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Severe renal toxicity due to intermediate-dose methotrexate

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Summary. Methotrexate (MTX) is a drug widely used in the treatment of patients with malignant disease. Its well-known side effects include myelosuppression, mucositis and renal damage. These problems are primarily dose-related, tending to occur more frequently when high doses (> 1 g/m^2) are given. We present four cases in whom severe renal and mucosal toxicity occurred with intermediate doses (200 mg/m^2) of MTX despite folinic acid rescue. Possible reasons for this occurrence are discussed and means of avoiding such toxicity are suggested. Three of four patients developed severe loin pain within a few hours of injection; the significance of this symptom in relation to subsequent renal toxicity has implications for early recognition of the problem.

Introduction

Methotrexate (MTX) is a cytotoxic drug that works by the inhibition of dihydrofolate reductase, preventing the regeneration of active tetrahydrofolate in dividing cells [5]. It is widely used in haematological malignancies and a number of other conditions, including psoriasis. Dose schedules vary tremendously, relatively small doses (e.g. 40 mg/week orally) being used in the maintenance treatment of acute lymphoblastic leukaemia, higher doses (e.g. 400 mg i.v. monthly), in the treatment of lymphoma, and very high doses (e.g. 4 g i.v.), in some therapeutic regimens for osteogenic sarcoma and high-grade lymphoma [5]. Its side effects can largely be ameliorated by folinic acid rescue; that is, the administration of adequate amounts of the reduced folate, folinic acid, 18-24 h after the MTX dose. Patients receiving high-dose MTX are also given sodium bicarbonate beforehand to alkalinise the urine, as this enhances its renal clearance and reduces toxicity [9]. When these measures are adopted, severe toxicity due to MTX is unusual.

4/118 patients (3.5%) who received 200 mg/m^2 MTX at a concentration of 25 mg/ml as part of their treatment for high-grade lymphoma are described. In spite of the fact that all four patients had a serum creatinine within normal limits prior to chemotherapy, were encouraged to maintain a high oral fluid intake (3 l/24 h) and received standard folinic acid rescue consisting of folinic acid tablets and mouthwash beginning 24 h after the MTX, they developed mucositis and renal failure, and one patient died.

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Case reports

Patient 1. This 62-year-old man was being treated for a large-cell, diffuse non-Hodgkin's lymphoma (NHL) of bone. The only past history of note was that he underwent a pyloroplasty and enterostomy for duodenal ulceration in 1962. He had uneventfully received one course of CHOP-Bleo (cyclophosphamide, Adriamycin, vincristine, bleomycin and prednisolone) 2 weeks prior to receiving MTX, when his serum creatinine was normal. At the time of MTX administration, the only other drug he was taking was a non-steroidal anti-inflammatory drug (NSAID) for pain in the hip. He received 350 mg MTX by i.v. injection followed by 15 mg folinic acid p.o. plus folinic acid mouthwash 6 hourly for a total of six doses starting 24 h after the MTX. He returned to the clinic 5 days later, complaining of acute, severe bilateral loin pain starting 12 h after the MTX followed by increasing listlessness and drowsiness and accompanied by polyuria, polydypsia and the development of a painful, dry mouth. On examination he was pyrexial and dehydrated, with signs of oral mucositis. Laboratory tests revealed that his urea was 28.2 mmol/l (normal range, 2.5–7.3 mmol/l), creatinine, 345 μmol/l (normal range, 74–108 μmol/l) and potassium, 5.3 mmol/l (normal range, 3.1–4.4 mmol/l). He was treated with extra folinic acid mouthwashes, broad-spectrum antibiotics and fluid replacement. His urea and creatinine gradually returned to normal levels over the next 2 weeks. Subsequently, he received radiotherapy to the site of his original disease and is still in complete remission, with a normal serum creatinine.

