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Ketamine as a Sedative for Methotrexate-Induced Neurotoxicity with Added NMDA Antagonism

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Abstract

MTX is used in the treatment of several childhood cancers and has side effects of varying severity [1]. Neurotoxicity can occur in up to 15% of patients receiving high-dose MTX [2, 3]. Elevated homocysteine in CSF are documented in such cases. Dextromethorphan, an NMDA receptor antagonist, suppresses homocysteine activity and is the initial treatment. Ketamine, also an NMDA receptor antagonist, may be considered as an optimal treatment choice in intubated patients requiring sedation. We describe the use of ketamine in a pediatric patient with methotrexate-induced neurotoxicity. Ketamine as treatment of MTX-induced neurotoxicity has not been described in the literature.

Case Report

Abstract

MTX is used in the treatment of several childhood cancers and is a main component of the treatment regimen for osteosarcoma. MTX has been linked with side effects of varying severity; Headaches, nausea, emesis, lethargy, blurred vision, aphasia, hemiparesis, paresis, convulsions, leucoencephalopathy, and arachnoiditis are symptoms of MTX toxicity [1]. MTX-induced neurotoxicity can occur in up to 15% of patients receiving high-dose MTX [2, 3]. The effects may be transient but can have life-threatening implications, sometimes requiring intubation for respiratory support.

Elevated homocysteine levels in the CSF are documented in cases of MTX-induced neurotoxicity; Dextromethorphan is used as an initial treatment for MTX-induced neurotoxicity as it works as a non-competitive antagonist for the NMDA receptors and suppresses homocysteine activity. In severe cases requiring intubation, medications for sedation are utilized. Ketamine is also an NMDA receptor antagonist, and as such, may be considered as an optimal treatment choice when sedation is required. We describe the use of ketamine in a pediatric patient with methotrexate-induced neurotoxicity. The use of ketamine in the treatment of MTX-induced neurotoxicity has not been described in the literature.

A 15 -year -old male patient undergoing treatment for a distal femur osteosarcoma, status post ten weeks of chemotherapy with a regimen containing adriamycin, cisplatin, and Methotrexate (MTX), presented to the Emergency Department (ED) reporting left upper extremity weakness. He was discharged from the hospital after clearing high-dose MTX two days prior to presentation. The day prior to ED presentation, he felt weakness in his left hand when playing videogames, which progressed the next day to involve his left arm. Upon arrival to the ED, his neurological exam was significant for left upper extremity strength 1/5 with all other extremities 5/5 strength. Sensation in the left upper extremity was intact. He was alert and interactive and in no apparent distress, with stable vital signs.

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CT scan of the head and CT angiogram of brain and neck did not show any abnormalities. MRI of the brain showed hazy signal abnormality within the fronto-parietal white matter (right side greater than left), demonstrating restricted diffusion on DWI sequence. Diagnostic concerns for demyelination and leukoencephalopathy were noted. While still in the ED, patient developed a left-sided facial droop and was unable to swallow liquid medication. He soon become somnolent with respiratory distress and was intubated.

The patient was sedated with dexmedetomidine and fentanyl infusions and was started on levetiracetam for seizure prophylaxis. Dextromethorphan was initiated through an orogastric tube to treat presumed MTX-induced neurotoxicity and was continued throughout hospital stay. Within 12 hours of initial treatment, a slight improvement in strength was noted and treatment with aminophylline was discussed but not given at that time. The dexmedetomidine and fentanyl infusions were replaced by a ketamine infusion for its NMDA receptor antagonist properties and was dosed at 30mcg/kg/min, in consultation with toxicology recommendations. While on ketamine, the patient was able to communicate by shaking or nodding his head. He also was able to demonstrate improved strength in his left hand as he was able to squeeze when requested.

36 hours after admission, the patient was extubated and the ketamine was discontinued at this time and the patient regained all bulbar function. While all bulbar nerves were intact, the patient was sleepy and did not initiate communication but was responsive to questions. The patient received his normal morning medications, and after his levetiracetam dose had a change in mental status with depressed mood, minimal responsiveness to commands, responding only to noxious stimuli. Aminophylline 2.5mg/kg was administered and during the infusion the patient returned to his baseline mental status with normal musculoskeletal strength exam. VEEG was initiated and showed intermittent semi-rhythmic short runs of bisynchronous frontal hemispheric slowing, consistent with cerebral electrophysiological dysfunction that resolved the following day. No seizure activity was noted. Patient was discharged 4 days after admission with no focal neurological deficit and back to baseline behavior.

