

Treatment of intrathecal methotrexate overdose with folinic acid rescue and lumbar cerebrospinal fluid exchange: A report of two cases

Yüksek doz intratekal metotreksat'ın folinik asit ve beyin omurilik sıvısı değişimi ile tedavisi: İki olgu sunumu

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Abstract

We report two male cases (4- and 5-years-old) of intrathecal methotrexate overdose. The two boys with acute lymphoblastic leukemia were to receive intrathecal injection of methotrexate. Instead of the prescribed 12 mg, they both received a dose of 120 mg. The initial cerebrospinal fluid samples showed methotrexate concentration of $2.24 \times 10^{-2} \text{M}$ in case 1 and $1.32 \times 10^{-2} \text{M}$ in case 2. The cases were successfully treated with cerebrospinal fluid (CSF) exchange and intravenous folinic acid rescue. The favorable outcome in our cases suggests that CSF exchange is safe and that folinic acid rescue may be adequate to prevent sequelae in patients subjected to intrathecal MTX overdoses up to 120 mg. We propose CSF exchange and intravenous folinic acid as the mainstay of treatment. In addition to the staff's failure to check the drug label carefully, the marked resemblance of the two dose preparations of MTX may have been contributory. (*Turk J Hematol* 2011; 28: 63-7)

Key words: Methotrexate, intrathecal, overdose, treatment

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Özet

İntratekal (IT) metotreksat uygulaması, merkezi sinir sistemi lösemisinin önlenmesi ve tedavisinde yaygın olarak kullanılmaktadır. Metotreksatın yüksek dozda veya uzun süreli uygulamaları ciddi nörotoksititeye yol açabilir. Burada, hatalı olarak yüksek dozda intratekal metotreksat verilen iki olgu sunulmaktadır. Akut lenfoblastik lösemi tanısıyla izlenen 4 ve 5 yaşlarındaki iki erkek olguya, reçete edilen 12 mg yerine yanlışlıkla 120 mg dozunda intratekal metotreksat uygulandı. Uygulama sonrası başlangıç beyin omurilik sıvısı metotreksat düzeyleri sırasıyla $2.24 \times 10^{-2} \text{M}$ ve $1.32 \times 10^{-2} \text{M}$ idi. Olgular beyin omurilik sıvısı değişimi ve intravenöz folinik asit desteği ile başarılı bir şekilde tedavi edildiler.

Takiplerinde klinik gidişin iyi olması, 120 mg'a kadar yüksek doz intratekal metotreksat uygulanmış hastalarda, beyin omurilik sıvısı değişimi ve folinik asit kurtarma tedavisinin sekelleri önleme açısından yeterli olabileceğini göstermektedir. Bu hatalı uygulamaya asistanların ilaç dozlarını kontrol etmedeki hatalarının ve farklı dozlardaki metotreksat preparatlarının benzer kutularda üretilmesinin yol açtığı düşünülmüştür. (Türk J Hematol 2011; 28: 63-7)

Anahtar kelimeler: Metotreksat, intratekal, yüksek doz, tedavi

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Introduction

Intrathecal (IT) methotrexate (MTX) therapy is used widely for the prevention and treatment of central nervous system (CNS) leukemia [1,2]. IT injection of MTX is becoming more popular, and may be the only form of CNS-directed therapy in selected patients [2]. Exposure to MTX in high concentrations or for sustained periods is clearly neurotoxic, and various dosage recommendations have been suggested to avoid neurotoxicity [3,4]. Clinical studies indicate that adults should receive a maximal IT dose of 12.5 mg of MTX to avoid acute clinical neurotoxicity. Rescue treatments of IT MTX overdose may include cerebrospinal fluid (CSF) exchange, ventricular washout, folinic acid rescue, and the investigational agent carboxypeptidase G2, an enzyme that rapidly hydrolyzes MTX into inactive metabolites [5-9]. There are only a few reports of patients with IT MTX overdose in the literature, and the management has not been uniform. In this paper, we report two cases of IT MTX overdose. Similar reports from the literature and their management are reviewed.

