

Methotrexate induced ventricular arrhythmia as a medication error: a case report

Shailja S. Shah¹, Sapna Gupta^{2*}, Jasvin Vala², Supriya D. Malhotra¹, Pankaj Patel³

¹Department of Pharmacology,

²Department of Emergency Medicine, ³Dean, Smt. NHL Medical College, Ahmedabad, Gujarat, India

Received: 08 July 2019

Revised: 09 August 2019

Accepted: 13 August 2019

***Correspondence to:**

Dr. Sapna Gupta,

Email: sapna_gupta76@yahoo.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Methotrexate (MTX) is the most widely used drug in clinical practice for long term treatment of connective tissue disorders. As this drug has narrow therapeutic index, if it goes unmonitored can lead to life threatening complications. Herein we are describing the case of a patient who presented with ventricular arrhythmia, due to failure to execute MTX therapy in the prescribed frequency and took daily dose of MTX which was meant to be taken as a weekly dose pointing to failure of patient education or patient comprehension regarding MTX and finally succumbed due to cardiogenic shock. We concluded this causality as probable/likely category according to WHO-UMC causality categories.

Keywords: Methotrexate toxicity, Mucositis, Ventricular arrhythmia

INTRODUCTION

MTX is now the disease modifying anti-rheumatic drugs (DMARD) of first choice and the standard treatment for most patients, including cases of juvenile rheumatoid arthritis (RA). MTX is a dihydrofolate reductase inhibitor having prominent immunosuppressant and anti-inflammatory property. Beneficial effects in RA are probably related to inhibition of cytokine production, chemotaxis and cell-mediated immune reaction. Induction of oral low-dose (7.5-15 mg) weekly MTX regimen has

improved acceptability of this drug in RA.¹ Since folic acid plays a major role in cell division, its inhibition is associated with major toxicity to blood cells, the oral mucosa, hepatocytes, and lungs.² MTX toxicity can be manifested as gastrointestinal symptoms, mucositis, cardiotoxicity, hepatotoxicity and bone marrow suppression.

Herein we are reporting a case of medication error in a patient on MTX who ingested Tab. Methotrexate 7.5 mg

BD instead of once weekly for 10 days and presented with ventricular arrhythmia.

CASE REPORT

A 70-year-old hypertensive, diabetic male and a known case of rheumatoid arthritis was brought to Emergency Medicine Department of our hospital with complain of multiple oral ulcers, vomiting and diarrhoea since 4 days. On arrival suddenly he developed breathlessness, palpitation and dizziness. On examination he was conscious, vitals were blood pressure: not recordable, pulse: 210/min on monitor with rhythm suggestive of

ventricular tachycardia, ECG of the patient suggestive of ventricular tachycardia is shown in Figure 1. For which 2 times DC shock of 200 J was given followed by one DC shock of 250 J and inj. amiodarone (150 mg) and inj. lignocaine given stat. Post DC shock vitals were temperature: 98 F, BP: 100/70 mmHg, Pulse: 140/min, Respiratory rate: 22/min, SPO2: 97%, RBS: 325. Patient was given BIPAP support for tachypnoea because he was conscious after cardioversion and was following verbal commands. 2D echo was suggestive of LVEF: 30-35%, anterior wall hypokinesia. Clots, vegetations and effusions are not seen and moderate MR, grade II TR present.

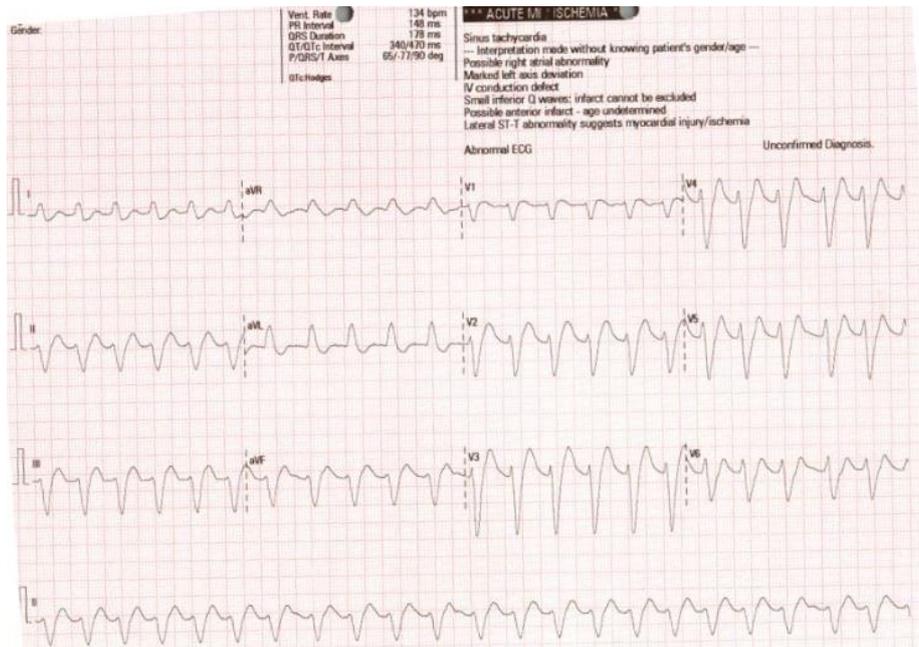


Figure 1: ECG showing VT.

