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A Case Report on Methotrexate Overdose in Rheumatoid Arthritis Patient

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Abstract: *Methotrexate is the most commonly used disease-modifying antirheumatic drug (DMARD) in the treatment of rheumatoid arthritis. The most common cause of acute Methotrexate (MTX) toxicity is an accidental overdose of MTX tablets by the patient or physician's prescription error. Here's a case of accidental overdose of MTX (15mg daily for 10 days) by a geriatric patient. This case report is intended to create awareness that MTX toxicity can be fatal. The risk of fatality increases with increase in age.*

Keywords: *Methotrexate, Rheumatoid arthritis, DMARD's, leucovorin, Overdose*

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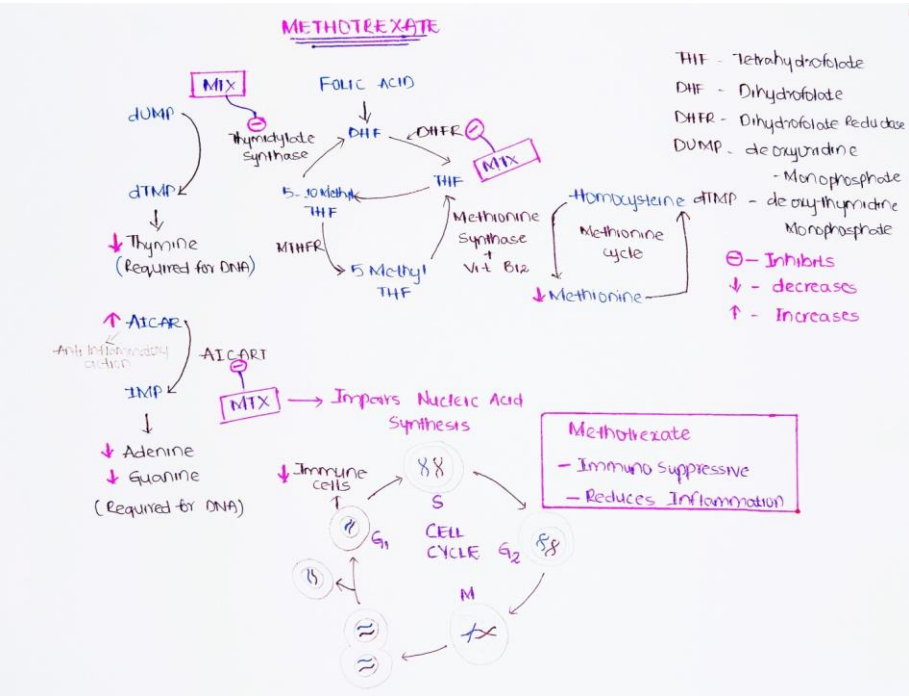
I. Introduction:

Methotrexate (4-amino-10-methylfolic acid, MTX), an analog and antagonist of folic acid, is commonly used in the treatment of a wide range of malignant and non-malignant diseases [(1)] commonly used in treating blood and solid organ malignancies, dermatological and rheumatic diseases[(2)] One of several disease-modifying antirheumatic drugs (DMARDs), MTX received an FDA indication for use in adults with severe, active rheumatoid arthritis in 1988 with extension to children with active polyarticular-course juvenile rheumatoid arthritis[(3)] The features that make the MTX as the DMARD of first choice are related to its low price, its favorable safety profile, its slowing of radiographic progression, clinical experience with high response rates, therapeutic continuity, availability and versatility of doses and routes of administration. Thus, after the diagnosis of the disease, it is indicated as the first-line treatment for early and in clearly defined Rheumatoid Arthritis (RA), as recommended by different societies[(4–6)], and it is also suitable as an anchor drug for combination therapies.[(7)]

MECHANISM OF MTX:



Methotrexate (MTX) inhibits mitosis of the cells by antagonizing folic acid required for deoxyribonucleic acid (DNA) synthesis of cells. Once in the cell, MTX inhibits dihydrofolate (DHF) reductase, an enzyme responsible for the conversion of DHF to tetrahydrofolate (THF). Consequently, there is a reduction in thymidylate and purine biosynthesis. DNA synthesis eventually halts and cells can no longer divide. Polyglutamination of MTX prolongs its intracellular presence. Hence, cells with the capability of effective polyglutamination such as leukemic myeloblasts, synovial macrophages, lymphoblasts, and epithelia are more susceptible to the action of MTX.[8] Cytokines are major mediators in inflammatory and immune responses and have been of great interest in recent therapeutic developments in chronic arthritis, initially with TNF-α as a pivotal targeted cytokine[9]. The extent to which MTX modulates the pathogenesis of inflammatory autoimmune diseases via a direct effect on cytokine production by immune cells remains to be fully elucidated. MTX has been reported to decrease TNF-α, IL1β, and adhesion molecules (E-selectin and VCAM-1) expression on RA synovial biopsies[10].

