Case Report

Deaths Following Methotrexate Overdoses by Medical Staff

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ABSTRACT. Methotrexate (MTX) is an effective disease modifying antirheumatic drug (DMARD) with a relatively safe profile, and it is widely used to treat neoplastic diseases and dermatologic and rheumatologic disorders. As indications for use of MTX increase, more accidental overdoses are noted to occur. Typical problems include deficiencies in labeling, instructions, or packaging, as well as erroneous use. We describe 5 fatal cases of repeated oral overdose of MTX prescribed by physicians in the treatment of rheumatoid arthritis to focus attention on the design of the underlying system and the organizational practices as sources of problems. (J Rheumatol 2005;32:2009–11)

Key Indexing Terms:
METHOTREXATE OVERDOSE PANCYTOPENIA

Methotrexate (MTX), a broad-spectrum anticancer agent, has become established as the most commonly used disease modifying antirheumatic drug (DMARD) in the management of rheumatoid arthritis (RA)[1]. In recent years there has been a trend to more aggressive use of MTX in the treatment of inflammatory arthropathy, in terms of dose and early intervention[2,3]. For treatment of RA, MTX at a low dose (7.5–15 mg weekly) is increasingly used and is considered to be safe. Schnabel, *et al*[4] have shown that in the majority of patients with RA the balance of maximum efficacy and tolerability is achieved at doses between 15 and 20 mg/week. Further, it has been shown that MTX was associated with a 60% reduction in risk of all-cause mortality. In contrast, no reduction of mortality has been demonstrated for other DMARD[5]. The use of a highly toxic substance such as MTX, however, requires proper knowledge of the drug's effects, a timely access to complete and accurate patient information, and efficient collaboration and communication between caregivers.

From 1992 to 2003, five fatal outcomes following oral MTX therapy of RA were investigated by the Institute of Legal Medicine, Ludwig-Maximilians-University, Munich, Germany. Postmortem examination and histological analysis of the organ probes were performed in all cases in order to confirm the cause of death. Measurements of MTX levels were also determined in all cases. Additionally, the clinical charts of all patients were studied extensively.

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CASE REPORTS (Table 1)

Case 1. A 65-year-old man with RA was directed by his orthopedist to take 10 mg MTX daily. He was not given therapy instructions in written or verbal form. MTX was dispensed by a retail pharmacy. On the 18th, 19th, and 20th days after beginning the treatment with MTX, he visited his general practitioner, as he had widespread painful erosions in the oral cavity. The physician diagnosed a stomatitis due to a herpes simplex virus infection and prescribed an antiviral agent. On the next day the inflammation of the oral mucous membrane advanced further and the patient consulted an otorhinolaryngologist. There he got some sprays, but his general condition worsened considerably. Two days later the general practitioner ordered hospitalization in a rheumatologic department, where an MTX intoxication was immediately suspected. Thus, the inappropriate prescribing was noted after 23 days (230 mg had been administered overall) of the treatment. A MTX level of 0.25 μmol/l was measured one day after the medication was stopped, although a level of > 0.1 μmol/l MTX should not be exceeded during low dose therapy. Leucovorin rescue therapy was started immediately. After 3 days the MTX concentration had fallen below the critical value (< 0.1 μmol/l). However, the patient died of sepsis 5 days after the last dosage.

Case 2. A 56-year-old woman with RA and impaired renal function Stage III, National Kidney Foundation guidelines was admitted to hospital due to anemia (hemoglobin 5.0 g/dl). Since she did not respond to nonsteroidal antiinflammatory medication, MTX 20 mg weekly was prescribed. After the third dose (total dosage 60 mg), she developed multiple superficial lesions of the oral mucosa and skin. An otorhinolaryngologist and a dermatologist were consulted. The diagnosis was mucositis and erysipelas of both lower legs. The inappropriate dosage was discovered after occurrence of pancytopenia, and the patient was transferred to a hematooncologic center. A MTX concentration of 0.2 μmol/l was measured 7 days after stopping the MTX therapy and leucovorin rescue therapy was started. The patient died of sepsis 14 days after taking the last dose of MTX.