Discussion

Elevated homocysteine and elevated adenosine levels in the cerebrospinal fluid have both been implicated in MTX-induced neurotoxicity. MTX inhibits dihydrofolate reductase (DHFR), which results in decreased folate and cobalamin, and increased homocysteine levels. Elevated homocysteine levels has been reported in the cerebrospinal fluid (CSF) of patients with MTX toxicity and can cause seizures and vascular disease. An analogue of glutamate, homocysteine is an NMDA receptor agonist; thus, accumulation of large quantities of homocysteine in the CNS can cause neuronal damage and apoptosis via excitotoxicity [1, 4, 5]. Dextromethorphan is a non-competitive antagonist for the NMDA receptors and suppresses homocysteine activity, so is often used as the first line treatment for MTX-induced neurotoxicity [6]. MTX treatment is reported to lead to high levels of adenosine in the CSF. Adenosine interferes with neurotransmitter synthesis and release, further contributing to MTX-induced neurotoxicity [7]. Aminophylline is a competitive agonist of adenosine receptors and therefore is used in treatment of MTX-induced neurotoxicity [8]. Ketamine has historically been used for sedation however, more recently, studies have proven that sub-anesthetic doses of ketamine have immediate effects in treatment resistant major depressive disorder and bipolar depression [9]. An NMDA receptor antagonist and synaptic glutamatergic modulator, ketamine exerts antidepressant effects as rapidly as 24 hours after administration. The behavioral changes seen in response to the rapid-acting antidepressant effects associated with ketamine may be more directly linked to direct modulation of glutamate in affected brain regions [10]. Apart from its competitive antagonistic properties at the NMDA receptor to counter the effects of MTX, the immediate mood changes in our patient after withdrawal of ketamine may be explained through the mechanism discussed above. This case highlights the clinical benefits of using ketamine for patients with MTX-induced neurotoxicity. Once the ketamine infusion was started, in conjunction with the continued dextromethorphan, our patient's clinical condition improved with increased strength on the left side of his body and improved mental status. Once the ketamine was discontinued, and after the levetiracetam was administered, the patient clinically regressed. However, it is important to note that the regression was most likely attributed secondary to the ketamine withdrawal as opposed to the levetiracetam, and that the timing was coincidental. He displayed mood changes and appeared agitated as

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demonstrated by facial grimacing. He was also unresponsive to commands unless he was firmly addressed, which was different from his demeanor while on ketamine. However, after administering aminophylline, these symptoms quickly reversed back to baseline. Patients with MTX-induced neurotoxicity may require intubation for rapidly declining mental status and airway compromise, thus requiring sedation. Ketamine is an NMDA receptor antagonist and should be strongly considered for sedation as it may lower the toxic effects of homocysteine at the receptor level. This report describes the effect of ketamine as a choice of sedative in a teenage patient with osteosarcoma intubated due to MTX-induced neurotoxicity and also highlights the potential side effects of abrupt withdrawal of this medication which could be weaned more slowly peri-extubaiton

Conclusion

While dextromethorphan and aminophylline are known treatments for MTX-induced neurotoxicity, ketamine may be a useful adjunct if the patient requires sedation, as it contributes to NMDA receptor antagonism. We present a case of MTX-induced neurotoxicity in a pediatric patient treated with dextromethorphan, aminophylline and ketamine. We are not aware of any other documented cases of MTX-induced neurotoxicity treated with ketamine.

Conflict of Interest

We have no conflicts of interest to disclose.

References

1. Schmidt LS, Kjær TW, Schmiegelow K, Born AP. EEG with extreme delta brush in young female with methotrexate neurotoxicity supports NMDA receptor involvement. *Eur J Paediatr Neurol* . 2017;21(5):795-797. doi:10.1016/j.ejpn.2017.05.008
2. Oarbeascoa G, Rodriguez-Macias G, Guzman-de-Villoria JA, et al. -Induced Subacute Neurotoxicity Surrounding an Ommaya Reservoir in a Patient with Lymphoma. *Am J Case Rep* . 2019;20:1002-1005. Published 2019 Jul 11. doi:10.12659/AJCR.915632
3. Brugnoletti F, Morris EB, Laningham FH, et al. Recurrent intrathecal methotrexate induced neurotoxicity in an adolescent with acute lymphoblastic leukemia: Serial clinical and radiologic findings. *Pediatr Blood Cancer* . 2009;52(2):293-295. doi:10.1002/pbc.21764
4. Li Y, Vijayanathan V, Gulinello M, Cole PD. Intrathecal methotrexate induces focal cognitive deficits and increases cerebrospinal fluid homocysteine. *Pharmacol Biochem Behav* . 2010;95(4):428-433. doi:10.1016/j.pbb.2010.03.003
5. Vijayanathan V, Gulinello M, Ali N, Cole PD. Persistent cognitive deficits, induced by intrathecal methotrexate, are associated with elevated CSF concentrations of excitotoxic glutamate analogs and can be reversed by an NMDA antagonist. *Behav Brain Res* . 2011;225(2):491-497. doi:10.1016/j.bbr.2011.08.006
6. Afshar M, Birnbaum D, Golden C. Review of dextromethorphan administration in 18 patients with subacute methotrexate central nervous system toxicity [published correction appears in Pediatr Neurol. 2014 Oct;51(4):593]. *Pediatr Neurol* . 2014;50(6):625-629. doi:10.1016/j.pediatrneurol.2014.01.048
7. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. *Oncologist* . 2016;21(12):1471-1482. doi:10.1634/theoncologist.2015-0164
8. Bernini JC, Fort DW, Griener JC, Kane BJ, Chappell WB, Kamen BA. Aminophylline for methotrexate-induced neurotoxicity. *Lancet* . 1995;345(8949):544-547. doi:10.1016/s0140-6736(95)90464-6
9. Lener MS, Kadriu B, Zarate CA Jr. Ketamine and Beyond: Investigations into the Potential of Glutamatergic Agents to Treat Depression. *Drugs* . 2017;77(4):381-401. doi:10.1007/s40265-017-0702-8
10. Zhuo C, Lin X, Tian H, Liu S, Bian H, Chen C. Adjunct ketamine treatment of depression in treatment-resistant schizophrenia patients is unsatisfactory in pilot and secondary follow-up studies. *Brain Behav* . 2020;10(5):e01600. doi:10.1002/brb3.1600