**RESEARCH ARTICLE**

**PEDIATRIC CASE OF ACCIDENTAL ORAL OVERDOSE OF METHOTREXATE.**

Mohammed Almadan, Hedayah Hodyah and Ghurran Hodyah.
Pediatrics Department, King Fahad of The University Hospital, Khobar, Kingdom of Saudi Arabia.

---

**Manuscript Info**

**Abstract**

We present the second youngest reported case of a single oral overdose of methotrexate in a 19-month-old child. Initial history revealed possible ingestion of 10 tablets, each containing 2.5 mg. The peak methotrexate level was 92 mmol/L measured 8 hours following ingestion.

---

**Introduction:**

Paediatric cases of accidental overdose have been one of the most common causes of injury in children less than 5 years of age. Although preventive measures have decreased the incidence of paediatric overdose, it continues to occur. Early recognition and treatment is essential to prevent morbidity and mortality. Our case is a paediatric accidental oral overdose of methotrexate, the management is not well established, it's mainly based on experience following parenteral overdose of methotrexate in children.

**Case Report:**

A 19-month-old girl presented to the paediatric emergency of King Fahad Hospital of the University. Two hours after she was discovered by her mother that she was playing with her grandmother's methotrexate tablets at had fallen to the floor, and some were in her mouth. The exact number of tablets was not known, but each tablet contained 2.5 mg of methotrexate. The total tablet was 50 tablets. There was no history of ingestion and presentation to local hospital. The patient was given activated charcoal and sent home, but she presented to the emergency department. The child was otherwise well with no significant medical history. The child had no history of nausea, vomiting, abdominal discomfort or stool changes, and was not on any medication.

She appeared well and alert with normal observation. Her weight was 11.2 kg and clinical examination was unremarkable. The patient was admitted for observation. A peripheral intravenous line was established and blood samples were sent for routine laboratory studies with determination of methotrexate levels. The initial methotrexate level was not available from a reference laboratory; however, because the patient had not taken any 25 mg of methotrexate (51 mg/m²), she was admitted to the paediatric ICU for monitoring. Serial laboratory studies and leucovorin therapy were given as needed. She was managed initially with IV hydration with sodium bicarbonate (40 mg/l) and folinic acid given orally in doses of 1 mg/day.

The following morning it was decided to start treatment with 10 mg of calcium folinate infusion (leucovorin) every 8 hours, which is equal to 40 mg/day equivalent to the maximum dose of methotrexate ingested (1 mg/mgMTX).

**Corresponding Author:** Mohammed Almadan.
Address: Pediatrics Department, King Fahad of The University Hospital, Kobar, Kingdom of Saudi Arabia.
The children remained in the paediatric ward while she completed 72 hours of leucovorin rescue. Later that first day of admission, the methotrexate level from the initial blood test confirmed a toxic level 0.92 µmol/litre. The dose of calcium folinate was 10 mg six hourly on day 2, and 15 mg six hourly on day 3 based on the corresponding methotrexate level. On day 4, the methotrexate level was less than 0.02 µmol/litre and calcium folinate discontinued.

**Discussion:**

Methotrexate (MTX), a folic acid analogue and antagonist, is used in the treatment of particular cancers, autoimmune diseases, placenta accrete and ectopic pregnancy. MTX binds to the enzyme dihydrofolate reductase (DHFR), inhibiting the formation of reduced folate and thymidylate synthetase, resulting in the inhibition of de novo thymidylate, purine and protein biosynthesis.

At oral doses of < 20 mg/m², MTX is rapidly absorbed by an active saturable transport mechanism with a bioavailability of 50–95%. A peak concentration of 0.3–2.2 mmol/l being reached within 1.5–2.5 h from intake, and elimination half-life of 4–6 h, which is dependent on numbers of factors including age, concentration, duration of exposure, and renal function.

There is a great variability in blood levels, toxicity, and response among patients receiving the same dose per weight or body surface area. This diversity can be linked to some extent to the sequence of variations in genes involved in drug absorption, metabolism, excretion, cellular transport, and effector targets or target pathways.

Millimolar concentrations of MTX for minutes to hours may lead to acute renal, CNS, and liver toxicity, whereas concentrations of 0.05–0.1 µmol/l for more than 24–48 h will result in haematological and gastrointestinal toxicity. DNA synthesis in bone marrow and intestinal epithelium will be inhibited if MTX concentration was greater than 10 mmol/L.