Case 3. A 71-year-old woman with RA was given 50 mg MTX twice within 8 days (total dose 100 mg over 8 days, intended dose 15 mg weekly) due to a misunderstanding pertaining to the dosage while she was transferred to another hospital without accompanying documents. The physician telephoned the patient's former hospital to enquire about the medication. In the doctors' absence, she took the information from a nurse. The nurse in the

Table 1. Cases of MTX overdose 1992–2003.

Case	Year	Age, yrs Sex	Intended Weekly Dose, mg	Dose Administered	Leucovorin Rescue	Prescribed by	Other Attending Doctors/Departments	Death*
1.	1992	65 M	10	230 mg in 23 days (23 × 10 mg)	Yes	Orthopedist	General practitioner, otorhinolaryngologist	Sepsis, 5 days
2.	1998	56 F	20	60 mg in 16 days	Yes	Doctor in Dept. of Internal Medicine	Otorhinolaryngologist, dermatologist	Sepsis, 14 days
3.	1999	71 F	15	100 mg in 8 days (2 × 50 mg)	No	Doctor in Dept. of Internal Medicine		Multiple organ failure, 11 days
4.	2000	74 F	10	90 mg in 9 days (9 × 10 mg)	No	Doctor in Dept. of Surgery	Dept. of Internal Medicine	Pneumonia, 7 days
5.	2003	26 F	15	90 mg in 6 days (6 × 15 mg)	No	Physician in a nursing home		Multiple organ failure, 5 days

* Days after stopping MTX.

previous hospital, however, mistook "15 mg" for 50 mg. This information was accepted by the doctor at the second hospital, where the patient had been treated further. Two days after the first application of MTX (50 mg) a slight pancytopenia was observed. After the second application (a total of 100 mg) a further marked reduction of blood cell count was observed. The inappropriate dispensing of the drug was discovered when the patient developed pneumonia and sepsis. The MTX concentration 48 hours after the last MTX administration was 0.1 μmol/l. She died on the 11th day after the overdose was discovered.

Case 4. A 74-year-old woman with RA was admitted to the department of vascular surgery of a teaching hospital. Her internist listed her medicine for hospital doctors, intending a weekly dose "currently MTX 10 mg." A state employed nurse in the surgical department, inexperienced in MTX use for RA therapy, interpreted this order as "MTX 10 mg 1-0-0." The attending surgeons had only occasionally dealt with patients with MTX medication due to RA and thus did not question the dosage. The patient herself trusted the doctors and assumed that the change in MTX medication was necessary, since her medication was almost completely replaced by generics and she also received additional medication. Thus, she received an intended weekly dose of 10 mg daily for 9 days (total dose 90 mg over 9 days; intended dose 10 mg weekly). After a few days she developed an exanthema and mild pancytopenia, and was transferred to a department of internal medicine. Her situation during therapy worsened continuously. Nevertheless, the dose of MTX was not considered to be too high. Instead, an allergic reaction to antibiotics was assumed and her medication was completely withdrawn. Two days later severe pancytopenia developed and she was transferred to a hematooncological department of another teaching hospital, where MTX intoxication was diagnosed. Since the MTX concentration on admission (48 hours after stopping the medication) was below 0.1 μmol/l, leucovorin rescue therapy was not performed. The patient died of pneumonia one week after the last MTX dose.

Case 5. A 26-year-old woman with Down syndrome and RA received an intended weekly dose of 15 mg MTX daily for 6 days (total dose 90 mg over 6 days; intended dose 15 mg weekly). The dosage was prescribed by a doctor in a nursing home. The mistake was detected because the patient complained of multiple painful erosions in the oral cavity, preceding severe pancytopenia. She died of multiorgan failure 5 days after ceasing MTX. As the MTX level was below 0.1 μmol/l, leucovorin rescue was not indicated.

