Methotrexate therapeutic error in non-oncology setting

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Methotrexate (MTX) originate as antineoplastic drug, but, from several years, it is largely used also in autoimmune/rheumatic diseases for its antiphlogistic properties. Adverse reactions are described after therapeutic dose, especially in patients with risk factors (e.g. renal impairment, drug-drug interactions, predisposing genetic polymorphisms). Moreover, MTX spread in outpatients may increase also the possibility of therapeutic error. High risk of toxicity is related to overdose. Objective: To evaluate the characteristics of the cases of MTX overdose due to therapeutic error in non-oncology patients. Methods: All cases of MTX overdose due to therapeutic error in non-oncology patients referred to our Poison Control Centre were retrospectively evaluated in a 8-year (06/2007-06/2016) retrospective study. Data about patients, intoxication circumstances and clinical manifestations were analysed. Results: 35 cases were included (50% male), aged between 17 and 86 years. In 5 cases patients were nursing mothers (not in treatment) to which MTX was wrongly sold by pharmacist instead of methylergometrine. In the remaining 30 cases, it came to patients who assumed prescribed MTX for the first time in their life for an autoimmune/rheumatic disease. In 27 cases wrongly assumption of prescribed dose occurred, in 2 patients MTX was administrated by incorrect way, and in 1 case was administrated despite presence of severe renal failure. In all the 28 patients that underwent an assumption error, the weekly prescribed dose (range: 2.5–12.5 mg/week) was daily assumed (=17.5-87.5 mg/week); this mistake was recognized after a period ranging from 2 to 21 days. Clinical manifestations were characterized by mucositis (14/35), myelosuppression (12/35), asthenia (6/35), acute renal failure (5/35), diarrhea (4/35), vomiting (4/35), headache (2/35), hepatitis (2/35). All patients were treated with calcium levofolinate and forced alkaline diuresis. N-acetylcisteine was administered in 2 patients with hepatitis, and growth-factors in one. MTX plasma levels were available for 6 patients, resulting within recommended therapeutic range. No lethal cases were registered. In the 5 nursing mothers breastfeeding was stopped for 4 days. Conclusions. Medication errors is a cause of MTX toxicity. Most assumption errors are due to misunderstanding of medical prescriptions. Clear indications, possibly with electronic systems and explication to the patients are necessary in order to avoid these errors and the consequent toxicity. MTX serum quantitative determination is useful during therapy and to administer the correct dose of antidote in acute overdoses, but is not a good predictor of outcome in chronic overdose, due to the pharmacokinetic characteristics of the drug.