

Methotrexate exposures reported to the Poisons Information Centre Erfurt

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Objective

Methotrexate (MTX) is a commonly used immunosuppressive agent. The Poisons Information Centre (PIC) Erfurt observed gradually increasing numbers of MTX exposures since 2000, particularly due to misapplication (Fig. 1). We evaluated the causes and risks of these cases.

Causes of methotrexate poisonings

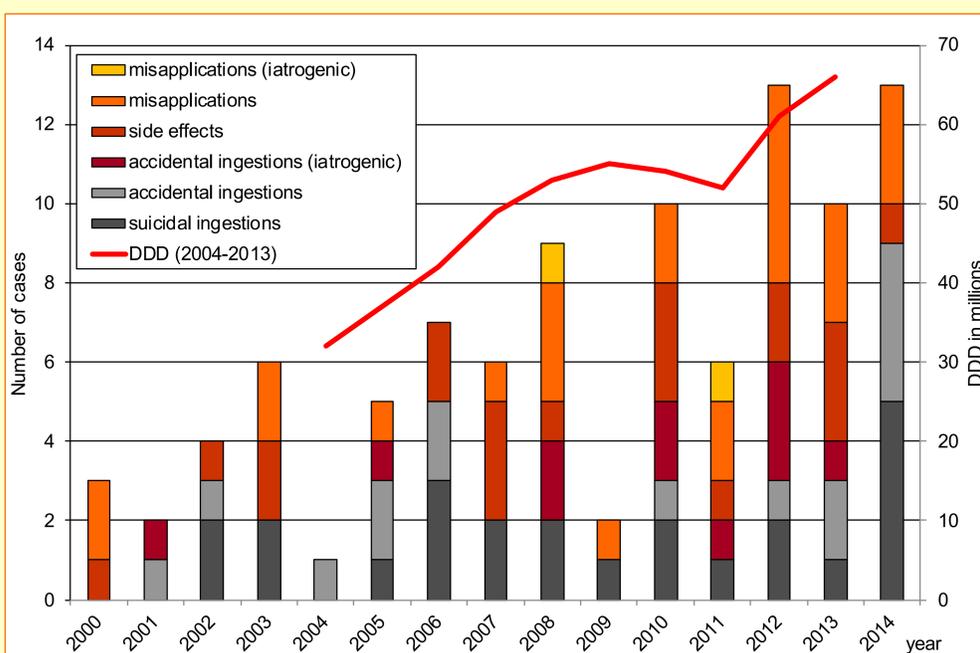


Figure 1 - Methotrexate exposures reported to the PIC Erfurt (2000 - 2014) in correlation with the number of prescriptions in Germany given in defined daily doses (DDD) (2004 - 2013) (1)

Case series

Between September 2000 and December 2014, a total of 97 exposures to MTX were reported to the PIC Erfurt.

24 cases (24.7 %) were suicide attempts, 15 cases (15.4 %) were accidental ingestions - mostly by children - and in 20 cases (20.6 %) adverse events at therapeutic doses had occurred. Misapplications were observed in 38 cases (39.2 %), of which one third (13 cases) happened in hospitals or care homes, and two-thirds (25 cases) at home.

Daily application of a weekly dose of MTX for 4 to 21 days (14 cases) resulted in pancytopenia and mucositis, and one fatality.

In 2 cases, high-dose cytotoxic therapy (7600 mg) resulted in renal failure as severe adverse effect, and one case of misapplication (300 mg/10 d) led to renal impairment.

Case report

A 76 year-old male developed pancytopenia following ingestion of 15 mg/d for 8 days (120 mg in total) in hospital and died in the course of the next 4 days (no information concerning other symptoms).

Case report

A 78 year-old male with rheumatoid arthritis, type II diabetes mellitus, condition after myocardial infarction with pacemaker implantation and congestive heart failure developed severe symptoms (pancytopenia, mucositis, gastrointestinal bleeding, oesophagitis, haemorrhagic cystitis and methotrexate-induced pneumonia) following ingestion of 10 mg/d MTX for 4 days (40 mg in total) in hospital. He recovered gradually over a period of six weeks.

