Unexpected outcome (positive or negative) including adverse drug reactions

Accidental methotrexate ingestion in a 19-month-old child

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Summary

The authors present the youngest reported case of a single oral overdose of methotrexate in an otherwise well 19-month-old child who was treated with delayed folinic acid rescue. Initial history revealed possible ingestion of up to 10 tablets, each containing 2.5 mg of methotrexate. The peak methotrexate level was 0.67 $\mu\text{mol/l}$ measured 8 h following ingestion. Depending on the protocol, methotrexate levels that remain greater than 0.05–0.1 $\mu\text{mol/l}$ for 24–48 h are associated with risk of toxicity. No adverse sequelae were noted during hospital admission despite delayed folinic acid rescue and there was no evidence of myelosuppression for up to 3 weeks following the overdose.

BACKGROUND

Paediatric cases of oral methotrexate overdose in an otherwise well child are rarely reported despite widespread clinical use of the drug, and outcomes following acute oral overdoses are poorly defined. Current recommendations for treating oral overdose of methotrexate are based mainly on experiences following parenteral overdoses in children with other co-morbidities. There is, however, little data to inform the level of treatment required or prognosis in paediatric cases with a single oral overdose. National Poisons Index (Toxbase) advice states that any single dose in excess of 10 mg orally may lead to adverse effects and treatment should be continued until the blood methotrexate level is below 0.05 $\mu\text{mol/l}$.¹ The antidote to methotrexate is folinic acid preparations such as leucovorin that supply cells with the required tetrahydrofolate.

CASE PRESENTATION

A 19-month-old girl presented to the emergency department 6 h after she was discovered playing with her grandmother's methotrexate tablets that had toppled onto the floor. Initial history revealed possible ingestion of up to 10 tablets, each containing 2.5 mg of methotrexate. There was, however, some uncertainty as to whether the pet dog had consumed some or all of the tablets. No adverse symptoms were reported between the overdose and presentation. The child was otherwise well with no significant medical history, and was not on any medications. She appeared alert and well, baseline observations were within normal ranges, her weight was 10.6 kg and clinical examination was unremarkable.

INVESTIGATIONS

The child was admitted for observation and possible treatment according to Toxbase advice. Blood tests performed 8 h post-ingestion were all within normal ranges apart from a raised alkaline phosphatase (table 1). Blood was sent to a reference laboratory for measurement of methotrexate levels.

TREATMENT

Folinic acid therapy was initially delayed pending results of the methotrexate level given the uncertainty as to whether the child had indeed consumed the tablets. The following morning it was decided treatment was warranted and she was given a single 25 mg calcium folinate infusion equivalent to the maximum possible dose of methotrexate ingested, approximately 23 h following the overdose. Later that day, the methotrexate level from the initial blood tests confirmed a toxic level of 0.67 $\mu\text{mol/l}$. The dose of calcium folinate was reduced to 15 mg six-hourly on day 2, and 5 mg six-hourly on day 3 based on corresponding methotrexate level according to Toxbase guidance.¹ On day 3, the methotrexate level was <0.02 $\mu\text{mol/l}$ and calcium folinate was discontinued.

OUTCOME AND FOLLOW-UP

The child remained well throughout admission. She was discharged on day 3 and returned for weekly blood tests in the subsequent month to monitor delayed pancytopenia which commonly occurs 6–12 days after overdose.¹ Her full blood count remained normal and her alkaline phosphatase normalised after 3 weeks (table 1).

