Severe Bone Marrow Suppression in a Patient with Rheumatoid Arthritis on Methotrexate

Pages with reference to book, From 262 To 263

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Introduction

Methotrexate (MDC) in low doses has been commonly and effectively used in the treatment of rheumatoid arthritis (RA)[1,2]. Such small weekly doses of the drug, in general, are considered to be safe and non-toxic. However, when there is impairment of renal function or in patients having altered metabolism due to infection or metabolic disease the cumulative effect of these small doses of MDC can become life threatening[3,4]. We report a case of severe bone marrow suppression in a rheumatoid arthritis patient on low dose MDC therapy.

Case Report

In September 1992, a 52 years old woman with a history of bronchial asthma for 35 years, diabetes mellitus for 3 years and RA for six years was prescribed MDC (oral, 10 mg/week) for her exacerbating RA. Five months later she developed benign leiomyoblastoma, which was surgically removed. After the operation, she was put back on low-dose oral MDC. However, she failed to show up in any of her follow-up appointments and 10 weeks later was admitted with very high fever and gum bleeding. On examination she was found to be pancytopenic (hemoglobin 7.6 gm/dl; white blood cells $0.9x10^9/1$; platelets $29x10^9/l$), havingasevere infection of E. coli and a compromised renal function. She was neutropenic (24% neutrophils; 69% lymphocytes; 7% eosinophils) and her chest X-ray revealed no active disease in lungs. Her urinary pH of 5.5 may have been because of diabetic acidosis or severe infection. Bacterial infection with E. coli was found resistant to ampicillin, amoxicillin and nalidixic acid, but its sensitivity to amikacin facilitated management of this problem. For MDC toxicity, the patient was given folinic acid 15 mg, 6 hourly for 4 days. Platelets were transfused repeatedly for her thrombocytopenia. After 1 week of treatment, there was a significant improvement in her condition. She became afrebrile and her neutropenia resolved to a great extent. WBC count increased to $3.5x10^9/1$ while neutrophils' percentage rose to 44 (Table).

Table. Values of various hematologic and biochemical parameters in a patient with rheumatoid arthritis.

Parameters (units)	At the time of admission	1 week after treatment	2 weeks after treatment
Hemoglobin (gm/dl)	7.6	9.8	8.4
Hematocrit (%)	23.1	27.8	24.5
White blood cells ($x10^9$/l)	0.9	1.9	17.5
Neutrophils (%)	24	34	75
Platelets ($x10^9$/l)	29	3.0	210
Blood urea nitrogen (mg/dl)	45	25	Not done
Serum creatinine (mg/dl)	2.3	1.2	1.1
Total bilirubin (mg/dl)	5.0	6.9	1.4
Direct (mg/dl)	2.0	3.4	0.2
Indirect (mg/dl)	3.0	3.5	1.2
Alanine aminotransferase (I.U./l)	38	21	33
Alkaline phosphatase (I.U./l)	155	111	167

After another week of treatment (Table), the values of most hematologic and biochemical parameters were within the normal range. Her neutropenia had completely resolved, but slight anemia which was normocytic and normochromic still persisted. MDC levels in serum and erythrocytes were determined using a sensitive radioassay[5]. Even a month after her last dose (10 mg) of MDC, the drug was detected in serum (1.59 nM) as well as in erythrocytes (0.99 nM).

Discussion

By a number of pharmacokinetic studies on MDC, it has been shown that more than 90% of the thug is cleared within the first 24 hours after its administration[6]. With such a low dose (10 mg/week) of MDC, there should hardly be any amount of drug detectable in plasma of the patient after 1 week post ingestion. However, appreciable quantity (1.59 nM) of MDC was found in serum of the patient even 4 weeks after its ingestion. This suggests that her severe bone marrow suppression may have been because of gradual accumulation of MDC in the body due to delayed plasma clearance of the drug. This delayed clearance of MDC in the patient could have been mainly due to compromised renal function (serum creatinine levels 2.3 mg/dl at the time of admission as shown in Table) and partly because of her metabolically altered state due to diabetes mellitus. Although there is hardly any information on the kinetics of MDC in diabetes patients, yet a number of studies have revealed that alterations in the physiological environment of the body influence the biodisposition and fate of drugs[7]. Moreover, MDC has been shown to precipitate In the acidic environment. Urinary pH, therefore, can affect renal clearance of MTX[8]. The fact that the patient was a chronic diabetic and at the time of admission had a urine pH of 5.5 suggests that she may have had an episode of diabetic aciduria which resulted into precipitation of MDC in the kidneys leading to compromised renal function and further decrease in the renal clearance of this drug. This impainnent of renal function with decreased renal excretion of MDC could easily convert low- dose to intermediate-dose MDC therapy[9]. The accumulation of MDC in the plasma could be the major cause of bone marrow suppression. It is not

clear whether severe bacterial infection was also the cause or the effect of neutropenia in this patient. Hematopoietic toxicity following low-dose methotrexate therapy in RA patients has previously been reported as well[3,4,9]. It has been estimated that 3-4% of the patients on MDC would experience pancytopenia as its side effect[10]. In view of this case of bone marrow suppression following low dose MDC therapy, it is suggested that those RA patients who have accompanying metabolic problems, such as diabetes mellitus must be managed more carefully. There should be a regular follow-up of the patients where they should be regularly monitored. According to the guidelines by the Health and Public Policy Committee, American College of Physicians[10], laboratory studies (total and differential blood counts and platelet count, serum creatinine and liver enzymes) should be repeated every month. MDC treatment is not recommended for an unreliable patient who is more likely to miss follow-up appointments[11] and utmost caution is needed when the patient, in addition to RA, has other metabolic disorders, such as diabetes mellitus[2].

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