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## Treatment for acute and chronic methotrexate poisoning

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**Objective**: This presentation aimed to review acute and chronic methotrexate (MTX) overdoses as well as therapeutic studies that provide pharmacokinetic or clinical data on MTX to provide a better understanding on its toxicities.

**Methods**: A retrospective audit was performed for acute and chronic MTX poisoning through the New South Wales Poisons Information Centre from April 2004 to July 2015 to determine the clinical syndrome and toxicity of MTX. In addition, a literature search was performed on MTX poisonings and high dose MTX use, bioavailability, drug interaction and treatment.

**Results**: In the NSW PIC audit data (2004-2015), there were 42 cases of acute MTX poisoning, 15 paediatric and one intrathecal overdose. Of the 26 adult patients, median age and dose were 47 years (IQR: 31 – 62; range: 10-85) and 325mg (IQR: 85 – 500, range: 40-1000) respectively. Median reported paediatric age and ingestion were 2(IQR: 2-2; range: 1-4) and 50mg (IQR: 10-100). Of the patients who had serum MTX concentration measured, none were above the nomogram. No patients reported adverse sequelae. There were 21 chronic MTX poisonings. Median age was 62 years (IQR: 52-77), with stomatitis/mucositis (30%) and neutropenia (30%) being the most common symptoms.

There were 66 papers included in the review. Pharmacokinetic data showed that MTX bioavailability is greatly reduced as oral doses increase with a possible ceiling dose in acute ingestion. Oncology data suggested that patients treated with an intravenous dose of <1g/m$^2$ MTX do not generally require or need folinic acid rescue. There is no feasible acute oral overdose that is likely to provide >1g/m$^2$ of systemically absorbed MTX or lead to serum MTX concentrations above the oncology folinic acid treatment line, unless the patient has renal impairment. In contrast, daily administration of low dose MTX for as little as three days has caused significant morbidity. Serum MTX concentration did not correlate well with toxicity or mortality in these patients.

**Conclusion**: Accidental oral MTX paediatric ingestion is unlikely to ever cause toxicity. In acute deliberate MTX poisoning, there are no situation in which it would be expected that toxicity will occur unless patient has renal impairment, although clinical experience confirm that are generally limited to overdoses $\leq$500 mg. In chronic poisoning, neutropenia and stomatitis/mucositis are sensitive markers of MTX toxicities. Folinic acid and supportive care are recommended until patient makes clinical recovery. There is no rationale to monitor MTX concentration in either acute or chronic poisoning