Patient 2. This 50-year-old man was receiving therapy for a poorly differentiated lymphocytic NHL confined to the antrum of his stomach. This was initially treated by partial gastrectomy and gastroenterostomy, but it was felt that he required additional systemic chemotherapy, which started uneventfully with methyl-prednisolone, vindesine, VP16 and chlorambucil (PEEC) on 30 April 1987. At this time his serum creatinine was normal. He was due to receive MTX 14 days later; however, this was postponed due to leucopenia for a further week, when he was given 350 mg

MTX by i.v. injection, followed by 15 mg folinic acid given orally 6 hourly plus mouthwash for six doses starting 24 h afterwards. At the clinic 1 week later, he complained of nausea, vomiting and severe oral ulceration. On questioning, he gave a history of bilateral loin pain starting 6 h after the MTX. His urea was 54 mmol/l, his creatinine, 1461 μmol/l and his potassium, 7.5 mmol/l. The other biochemistry was unremarkable apart from a raised urate of 0.85 mmol/l (normal, 0.42 mmol/l), consistent with the renal failure. He was treated with i.v. fluids, calcium resonium, dextrose and insulin, broad-spectrum antibiotics and i.v. folinic acid, and haemodialysis was carried out by nephrologists. Although this resulted in decreases in his creatinine (to 550 μmol/l) and urea (to 20 mmol/l) levels, he became progressively pancytopenic, requiring platelet transfusions. His condition suddenly deteriorated 2 days later; despite attempts at resuscitation, he died. A post-mortem examination showed no evidence of lymphoma, and no specific cause of death could be identified.

Patient 3. This 42-year-old man was undergoing treatment for a high-grade lymphoma apparently confined to the liver. This started with CHOP plus bleomycin; when he returned 2 weeks later for MTX treatment, it was noted that his massive hepatomegaly had almost completely resolved. Urea, electrolyte, and creatinine tests were carried out immediately prior to the injection of MTX and were normal. He was given 400 mg MTX i.v. with folinic acid rescue as described above. At 4 h post-injection he experienced headache and shivering, and at 12 h, severe bilateral loin pain. By 48 h post-injection he had developed mouth soreness, and when he was examined at 5 days he had obvious oral mucositis. His urea was 12.9 mmol/l, his creatinine was 414 μmol/l, his urate was marginally elevated at 0.63 mmol/l and examination of his urine revealed a pH of 7.46, with no red cells or casts. He was treated with i.v. fluids, folinic acid and alkalinisation of his urine (1.2 g sodium bicarbonate five times daily), resulting in a rise in the urinary pH to 8. Broad-spectrum antibiotics were given for pyrexia; on this regime he gradually improved, with his urea falling to 7 mmol/l and his creatinine, to 201 μmol/l after 10 days. He is currently well and receiving further chemotherapy as an out-patient, although he has not been given further MTX.

Patient 4. This 67-year-old man was being treated for a diffuse immunoblastic NHL. He received one course of PEEC uneventfully, with 400 mg MTX given on day 14. He was then given CHOP-bleomycin followed 21 days later by 400 mg MTX (delayed because of neutropenia). On the day of MTX administration his serum creatinine was normal. He felt well for the next 3 days, experiencing no loin pain, and took his folinic acid as prescribed. He presented with severe oral and rectal mucositis 1 week later, and his blood urea had risen to 22 mmol/l. His plasma MTX level was 48 ng/ml. He was treated with i.v. rehydration and further folinic acid, and his serum creatinine completely recovered.

Discussion

MTX is used extensively as an anti-cancer drug; it is metabolised in vivo by the liver to 7-hydroxy MTX, which is excreted by the kidney. The drug is intrinsically nephrotoxic, although its renal toxicity is not deemed to be a major clinical problem. However, acute renal toxicity has been reported in association with high-dose MTX, probably due to precipitation of MTX crystals in the renal tubules in the presence of acidic urine [4]. In established mild to moderate renal failure, neither peritoneal dialysis nor haemodialysis is of major benefit in reducing high MTX levels. However, some clearance (30–40 ml/min) may be obtained by haemodialysis if the patient is totally anuric and no other therapeutic options are available [3].

Attention has recently been drawn to the increased toxicity of MTX to the kidney in the presence of non-steroidal anti-inflammatory drugs (NSAIDs) [1, 7, 10, 11]. NSAIDs are also intrinsically nephrotoxic and several underlying mechanisms have been suggested: (a) inhibition of renal prostaglandin synthesis; (b) immunologically mediated mechanisms; (c) direct tubular toxicity; and (d) uric acid precipitation in renal tubules [2]. Any of these mechanisms might decrease renal function and reduce MTX clearance, leading to prolonged, high MTX levels and toxicity. In addition, aspirin can increase the toxicity of MTX by prolonging serum concentrations of the drug by either displacing MTX from plasma proteins or competing for common elimination pathways; this may apply to other NSAIDs as well [6]. However, whereas our first patient was taking NSAIDs for pain in his hip, which could have contributed to the toxicity he suffered, NSAID ingestion did not appear to be a factor in the other patients, although the consumption of NSAIDs in proprietary medicines cannot be fully excluded.

