerebral subarachnoid space and ventricular system. The injected volume required for the drug to reach the basal cisterns should exceed 10% of the estimated total volume of human CSF which is 135 ml (Reiselbach et al., 1962). However, it is difficult to assess the adequate subarachnoid distribution of the drug after IT administration via routine lumbar puncture. Extradural and subdural leakage of drug might occur despite the fact that lumbar punctures are performed under strict scrutiny (Shapiro, Young and Mehta, 1975).

IT-MTX can also cause chronic delayed leukoencephalopathy characterized by progressive personality changes and dementia, focal neurological signs and occasionally seizures. These signs and symptoms are usually irreversible. A few cases of chronic delayed leukoencephalopathy have been reported following high-dose or even standard dose IV-MTX (Prince and Jamieson, 1975; Rubinstein et al., 1975). Symptoms may appear months to years after therapy beginning typically three months after MTX administration and resulting in dementia (Keime-Guibert, Napolitano and Delattre, 1998).

White matter changes can be observed on magnetic resonance imaging (MRI) before neurologic symptoms occur (Lien et al., 1991). These changes reflect the pathological findings of demyelination, necrosis and angiopathy. In patients with acute or subacute encephalopathy, CSF analysis and computerized tomography (CT) of brain are within

normal limits. However, EEG usually shows diffuse or focal slowing of electrical activity (Walker et al., 1986).

Several mechanisms may contribute to the occurrence of widespread periventricular lesions and leukoencephalopathy. The periventricular white matter is exposed to particularly high concentrations of MTX, penetrating from the ventricles only a few millimeters into the surrounding parenchyma (Blasberg, Patlak and Shapiro, 1977). White matter seems to be sensitive to MTX, administered IT or intraventricularly via an Ommaya reservoir (Blasberg, Patlak and Shapiro, 1977). Clinically symptomatic or asymptomatic white matter lesions have also been observed in young patients treated with high-dose or ultrahigh-dose IV-MTX (Lien et al., 1991; Lovblad et al., 1998).

Treatment

There are few reports, and therefore, there are limited data for the management of major intrathecal methotrexate overdose. The highest reported intrathecal dose after which the patient survived was 1200 mg, an 80-fold overdose (Finkelstein et al., 2003).

We propose CSF exchange and intravenous leucovorin as the mainstay of treatment. CSF exchange facilitates the removal of methotrexate following massive overdose and persistent extremely high CSF levels.

Prompt administration of high-dose intravenous leucovorin (mg per mg of IT- MTX) followed by a regular leucovorin protocol eliminates systemic manifestations of MTX toxicity, which is highly likely due to high plasma levels due to continuous MTX absorption from the CSF reservoir (Finkelstein et al., 2003).

Leucovorin (folinic acid) is a tetrahydrofolate (THF) derivative, which is a cofactor in 1-carbon transfer reactions in purines and pyrimidines synthesis. Since MTX inhibits the formation of THF as well as THF-dependent enzymes in the purines and pyrimidines synthesis pathway, leucovorin is used as rescue therapy for MTX. Leucovorin enters normal cells in preference to tumor cells because of differences in membrane transport mechanisms (Jaffe et al., 1974; Frei et al., 1975). Systemic leucovorin is a mainstay of therapy for MTX overdose.

There is a controversy regarding the toxicity of IT injection of leucovorin. Leucovorin can lower seizure threshold and therefore has epileptogenic potential (Meropol et al., 1995; Smith and Carl, 1982). IT leucovorin was implicated in causing neurotoxicity and death in a child following a mild overdose (20 mg) of IT-MTX (Jardine, Ingram and Bleyer, 1996). We propose to administer low-dose IT leucovorin along with dexamethasone at the end of the exchange if significant CSF levels of MTX persist. In our experience no leucovorin neurotoxicity was detected during follow up.