Table 1: Laboratory findings.

No	Investigations	Findings
1	CBC	Hb: 5.6 g/dl, WBC: 840/cu mm, RBC: 2.63 mil/cu mm Haematocrit: 15% (34–52) MCV: 64.8 fl, MCH: 21.2 pg/ml, MCHC: 32.8 g/dl
2	PT/INR	17.5/1.38
3	APTT	20.3 (Control- 30.0)
4	Arterial blood gases (ABG)	pH: 7.11 (7.35–7.45), pCO2: 39.4 mmHg (35–45), pO2: 198 mmHg (80–100), Na: 130 mmol/L, K: 5.3 mmol/L, Cl: 92 mmol/L, HCO3: 12.0 mmol/L (22–26)
5	Renal function test	S. creatinine: 1.49 mg/dl (0.7–1.3) Blood urea: 109.1 mg/dl (15–45) S. sodium: 125, S. potassium: 4.7, S. chloride: 95 (mmol/L)
6	Liver function test	SGOT (AST): 104 U/L (0–34), SGPT (ALT): 60 U/L (10–49) S. ALP: 73 U/L (45–129), S. AG ratio: 0.86 (1.5–2.5), S. albumin: 3.0 g/dL (3.2–4.8), S. globulin: 3.5 g/dL (2–3.5) Bilirubin (mg/dL): total: 1.59, direct: 0.90, indirect: 0.69
7	TNIU	Troponin I ultra: 1.43 ng/ml (0–0.1)

On detailed inquiry, he was a known case of hypertension and diabetes since 10-12 years and he was a diagnosed case of Rheumatoid arthritis since 5 years, but he wasn't taking medicines regularly. He was relatively asymptomatic before 10 days when he consulted a private rheumatologist for joint pains and was prescribed, tab. febuxostat (40 mg) OD, tab. hydroxychloroquine (300 mg) OD, tab. neurokind next, tab. methotrexate (7.5 mg) once a week. After starting the treatment, he developed 6 to 7 episodes of vomiting, diarrhoea and multiple oral ulcerations as well as tiny ulcers over trunk and legs. Important information obtained was that patient taking tab. methotrexate (7.5 mg) twice a day instead of once weekly. So, he took total dose of 150 mg of MTX in 10 days. His laboratory findings are shown in Table 1.

Rheumatology opinion was taken, findings were consistent with mucositis and diagnosis of RA with MTX toxicity was made and managed with inj. folinic acid along with filgrastim. Dermatology reference was done and on examination multiple discrete annular tiny ulcers present over trunk and legs, multiple superficial erosions with haemorrhagic crusting present over lower lip mucosa and tongue and advised barrier nursing, fusidic acid cream twice a day over leg lesions, chlorhexidine gargles BD. During hospitalization he was managed with Inj. amiodarone, inj. ceftriaxone, inj. pantoprazole, inj. ondansetron, inj. heparin, inj. H insulin, tab. aspirin, tab. febuxostat, tab. hydroxychloroquine, tab. Nurokind Next.

His clinical condition worsened rapidly on day 2 due to cardiogenic shock. He was intubated and mechanically ventilated due to deterioration of oxygenation levels and worsening of sensorium. He went into cardiorespiratory arrest on same day and expired even after aggressive resuscitation measures.

DISCUSSION

With the growing reliance on medication therapy as the primary intervention for most illnesses, patients receiving medication interventions are exposed to potential harm as well as benefits. Harm from medications can arise from unintended consequences as well as medication error (wrong medication, wrong time, wrong dose, etc.). Medication error can be defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use".³ In our case patient took the inappropriate dose of MTX pointing towards medication error and he developed mucositis, vomiting, diarrhoea, bicytopenia, elevated liver enzymes, ventricular arrhythmia.