DISCUSSION

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. The forensic medicine authorities are then obliged to perform an autopsy, to study the medical charts and statements of the attending doctors, and to report results of the investigation to the prosecution authorities. Thus, the institutes of forensic medicine are currently the only independent investigative body in Germany with the responsibility of collecting all information required for the analysis of fatal medical errors.

MTX misuse in RA therapy is not a new problem. The major risk relates to frequency of dosing. MTX overdose due to confusion of tablet strength by patients has been repeatedly described[6-10]. As well there are reports of single intrathecal administration of MTX in a high dosage by hospital personnel. Reports concerning fatal errors in oral MTX therapy by medical staff are rare[11]. In the cases described here, the errors in oral MTX administration occurred repeatedly and simultaneously involved senior officers, residents, state employed nurses, general practitioners, and other medical specialists. Thus, in case 1 a general practitioner, an otorhinolaryngologist, and an orthopedist shared the treatment of the patient but did not suspect an MTX overdose. In the second report an otorhinolaryngologist and a dermatologist attended a hospitalized patient but did not question the MTX dosage despite the marked signs of overdose (severe mucositis, skin lesions, and pancytopenia). Severe pancytopenia — a rare adverse effect of low dose oral MTX therapy — has been repeatedly reported in patients with renal impairment, since glomerular filtration is a dominant pathway of MTX elimination[12-14]. Thus, Bressolle, *et al* showed that creatinine clearance between 40 and 60 ml/min is associated with a 20% decrease of the elimination half-life of MTX[15]. However, the restricted kidney function in this case was not considered by hospital doctors to be a reason for adjusting the drug regimen.

Study of the circumstances of MTX misuse in these cases proved that all deaths were ultimately preventable, and that significant system failures such as poor communication, high staff workload, an unfamiliar task, and training deficiencies contributed to these errors in a convergent manner.

However, the repeated oral overdoses of MTX, the insufficient monitoring of blood variables, and the suboptimal responses by physicians to clinical signs and symptoms of

MTX overdose were considered acts of gross negligence by the public prosecution office.

However, blaming one or a few people for an error that may be the result of difficulties at many stages in a complex process is dangerous. This encourages secrecy and inhibits systemic changes that would reduce the likelihood of future errors, especially when the entire system has exhibited several shortcomings:

1. In contrast to other countries, every practicing and even nonpracticing German physician is allowed to prescribe and apply pharmaceuticals such as MTX.
2. Pharmacies and hospital pharmacy departments may, but are not obliged to, review the physician's order.
3. Only a small fraction of hospitals in Germany have clinical pharmacists who take part in treatment.
4. Most German hospitals do not have active safety programs with regard to reviewing medical prescriptions.

Most physicians and authorities are not convinced that there is a problem with procedures regarding the prescription of medication. The most important problem is the lack of a clear national commitment to improving safety standards at the federal government level. Publications focusing on patient safety and the report of the American Institute of Medicine entitled "To err is human" have called for new ways of thinking about healthcare quality in some countries[16-18]. For instance, Britain's response was to establish a National Patient Safety Agency. Swiss hospitals will be obliged to report medical errors starting in 2006[19]. In Germany, there is only a program allowing voluntary reporting of adverse drug reactions, and a similar program for medical errors does not exist. Yeoh and Siderov have proposed that MTX should not be prescribed by a general practitioner without a specific written request, with complete dosing details, from the treating specialist[8,10]. However, in the current political environment in Germany it is extremely unlikely that the prescription of potentially dangerous pharmaceuticals will be restricted to certain physicians or that reporting of adverse drug events will be made obligatory. Thus, alternative strategies for improvement of patient safety must be developed. For instance, a medical error reduction program could include computerized physician order entry. Gandhi, *et al* reported that one-third of prescribing errors by primary care practices could have been prevented or ameliorated by the use of advanced computerized systems of prescribing medication[20]. The hospital systems that link patient history, laboratory results, and prescribing data, and that present a hierarchy of warnings to inform, advise, and occasionally forbid the prescriber to continue were shown to be an effective tool in decreasing the incidence of adverse drug events[21].

