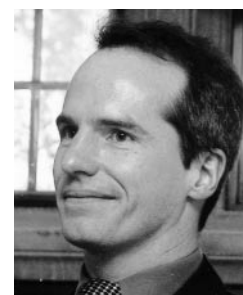


# Preventing Deaths from Methotrexate Overdose



In this issue of *The Journal*, Sinicina, *et al*<sup>1</sup> describe 5 cases of fatal methotrexate (MTX) overdose. I am a hospital based general internist, so I occasionally encounter a patient with rheumatoid arthritis who is taking MTX. In the Discussion, I read that “errors are failures in the process of medical management that may or may not harm the patient. If a patient dies, the judiciary considers that a criminal charge of manslaughter is justified.” I breathed a sigh of relief. I could have made those dosing errors.

These cases are symptoms of a much broader disease: unsafe healthcare. The key question is: What is the best treatment for the disease? Sinicina, *et al* report that “The repeated oral overdoses of MTX, the insufficient monitoring of blood parameters, the suboptimal responses by physicians to clinical signs and symptoms of MTX overdose were considered by the office of public prosecution as acts of gross negligence.” One message is that an important treatment for unsafe healthcare is to punish practitioners involved in harmful medical errors. I do not agree. If I ever needed a prescription for MTX, I would be perfectly comfortable receiving it from any of the practitioners involved in the cases described. If we focus only on the individuals, there will be many more MTX overdoses. The only difference will be the patients and the healthcare professionals involved.

Unfortunately, the person-focused response probably leads to very little improvement in patient safety. Although drugs and procedures have changed dramatically over the past 40 years, the safety of the system that delivers these treatments appears to have changed little. (One notable exception is the practice of anesthesia.) In 1964, Schimmel found that 10% of 1014 hospitalized patients suffered noxious response to drugs<sup>2</sup>. In 1967, Ogilvie and Ruedy found that 15% of 731 hospitalized patients had onset of an adverse drug event after admission to hospital<sup>3</sup>. In 1979, Steel, *et al* found that 15% of 815 hospitalized medical

patients experienced an iatrogenic illness caused by a drug<sup>4</sup>. In 1993, Bates reported that 6.5% of patients experienced adverse drug events<sup>5</sup>. When differences in methods are taken into account, it is difficult to detect a substantial improvement in drug safety over the past 40 years from these studies. The only definite change is the drugs involved. The 1964 study included an adverse reaction to intravenous bacitracin, a reaction that we are unlikely to observe today!

Chart review studies from many countries over the past 20 years also show a reasonably consistent rate of adverse events among hospitalized patients. Although the reported range is 2.9%–16.6%<sup>6–9</sup>, this wide range reflects differences in reporting methods rather than differences in safety. The rate of major adverse events (death or permanent morbidity) was virtually identical in large US and Australian chart review studies<sup>10</sup>. Not all adverse events are related to medical error. Retrospective judgments show that 28%–51% of adverse events are potentially preventable; the rest are judged unavoidable consequences of care.

The cases reported by Sinicina, *et al* have some common safety themes: medication error, and diagnostic delay<sup>1</sup>. We know that medication errors are common. In one study, for every 10,000 medication orders in a teaching hospital, there were 530 errors associated with 5 preventable adverse drug events<sup>11</sup>. We also know that diagnostic error is common, although there are fewer data on this type of error. A recent prospective observational study found that interns working a traditional 85-hour call work week made 19 serious diagnostic errors per 1000 patient-days. Assuming that an intern cares for 14 patients per day, this works out to about 2 serious diagnostic errors per week or about 100 serious diagnostic errors per year<sup>12</sup>.

Clearly, the cases reported by Sinicina, *et al* are not aberrations. Medical errors, including medication errors and diagnostic delay, are an inescapable reality of medical prac-

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See Deaths following methotrexate overdoses by medical staff, page 2009

tice. Through luck or random vigilance, the overwhelming majority of these errors will lead to no harm, or transient harm. For some unfortunate patients and healthcare professionals, these errors lead to serious harm or death.

What is the safety prescription? The first 2 key steps are to establish a climate (or culture) of safety, and to embrace the systems approach to patient safety. A climate of safety exists when individuals are encouraged and willing to report safety problems, and can expect positive constructive responses to these reports. Sinicina states that "the development of a new culture of safety is...a tedious process." I do not agree. It is a dynamic, uplifting, and exciting process. The safety climate can be quickly developed by encouraging discussion of potential adverse events (also called near misses or close calls). These are situations where patients are almost harmed, but harm was avoided by luck or interception. There are about 7 potential adverse drug events (near misses with drugs) for every preventable adverse drug event, so there are plenty of opportunities to learn from potential adverse drug events<sup>11</sup>. People are much more comfortable talking about "near misses," because the toxic emotions of fear and shame are absent. An example of a near miss would be an order for MTX 10 mg by mouth once daily that is changed after the patient voices a concern. It was nonsystematic vigilance by the patient that prevented harm; the same error could harm another patient the next week. Any healthcare professional can start building a climate of safety tomorrow by asking, "Were any of my patients almost harmed by care yesterday? What can I do to prevent similar harm in the future?"

A climate of safety must strike an appropriate balance between the individual and the system. In rare cases, the focus must be on the individual. Intentional harmful acts, staff illness, reckless behavior, and recurrent problems despite support and system changes warrant action at the level of the individual staff. Useful algorithms have been developed by national safety organizations<sup>13</sup>. There is not enough information in Sinicina's report to make such distinctions, so I am playing the odds that these were honest mistakes.