MTX, is a folic acid analogue that inhibits dihydrofolate reductase, thereby blocking DNA synthesis and causing cell death. MTX is now the DMARD of first choice and the standard treatment for most patients, including cases of juvenile RA. Now a days, MTX has gained acceptance among rheumatologists as an effective treatment alternative for patients with RA that is unresponsive to conventional DMARDs, such as antimalarial agents, gold salts, and D-penicillamine.⁴

Patients with rheumatoid arthritis (RA), are at an increased risk of developing cardiovascular disease (CVD). CVD is a leading cause of death in patients with rheumatic diseases.⁵ MTX elevates the level of homocysteine by inhibiting methionine synthase. Hyperhomocysteinemia is associated with an increased risk of cardiovascular disease, leading to the concern that MTX may secondarily increase the risk of CVD.⁶ In a study done by Perez-Verdia et al, they demonstrate an association between MTX therapy and development of myocardial arrhythmias that could lead to a potentially lethal arrhythmia.⁷ In one report, a 36-year-old man developed myocardial infarction and ventricular arrhythmias during treatment with low-dose oral MTX 15 mg/week. Cardiac evaluation consisted of a coronary angiogram that showed no evidence of significant coronary disease, an electrophysiologic study that failed to demonstrate inducible tachyarrhythmias, and an endomyocardial biopsy with normal histologic results. Frequency of premature ventricular contractions significantly decreased after discontinuation of MTX treatment, and the patient became asymptomatic. However, his premature ventricular contractions and symptoms returned a few hours after the drug was restarted, and again resolved after discontinuation.⁸

MTX induced hepatotoxicity is well recognised in the treatment of rheumatoid arthritis. Intracellular accumulation of methotrexate polyglutamate and consequent depletion of folate stores are suspected to play a role in the mechanism of liver injury. The possibility that MTX causes hepatic fibrosis and cirrhosis only in the presence of other contributing factors such as excess alcohol ingestion, diabetes mellitus, obesity and hypervitaminosis.⁹ MTX interferes with cellular replication leading to megaloblastic erythropoiesis and in toxic doses to bone marrow depression.¹⁰

In study shown by Moore et al, a total of 106 cases of reported medication errors associated with MTX were identified, including errors resulting in 25 deaths (24%) and 48 other serious outcomes (45%). The most common types of errors involved confusion about the once-weekly dosage schedule (30%) and other dosage errors (22%). The most frequently involved indication for use was rheumatoid arthritis (42%). Of the errors, 39 (37%) were attributable to the prescriber, 21 (20%) to the patient, 20 (19%) to dispensing, and 18 (17%) to administration by a health care professional. Overall, 52% of the reported errors involved some form of overdose, with the most

common problem being taking the drug daily instead of weekly (32 cases [30%]).²

CONCLUSION

Medication errors leading to toxicity are potentially hazardous. Cardiovascular side effects are life threatening and may not give adequate time to treat and reverse the effects till the drug levels clear and metabolized. So, prescription explanation with exact risks of overdosing should be explained to patient and his relatives.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Tripathi KD. Autacoids and related drugs. Essentials of medical pharmacology. 8th ed. Jaypee publishers; 2019: 228.
2. Moore TJ, Walsh CS, Cohen MR. Reported medication errors associated with methotrexate. Am J Health-System Pharmacy. 2004;61(13):1380-4.
3. National Coordinating Council for Medication Error Reporting and Prevention. What is a medication error? Available at: www.nccmerp.org/about/MedErrors.html. Accessed on 3 July 2019.
4. Alarcón GS, Tracy IC, Blackburn WD. Methotrexate in rheumatoid arthritis. Toxic effects as the major factor in limiting long-term treatment. Arthritis Rheumatism. 1989;32(6):671-6.
5. Rekedal LR, Massarotti E, Garg R, Bhatia R, Gleeson T, Lu B, et al. Changes in glycosylated haemoglobin after initiation of hydroxychloroquine or methotrexate treatment in diabetes patients with rheumatic diseases. Arthritis Rheumatism. 2010;62(12):3569-73.
6. Shen S, O'Brien T, Yap LM, Prince HM, McCormack CJ. The use of methotrexate in dermatology: a review. Australasian J Dermatol. 2011;53(1):1-18.
7. Perez-Verdia A, Angulo F, Hardwicke FL, Nugent KM. Acute Cardiac Toxicity Associated with High-Dose Intravenous Methotrexate Therapy: Case Report and Review of the Literature. Pharmacotherapy. 2005;25(9):1271-6.
8. Kettunen R, Huikuri HV, Oikarinen A, Takkunen JT. Methotrexate linked ventricular arrhythmias. Acta Derm Venereol. 1995;75:391-2.
9. Kevat S, Ahern M, Hall P. Hepatotoxicity of Methotrexate in Rheumatic Diseases. Med Toxicol. 1988;3(3):197-208.
10. Costello C, Mir N, Hughes RA, Riley B. Methotrexate-induced bone-marrow suppression. Clin Laboratory Haematol. 2008;13(3):322-3.

Cite this article as: Shah SS, Gupta S, Vala J, Malhotra SD, Patel P. Methotrexate induced ventricular arrhythmia as a medication error: a case report. Int J Basic Clin Pharmacol 2019;8:2163-6.