Case Reports

Case 1

A four-year-old boy, diagnosed with pre-B cell acute lymphoblastic leukemia (ALL) without CNS involvement, started treatment according to the TRALL-BFM 2000 protocol for standard-risk ALL. The incident occurred when he received the fourth course of a 36-hour (h) continuous infusion of high-dose MTX (HD-MTX, 1 g/m²). One hour later, a dose of 120 mg MTX instead of the prescribed 12 mg was administered IT. Fifteen minutes later, the patient complained of intense pain in his legs. Sixty minutes after the IT MTX, the patient developed headache and generalized hypertonia, and then IT MTX overdose was suspected. The other physical find-

ings of the patient were normal except for anxiety and generalized hypertonia. Systemic MTX infusion was stopped immediately and exchange of lumbar CSF was started 90 minutes (min) after the IT MTX. He was returned to the operating theater and a repeat lumbar puncture was performed under general anesthesia. Twenty milliliters of dark yellow CSF was removed by gravity over a period of 20 min. No complication was observed during the procedure. CSF MTX concentrations were measured by means of an enzyme-inhibition technique [10]. The initial CSF sample had MTX concentration of 2.24 x 10⁻² M. 20 ml saline was administered IT instead of CSF 1.5 h after the IT HD-MTX. Twenty milliliters of normal saline was then introduced, started approximately 1.5 h after the IT dose. Subsequently, 210 ml of CSF were removed in 5-ml portions and replaced by a corresponding volume of pre-warmed normal saline. Thus, a total volume of 230 ml was exchanged, equivalent to 200 ml/m², over a period of 2 h and 15 min [7]. Two hours after the IT MTX, folinic acid was started intravenously (IV) at a dose of 100 mg single, and then doses of 10 mg every 6 h for 24 h [5,13,15,16]. Dexamethasone was also used at a dose of 0.15 mg/kg IV every 6 h for 2 days. CSF examination, liver and kidney functions and electrolytes were found in normal limits. At 1 and 6 months, electroencephalogram (EEG) and a brain computed tomography (CT) scan were normal. The patient remained in normal neurological status thereafter. No signs of neurotoxicity were observed during the following four years.

Case 2

The second patient was a five-year-old boy with T cell ALL, without CNS involvement, in whom treatment was started according to the TRALL-BFM 2000 protocol for medium-risk ALL. During the maintenance phase (Protocol II 45th day therapy), an IT dose of 120 mg of MTX instead of the intended 12 mg was accidentally given by the pediatrics staff.

A vial with a 10-fold higher concentration of MTX had erroneously been used for the preparation of the injection solution. Ninety minutes after the IT, the patient developed headache. The mistake was discovered 2 h later, and then 200 ml of CSF were exchanged with normal saline in 5-ml portions over a 3-h period via lumbar puncture. The initial CSF sample had a MTX concentration of 1.32×10^{-2} M. Two hours after the IT MTX, folinic acid was started IV at a dose of 100 mg single, and then doses of 10 mg every 6 h for 24 h. Dexamethasone was also used at a dose of 0.15 mg/kg IV every 6 h for 2 days. No neurological signs were observed before or after the CSF exchange procedure. The child remained asymptomatic in complete remission, and EEG and CT of the brain performed six months after the incident were normal. Written informed consent was obtained from both of the patients' family.

Discussion

Methotrexate (MTX) has been used extensively in the treatment of various malignancies, including lymphoblastic leukemia and lymphoma. HD-MTX with leucovorin rescue is used to treat osteosarcoma ($8-12 \text{ g/m}^2$) and ALL ($\leq 8 \text{ g/m}^2$). The toxic effects of MTX are myelosuppression, mucositis, nephrotoxicity, hepatotoxicity, and neurotoxicity with acute or chronic encephalopathy [11-17]. Acute encephalopathy generally develops within 5-14 days after IT MTX or HD-MTX and may include headache, nausea, emesis, lethargy, altered mental status, blurred vision, aphasia, hemiparesis, and seizure. Chronic encephalopathy develops slowly, may progress, and can permanently impair neurologic function. Transient acute encephalopathy has been clinically observed in 3%-15% of cancer patients after HD-MTX [12,15,16]. Most patients can resume MTX therapy without permanent neurological sequelae, although 10% - 56% may experience recurrence on rechallenge [12,15,16]. The pathophysiology of MTX-induced acute encephalopathy is largely unknown but does not appear to be related to MTX pharmacokinetics [12]. The usual dose for IT administration is 12-15 mg. Management of IT MTX overdose is not uniform and, in fact, cases described in the literature have been treated with different approaches [18-24]. The highest reported IT dose given to patients who survived was 650 mg

[5]. The neurotoxicity of MTX is both route- and dose-dependent. There is little neurotoxicity when MTX is given orally or intravenously, as the drug does not reach significant concentration in the CSF. However, IV HD MTX has been associated with CNS toxicity, and systemic toxicity may be seen following IT administration. Common findings included behavioral abnormalities, focal sensorial and motor signs and abnormal reflexes [15]. Manifestations of IT MTX overdoses are dose-dependent. It is associated with little or mild toxicity at less than 100 mg. However, doses in excess of 100 mg, and particularly in excess of 500 mg, may cause significant morbidity and mortality [5,19].