The first two patients had undergone gastric surgery, and it is possible that this contributed to the toxicity of MTX by in some way decreasing the bioavailability of the folinic acid given as rescue; however, again, this mechanism could not account for the other cases.

Finally, it is possible that certain foodstuffs and beverages might contribute to MTX toxicity by reducing the pH of urine and thus causing the precipitation of MTX in the renal tubules. Drinks with a high acidic content, such as Coca-Cola, or with high sulphur amino acid content, such as yoghurt and buttermilk, are known to cause acidification of the urine [12]. Although it is impossible to assess whether diet was a contributing factor in these cases, it is interesting to speculate that it may have been so.

The striking feature in three patients was the severe loin pain (a feature known to be associated with drug-induced acute intestinal nephritis [8]) occurring prior to the time of folinic acid rescue, suggesting that a possible mechanism might be renal tubular deposition of MTX crystals in an acidic microenvironment, leading to acute renal failure, MTX retention and subsequent toxicity.

As a result of the above case reports, we have modified our protocol in lymphoma patients. The urea and electrolytes of all patients are measured on the day they are due to receive MTX; the drug is withheld if the results are abnormal. In addition, patients undergo urinary alkalinisation consisting of 1.5 g sodium bicarbonate four times a day, starting 7 days before and continuing for 2 days after the MTX injection. The urine is checked by dip stick on the day of MTX administration and if it is not adequately alkalinised, the MTX is withheld and increased doses of bicarbonate are given. Patients are also asked to return to the clinic 24 h after MTX administration and are then specifically questioned about loin pain. At this time, 20 mg in-

tramuscular folinic acid is given, followed by the oral administration of 15 mg folinic acid for a total of six doses, along with folinic acid mouthwashes. In this way, we believe that further problems associated with MTX-induced renal toxicity can be resolved without resorting to admission of all such patients for i.v. hydration and alkalinisation.

Conclusion

MTX is generally a safe drug that is widely used in cancer chemotherapy; however, as reported here, severe renal toxicity can occur even with moderate dosing. We recommend that all patients receive urinary alkalinisation prior to MTX treatment plus adequate folinic acid rescue and that they be urged to report immediately any loin pain experienced following MTX administration.

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References

1. Daly HM, Scoto GL, Boyle J, Roberts CJC (1986) Methotrexate toxicity precipitated by azapropazone. Br J Dermatol 114: 733
2. Favero A del (1987) Anti-inflammatory analgesics and drugs used in rheumatoid arthritis and gout. In: Dukes MNG (ed) Side effects of drugs annual 11. Elsevier Science, Amsterdam, New York – Oxford, p 82
3. Hende KR (1977) Methotrexate and haemodialysis (Letter). Ann Int Med 87: 495
4. Jacobs SA, Stoller RG, Chabner BA, John DG (1976) 7-Hydroxymethotrexate as a urinary metabolite in human subjects and Rhesus monkeys receiving high dose methotrexate. J Clin Invest 57: 534
5. Jolivet J, Cowan KH, Curt GA, Clendenini NT, Chabner BA (1983) The pharmacology and clinical use of methotrexate in man. Clin Pharmacol Ther 10: 849
6. Leigler DG, Henderson ES, Hahn MA, Oliverio VT (1969) The effect of organic acids on renal clearance of methotrexate in man. Clin Pharmacol Ther 10: 849
7. Ng HWK, MacFarlane AW, Graham RM, Verbov JL (1987) Near fatal drug interactions with methotrexate given for psoriasis. Br Med J 296: 752
8. Pusey CD, Saltissi D, Bloodworth L, Rainford DJ, Christie JL (1983) Drug associated acute intestinal nephritis: clinical and pathological features and response to high dose steroid therapy. Q J Med 52 (206): 194
9. Shen DD, Azaroff DC (1978) Clinical pharmacokinetics of methotrexate. Clin Pharmacokinet 3: 1
10. Singh RR, Malaviya AN, Pandey JN, Gulera JS (1986) Fatal interaction between methotrexate and naproxen (Letter). Lancet I: 1390
11. Thyss A, Milano G, Nanier M, Schneider M (1986) Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. Lancet I: 256
12. Vries EG de, Meyer C, Stubbe M, Mulder NH (1986) Influence of various beverages on urine acid output. Cancer Res 46: 430

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