DISCUSSION

Current recommendations for treating oral overdose of methotrexate include the use of activated charcoal, gastric lavage, folinic acid rescue and urinary alkalinisation depending on the time of presentation and severity of toxicity.¹ This advice is based mainly on experiences following parenteral overdoses; little data exists in the literature to guide management of oral methotrexate overdoses in children or to inform prognosis. Gibbon and Manthey² reported a case of methotrexate overdose up to 45 mg with a transient rise in lactate dehydrogenase. The child was treated with gastric lavage, activated charcoal and immediate folinic acid rescue and had a benign outcome. A similar transient rise in liver enzymes was also noted by Pruitt *et al*³ with no life-threatening consequences; however, there was no

Table 1 Results of blood tests including methotrexate levels taken at the times shown postingestion

	Time postingestion							
	8 h	24 h	Day 2	Day 3	1 Week	2 Weeks	3 Weeks	4 Weeks
Methotrexate, $\mu\text{mol/l}$	0.67	0.11	Insufficient sample	<0.02				
Haemoglobin, g/dl (10.5–13.5)	11.4	11.9	11.1	11.5	11.8	11.5	11.6	11.6
White cell count, $\times 10^9/\text{l}$ (4.5–15.0)	8.6	8.9	7.1	7.5	8	14.2	11.8	11
Platelets, $\times 10^9/\text{l}$ (150–450)	310	328	288	276	384	299	403	436
Neutrophils, $\times 10^9/\text{l}$ (1.50–8.00)	2.7	4.1	4.1	3.2	5	8.5	3.9	4.8
Lymphocytes, $\times 10^9/\text{l}$ (1.50–6.80)	4.8	3.8	2.1	3.2	2.3	4	6.8	5.4
Sodium, mmol/l (135–145)	139	139	137	138			139	
Potassium, mmol/l (3.6–5.3)	4.3	4.2	5	4.3			4.7	
Urea, mmol/l (1.7–6.7)	5.5	5.7	6.1	4.3			4.6	
Creatinine, $\mu\text{mol/l}$ (8–56)	21	22	18	21			25	
Albumin, g/l (35–50)	42	44	40	43			43	
Globulin, g/l (20–35)	22	24	24	25			34	
Bilirubin, $\mu\text{mol/l}$ (<20)	6	9	7	6			3	
Alkaline phosphatase, IU/l (30–350)	2645	2921	2644	2952			361	
Alanine transferase, IU/l (5–40)	28	30	25	32			17	
γGT , IU/l (7–32)			Insufficient sample				17	
Corrected calcium, mmol/l (2.20–2.65)	2.56	2.67	2.50					
Phosphate, mmol/l (1.20–1.70)	2.06	1.89						

Results shown in bold are outside the reference range.

accurate methotrexate level for correlation. In a case series of mainly adult oral 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 is therefore of limited value.⁴

The favourable outcome seen in our patient despite delayed folinic acid rescue brings into question the urgency and level of treatment required following a single oral overdose of methotrexate. The mechanism of action and adverse effects of methotrexate differ based on both concentration and time of exposure; millimolar concentrations for minutes to hours lead to neurological, renal and liver toxicity, while concentrations of 0.05–0.1 $\mu\text{mol/l}$ for more than 24–48 h result in haematological and gastrointestinal toxicity.⁵ In cases of single oral overdose with low to moderate levels of methotrexate, both the small concentrations and limited time of exposure to toxic levels of the drug may contribute to the benign outcome.

There is probably insufficient data in children at the current time to avoid intravenous leucovorin therapy and monitoring for toxic side effects. Oral doses of methotrexate more than 20 mg/m^2 are quickly absorbed from the gut with a bioavailability of 50–90% and individual responses vary significantly to similar levels of methotrexate overdose.⁵ When treatment has been initiated in such cases of single oral overdose, there little data to inform a safe level of methotrexate below which leucovorin therapy can be discontinued, or the duration of follow-up required. Further reports of clinical outcomes should be encouraged to better inform these decisions.

Learning points

- ▶ While parenteral methotrexate overdose is known to cause severe adverse effects in both children and adults, outcomes following oral overdoses are scarcely reported and there is little data in the literature to suggest a high risk of toxicity.
- ▶ In such cases of single oral overdose of methotrexate, both the relatively small concentrations and limited time of exposure to toxic levels may contribute to a lower risk of adverse effects.
- ▶ The favourable clinical outcome in this case despite delayed folinic acid rescue further brings into question the urgency and role of intravenous folinic acid in the treatment of a single oral overdose of methotrexate.

Competing interests None.

Patient consent Obtained.

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