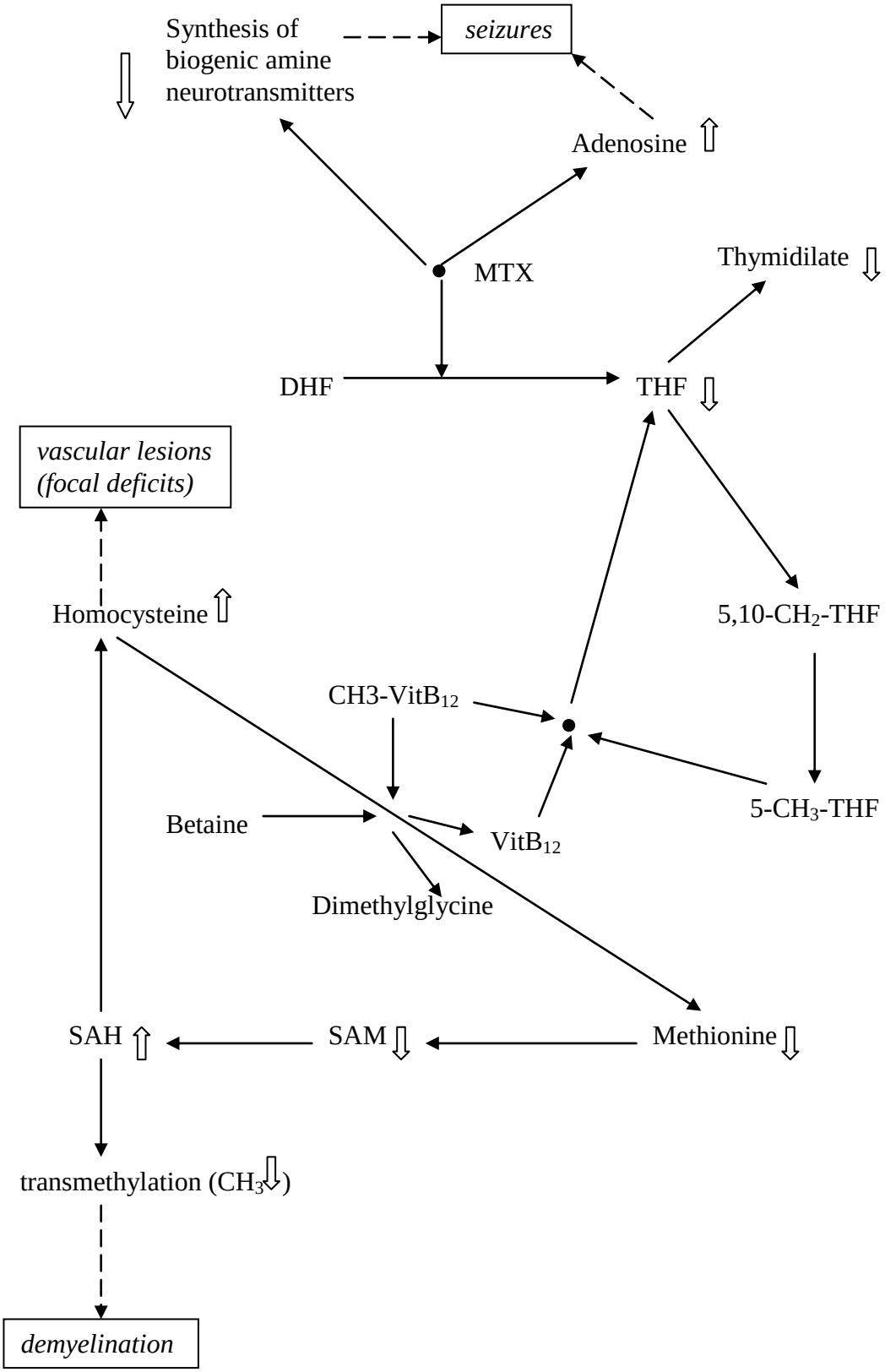
The rationale for the use of dexamethasone in IT-MTX overdoses has been the development of chemical arachnoiditis, manifested by headache, back pain, nuchal rigidity and fever (Bleyer, 1978). Indeed, this procedure enhances CSF flow via the intrathecal catheter thus increasing the amount of CSF exchanged (Finkelstein et al., 2003).

Regarding carboxypeptidase G2, this enzyme hydrolyzes MTX into inactive metabolites. It was tested experimentally in monkeys (Adamson et al., 1991) and used successfully in humans (O'Marcaigh et al., 1996).

Based on the reported cases and on our own experience we propose high-dose intravenous leucovorin, CSF exchange and intrathecal dexamethasone followed by low-dose IT leucovorin as an effective treatment protocol for extremely high IT-MTX overdose.

Figure 1 **– Neurotoxic effects of MTX –**

metabolic pathways and possible clinical correlates



Abbreviations

DHF=dihydrofolate
THF=tetrahydrofolate
SAH=S-adenosyl-homocysteine
SAM=S-adenosyl-methionine

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