The second step is to use the systems approach for addressing safety problems. Using this approach, adverse events are viewed as interactions between an imperfect working environment and the errors of unavoidably imperfect humans. The imperfect working environment can either promote error, or fail to detect errors before harm occurs. There are many algorithms and frameworks for reviewing the system of care<sup>14,15</sup>. The goal is to identify factors that promoted the likelihood of error, and weaknesses in the system that allowed the error to go undetected and uncorrected. These factors might include problems with teamwork, communication, staffing, scheduling, training, and protocols. In Sinicina's report, factors that increased the likelihood of prescribing error appear to be poor dissemination of drug

knowledge to physicians, and lack of availability of laboratory data (such as renal function) at the time of ordering; both these factors have been identified as important causes of medication errors<sup>16</sup>.

What safeguards could have made these errors visible, allowing interception before harm occurred? Several systematic opportunities to trap these dosing errors could be helpful, as discussed by Sinicina. First, computerized medication order entry systems with dose ceiling and dose-kidney checks could easily identify these errors before patients are harmed. Hospitals that have developed and implemented computerized systems report reductions in medication errors, although the impact on adverse events has been harder to prove<sup>17</sup>. Similarly, a computer alert system with laboratory drug checks could alert physicians to the possibility of MTX toxicity when a patient taking MTX develops low blood counts<sup>18</sup>. Of note, in one study of clinical alerts, clinicians were unaware of the hazard in 44% of cases. Another intriguing intervention is the rounding clinical pharmacist. The rounding pharmacist accompanies physicians during rounds, providing medication information at the time of ordering. The rounding pharmacist has reduced preventable adverse drug events in two studies<sup>19,20</sup>. In Sinicina's case 3, communication through verbal orders was a contributing factor, when a 15 mg dose was incorrectly interpreted as 50 mg. Staff can be trained to reduce errors with verbal orders using repeat-backs and "spelling out" drug dosages ("You have ordered fifteen 1–5 milligrams of MTX by mouth once weekly. Is that correct?"). Informed patients can also play an active role in their own safety. For example, educating the patient to never accept MTX more than once a week might have prevented 2 of the deaths.

Sinicina, *et al* have highlighted 5 deaths caused by a common disease: unsafe healthcare. Perhaps a more accurate title would be "Deaths from MTX overdoses by medical staff in the absence of automated dose ceiling checks and dose-kidney checks, computerized medication order entry systems, rounding clinical pharmacists, drug-laboratory alerts, formulary/prescribing restrictions for high alert medications, and gaps in patient information regarding drug related hazards." It is time to start initiating treatment. Legal remedies targeted at individuals will not be sufficient.

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**REFERENCES**

1. Sinicina I, Mayr B, Mall G, Keil W. Deaths following methotrexate overdoses by medical staff. *J Rheumatol* 2005;32:2009-13.

2. Schimmel E. The hazards of hospitalization. *Ann Intern Med* 1964;60:100-10.
3. Ogilvie RI, Ruedy J. Adverse reactions during hospitalization. *CMAJ* 1967;97:1445-50.
4. Steel K, Gertman PM, Crescenzi C, Anderson J. Iatrogenic illness on a general medical service at a university hospital. *New Engl J Med* 1981;304:638-42.
5. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. *JAMA* 1995;274:29-34.
6. Thomas EJ, Studdert DM, Burstin HR, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. *Medical Care* 2000;38:261-71.
7. Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *New Engl J Med* 1991;324:370-6.
8. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. *Med J Aust* 1995;163:458-71.
9. Baker GR, Norton P, Flintoft V, et al. The Canadian Adverse Events Study: the incidence of adverse events in Canadian hospitals. *CMAJ* 2004;170:1678-86.
10. Runciman WB, Webb RK, Helps SC, et al. A comparison of iatrogenic injury studies in Australia and the USA. II: reviewer behaviour and quality of care. *Int J Qual Health Care* 2000; 12:379-88.
11. Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. *J Gen Intern Med* 1995;10:199-205.
12. Landrigan CP, Rothschild JM, Cronin JW, et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. *N Engl J Med* 2004;351:1838-48.
13. National Patient Safety Agency. [Internet] Accessed August 9, 2005; Available from: [http://www.npsa.nhs.uk/health/resources/incident\\_decision\\_tree](http://www.npsa.nhs.uk/health/resources/incident_decision_tree).
14. Vincent C, Taylor-Adams S, Chapman EJ, et al. How to investigate and analyse clinical incidents: clinical risk unit and association of litigation and risk management protocol. *BMJ* 2000;320:777-81.
15. VA National Centre for Patient Safety. Accessed August 9, 2005. [Internet] Available from: <http://www.patientsafety.gov/rca.html>.
16. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. *JAMA* 1995;274:35-43.
17. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. *Arch Intern Med* 2003;163:1409-16.
18. Raschke RA, Gollihare B, Wunderlich TA, et al. A computer alert system to prevent injury from adverse drug events: development and evaluation in a community teaching hospital. *JAMA* 1998;280:1317-20.
19. Kucukarslan SN, Peters M, Mlynarek M, Nafziger DA. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medical units. *Arch Intern Med* 2003;163:2014-8.
20. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA* 1999;282:267-70.