To our knowledge, 13 cases of IT MTX overdose have been reported in the literature (Table 1). Twelve of the 13 reported incidents involved children between the ages of 2-12 years. Eight patients suffered from ALL and the other four had non-Hodgkin's lymphoma. Nine cases received 20-125 mg of IT MTX. In one of them, folinic acid rescue was administered IT and resulted in a fatal event. Nine cases were treated with folinic acid, dexamethasone and CSF exchange. No neurologic long-term sequelae were observed in any of these nine patients [20-24]. Three cases received 600-650 mg of IT MTX and underwent ventriculolumbar perfusion or CSF exchange, which are considered effective if performed promptly [5,6,18]. In ventriculolumbar perfusion, CSF is exchanged for warmed, isotonic saline solution [6,18].

From these reports, it is obvious that severe toxicity is expected when an IT MTX overdose of more than 600 mg occurs. Carboxypeptidase G1 and G2 are investigational agents that rapidly hydrolyze MTX into inactive metabolites [9]. It has been successfully used IT for treatment of IT MTX overdose [18]. However, these agents are not commercially available at present.

Incorrect prescription and failure to check the drug label carefully prior to the injection are apparently the most immediate errors [25]. In our reported cases, the marked resemblance of the two strengths of parenteral MTX preparations (i.e. 50 mg/5 ml and 500 mg/5 ml, respectively) may also have been contributory.

In conclusion, our patients were treated successfully with IV high doses of folinic acid and lumbar CSF exchange. Cases receiving overdoses of IT MTX should first be treated with CSF exchange and IV

Table 1. Reported cases of intrathecal methotrexate overdose

Reference	Age (year)	IT MTX dose (mg)	Rescue treatment	Folinic acid dose
Ettinger (5) *	9	650	CSF exchange IV folinic acid + dexamethasone	50 mg x2 + 12 mg q6 h x 2 wk
Spiegel et al. (6)	26	625	Ventriculolumbar perfusion IV folinic acid + thymidine	200 mg/m ² q3 h x 8 + 150 mg q3 h x 32
O'Marcaigh et al. (18)	6	600	Ventriculolumbar perfusion IV folinic acid + dexamethasone Carboxypeptidase-G2 IT	1000 mg/m ² +100 mg/m ² q3 h x 12
Riva et al. (23)	7	300	IV folinic acid + dexamethasone	120 mg/m ² levo product q3 h x 8 + q6 h x 4
Lee et al. (24)	3	125	IV folinic acid + dexamethasone	15 mg q3 h x 8 + 30 mg q6 h x 12
Lee et al. (24)	4	125	IV folinic acid + dexamethasone	15 mg q3 h x 8 + 30 mg q6 h x 12
Jakobson et al. (7)	11	120	CSF exchange IV folinic acid	90 mg + 15 mg q3 h x 16
Jakobson et al. (7)	4	100	CSF exchange IV folinic acid + dexamethasone	Not specified
Ettinger et al. (22)	2	85	IV folinic acid + dexamethasone	85 mg + 6 mg q6 h x 4
Addiego et al. (20)	12	50	CSF exchange IV folinic acid + dexamethasone	Not specified
Addiego et al. (20)	4	50	CSF exchange IV folinic acid + dexamethasone	12 mg q12 h x 6
Lampkin et al. (21)	4	52	IM folinic acid	12 mg + 6 mg q4 h x 9
Jardine et al. (19) *	11	20	IT folinic acid + IV folinic acid	100 mg q4 h x 24

*: Fatal outcome; IT: Intrathecal; IV: Intravenous; MTX: Methotrexate

folinic acid rescue. More important, doctors and nurses who treat malignant diseases must be very careful in all stages of disease care, such as in the prescribing, ordering and administering of medicines and the following of adverse or unexpected effects.

Conflict of interest statement

None of the authors of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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