The development of a new "culture of safety" is, however, a tedious process. In the interim period, hospitals could adopt internal guidelines, which would oblige the prescribing physician to consult with a rheumatologist or an oncologist prior to administration of MTX. Development of educational materials in written form for patients and their relatives, especially in outpatient settings, would considerably minimize the risk of medication errors, and result in speedier identification of potentially threatening symptoms of MTX intoxication by patients.

REFERENCES

1. Zink A, Listing J, Ziemer S, Zeidler H. Practice variation in the treatment of rheumatoid arthritis among German rheumatologists. J Rheumatol 2001;28:2201-8.
2. Weinblatt ME. Rheumatoid arthritis: more aggressive approach improves outlook. Cleve Clin J Med 2004;71:409-13.
3. Weinblatt ME. Rheumatoid arthritis in 2003: where are we now with treatment? Ann Rheum Dis 2003;62 Suppl 2:94-6.
4. Schnabel A, Herlyn K, Burchardi C, Reinhold-Keller E, Gross WL. Long-term tolerability of methotrexate at doses exceeding 15 mg per week in rheumatoid arthritis. Rheumatol Int 1996;15:195-200.
5. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 2002;359:1173-7.
6. Porawska W. Overdose of methotrexate with a fatal outcome in a patient with rheumatoid arthritis. Pol Arch Med Wewn 1995;93:346-50.
7. Brown MA, Corrigan AB. Pancytopenia after accidental overdose of methotrexate. A complication of low-dose therapy for rheumatoid arthritis. Med J Aust 1991;155:493-4.
8. Hordon LD, Le Gallez P, Isdale AH. Oral methotrexate: hazard of different tablet strengths [letter]. Rheumatology Oxford 1999;38:1304.
9. Lomaestro BM, Lesar TS, Hager TP. Errors in prescribing methotrexate [letter]. JAMA 1992;268:2031-2.
10. Yeoh S, Siderov J. Methotrexate misadventure: a case for counseling [letter]. Rheumatology Oxford 2001;40:230-2.
11. Bauer J, Fartasch M, Schuler G, Schell H. Ulcerative stomatitis as clinical clue to inadvertent methotrexate overdose. Hautarzt 1999;50:670-3.
12. Calvo-Romero JM. Severe pancytopenia associated with low-dose methotrexate therapy for rheumatoid arthritis. Ann Pharmacother 2001;35:1575-7.
13. Gutierrez-Urena S, Molina JF, Garcia CO, Cuellar ML, Espinoza LR. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:272-6.
14. Rheumatoid Arthritis Clinical Trial Archive Group. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. J Rheumatol 1995;22:218-23.
15. Bressolle F, Bologna C, Kinowski JM, Sany J, Combe B. Effects of moderate renal insufficiency on pharmacokinetics of methotrexate in rheumatoid arthritis patients. Ann Rheum Dis 1998;57:110-3.
16. Leape LL. Error in medicine. JAMA 1994;272:1851-7.
17. Leape LL, Berwick DM, Bates DW. What practices will most improve safety? Evidence-based medicine meets patient safety. JAMA 2002;288:501-7.
18. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human: Building a safer health system. Washington, DC: National Academy Press; 1999.
19. Aschwanden E. Spitäler müssen Kunstfehler melden. [Hospitals must report adverse medical events]. Neue Züricher Zeitung Online; 6 March 2005. [Accessed June 30, 2005] Available from http://www.nzzamsonntag.ch/2005/03/06/il/articleCN74P.print.html
20. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. N Engl J Med 2003;348:1556-64.
21. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1997;277:301-6.