Toxicity of methotrexate

The main therapeutic and toxic effects of methotrexate are due to MTX being a structural analogue of folate and thus competitively inhibiting dihydrofolate reductase. Polyglutamic derivatives of MTX also inhibit thymidilate synthetase - both mechanisms consequently limiting DNA and RNA synthesis (2).

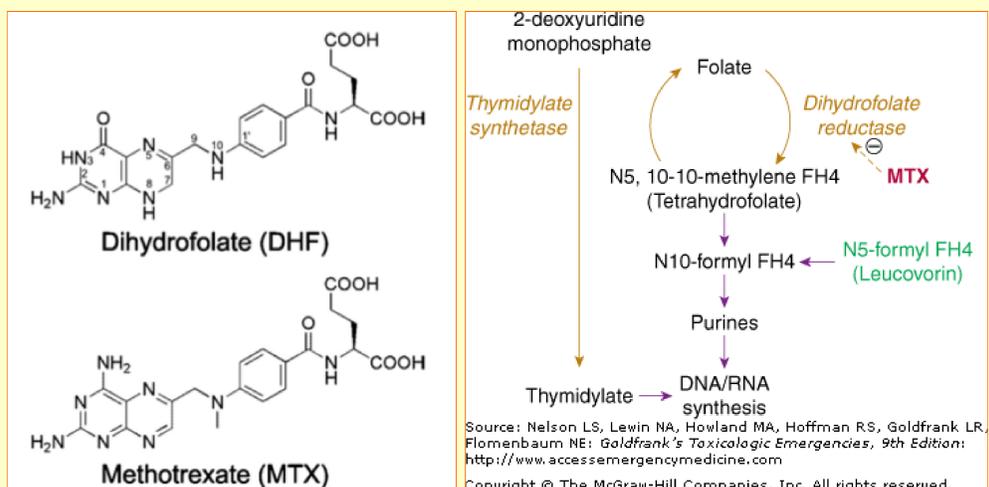


Figure 2 - Chemical structure of MTX and dihydrofolate; mechanism of MTX toxicity (2)

During low-dose MTX therapy, folic acid is often applied in order to prevent folic acid deficiency. In overdose, folic acid is not efficient (Fig. 2).

Management of methotrexate poisoning

In acute overdose, gastrointestinal decontamination is recommended. In chronic overdose, determination of MTX blood levels and application of a rescue agent (folinic acid = leucovorin) are necessary. Leucovorin treatment should be continued until the MTX concentration is below 0.01 $\mu\text{mol/L}$.

Another antidote for MTX toxicity is glucarpidase (carboxypeptidase G₂; VoraxazeTM) (2).

Conclusion

Doses exceeding the recommended daily dose can lead to severe symptoms and even death. Severity of adverse and toxic effects, respectively, seems to increase proportionally to the administered dose. Moreover, toxic effects of smaller doses were more severe when patients were of higher age and had underlying diseases, whereas accidental ingestions of small doses by healthy children and adults hardly resulted in any symptoms.

Since 2010, methotrexate is the standard treatment option for rheumatoid arthritis in Germany and is therefore widely used (see DDD in Fig. 1). Despite warnings by the German Federal Institute for Drugs and Medical Devices (BfARM) concerning correct dosage and overdose (3), as well as a warning printed on the packages (Fig. 3), misapplications both by patients and by hospital staff are common and unfortunately still increasing (Fig. 1).



Figure 3 - Warning on a German methotrexate package: "Ingestion once a week!"

References

- (1) Schwabe U., Paffrath D. (Hrsg.) Arzneimittelverordnungsreport 2014, Springer-Verlag 2014
- (2) Goldfrank's Toxicologic Emergencies, Ninth Edition, McGraw-Hill 2011
- (3) BfARM - Informationsbrief zu Methotrexat: Korrekte indikationsabhängige Dosierung 31.08.2009 (www.bfarm.de)