Oral ingestion of MTX results in little toxicity. This may be attributable to the pharmacodynamics of MTX. Toxicity from overdose, however, as its indications for use increase, more accidental overdoses can be expected. MTX toxicity can affect multiple organs systems including bone marrow, liver, intestinal tract, kidneys, lungs, skin, and blood vessels, resulting in death in severe cases.

The physical side effects of MTX in children are the same in adults, though children generally tolerate MTX well. The most common side effects involve the gastrointestinal tract, including nausea and vomiting, transient elevation of liver-associated liver enzyme levels, usually occurring within the first 24 hours. Most cases are mild, cause no symptoms, resolve within 7 to 10 days, and result in no permanent liver damage. Large overdose can result in acute hepatitis.
Few data exists in the literature to guide management of oral MTX overdose in children or to inform prognosis. (6) Treatment recommendations for pediatric MTX exposures do not differentiate between routes of exposure. Management of symptomatic patients involves supportive care, if available the administration of antidotes, and the removal of the offending drug from the body. (7)

In this case the patient was asymptomatic and had ingested unknown amount of MTX. Her initial serum level of 0.92 mmol/L, reported after admission, was 10 times the threshold for toxicity. Leucovorin rescue was dosage equal to the maximum amount of MTX ingested has been initiated along with urine alkaliisation and diuresis to enhance elimination. Additional care included continued leucovorin treatment, activated charcoal in ER and monitoring of MTX levels. The available recommendation of managing oral overdose of MTX include the use of activated charcoal, gastric lavage, folinic acid rescue and urinary alkaliisation. The factors which are important to address in the management of MTX poisoning are the time of presentation and severity of toxicity. (10)

In case series of mainly adulteral overdoses of methotrexate there were no adverse outcomes in patients where folinic acid rescue was withheld; however, there is no information regarding ingested amounts or serum methotrexate concentrations and therefore of limited value. (11)

In the context of MTX poisoning Luecovorin is given within a period of 4 hours of the overdose with most of its therapeutic effectiveness occurring within the first hour of the overdose. Moreover, the initial dose should be equal or greater than the maximum possible dose of MTX ingested. (4)
The favourable outcomes seen in our patient despite delayed folinic acid rescue brings into question the urgency and the level of treatment required following a single oral overdose of methotrexate. Low to moderate level of MTX and the limited time of exposure following a single oral overdose of MTX may contribute to the benign outcome in this case.

There is probably insufficient data in children at the current time to avoid intravenous leucovorin therapy and monitoring for toxic side effects. However, supportive care and observation only should be considered the mainstay of treatment.

Reference:
1. Schillie SF, Shehab N, Thomas KE, Budnitz DS. Medication overdoses leading to emergency department visits among children. Am J Prev Med. 2009;37(3):181-7.
2. LoVecchio F, Katz W, Watts D, et al. Four-year experience with methotrexate exposures. Med Toxicol 2008;4:149-50.
3. Tuffaha HW, Al Omar S. Glucarpidase for the treatment of life-threatening methotrexate overdose. Drugs Today (Barc). 2012;84:705-11.
4. Odedra GM, Rumack BH (eds): POISONDEX. Englewood, CO: Micromedix Inc, 1996.
5. Gibbon BN, Manthey DE. "Pediatric Case of Accidental Oral Overdose of Methotrexate". Anne Emerg Med 1999;34:98-100.
6. Hensley MD, Barta VS, Borys DJ. A Large Case Series of Acute Pediatric Methotrexate ingestions. Pediatr Emerg Care. 2016;32(10):682-684.
7. Meyer S, Eddleston M, Baily B, Desel H, Gottshling S, Gorter L. Unintentional Household Poisoning in Children. Klin Pediatr. 2007;219(5):245-70.
8. Vander Meer A, Wulffraat NM, Prakken BJ, Gijsbers B, Rademaker CM, Sinnema G. Psychological Side Effects of MTX Treatment in Juvenile Idiopathic Arthritis. Clin Exp Rheumatol. 2007;25(3):480-5.
9. Schmiegelow K. Advances in Individual Prediction of Methotrexate Toxicity. Br J Haematol. 2009;146(5):489-503.
10. Toxbase, UK. National Poison Information Service. http://toxbase.org/Poisons-index-A-Z/M-Products/Methotrexate.
11. Shiraz B, Sok LK, Muniasamy S. "Accidental methotrexate ingestion in a 19-month-old child" BMJ Case Rep. 2011;2011. bcr11201103477.
12. Chabner BA, Young RC. Threshold methotrexate concentration for in vivo inhibition of DNA synthesis in normal and tumorous target tissues. J Clin Invest 1973;52:1804-1811.