DOSING:

Methotrexate may be administered via intramuscular (IM), intrathecal (IT), intravenous (IV), or oral (PO) routes. Dosing is quite diverse due to the significant variations in MTX indication. High-dose methotrexate (HDMTX) for chemotherapy, which requires leucovorin rescue, is MTX, 1 g/m2 IV[11] Lower doses may be used in alternative chemotherapeutic regimens, while up to 8–12 g/m2 or more may be given for osteosarcoma, leukemia, and lymphoma[12-14] MTX is more appropriately dosed by age, as a fixed dose/m^2 was reported to result in low cerebrospinal fluid (CSF) methotrexate concentrations and reduced efficacy in children, and in high concentrations and neurotoxicity in adults[15,16] Psoriasis patients are normally provided with MTX 7.5–30 mg PO weekly [17]. Rheumatoid arthritis treatment involves MTX 7.5–20 mg PO weekly[18]. Multiple fatalities and serious adverse events have resulted from prescription, dispensing, administration, and patient errors in which the intended weekly dose was incorrectly consumed daily[19,20]

ADVERSE EFFECTS:

MTX toxicity has its impact on skin, gastrointestinal mucosa, liver, kidneys, and bone marrow. Ulcerations in skin due to MTX toxicity are restricted to the psoriatic plaques probably because of higher uptake of methotrexate by the hyperproliferative psoriatic plaques than normal skin[21] Pancytopenia due to MTX is attributed to the patients with renal dysfunction, presence of infection, folic acid deficiency, hypoalbuminemia, concomitant use of drugs such as trimethoprim, and advanced age.[22] Acute kidney injury impairs the renal clearance of methotrexate, resulting in the accumulation of toxic concentrations and an increased risk for additional adverse events. [23] Prolonged renal dysfunction with increased systemic methotrexate exposure can cause myelosuppression, mucositis, hepatotoxicity, and, in severe cases, multiorgan failure.[24]

CASE STUDY:

A male patient of age 59 years was hospitalized with a known case of RA since 5 months. Based on laboratory findings (Rheumatoid factor: 58.1 IU/ml (> 20 IU/ml +) C Reactive protein: 63.5 mg/L (> 6 mg/L +)) he was diagnosed as Rheumatoid Arthritis 5 months ago and on medications Tab;et Methotrexate 15mg, once a week; tablet prednisolone 10mg, once a day; tablet Leflunamide 10mg, once a day; tablet HCQ 200mg, once a day since 2 days; Tab Folvite 5mg, twice a week; tablet Etoricoxib, once a day.

His complaints on admission were, loose stools, headache, dysphagia, skin rash. k/c/o HTN since 10 years and on medication Telma+Metoprolol (40+50), Now c/o difficulty in swallowing since 10 days first to solids them to liquids, Fever with chills intermittent relieved on medication,

Generalized body weakness, H/O loose stools since 7 days, SOB grade II to III, H/O intake of Methotrexate 15mg daily for about 10 days.

His serum MTX levels after 5 days of drug withdrawal were:

MTX – 0.12 mmol/L (Non toxic drug conc after 72 hrs of dose < 0.1
Toxic drug conc after 72 hrs > 0.1
Toxic drug conc after 48 hrs > 1
Toxic drug conc after 12 hrs > 10)

Serum MTX levels after 9 days of withdrawal and with supportive treatment was found to be normal i.e Sr. Mtx – 0.0 mmol/L

Based on medication history and laboratory findings he was finally diagnosed as "Methotrexate Poisoning, Acute febrile illness with Thrombocytopenia with Hypokalemia, Dengue NS1 Igm reactive" and was treated appropriately.

As MTX suppresses bone marrow abnormal blood counts were seen especially Low WBC is to be primarily focused as it increases the chances of infection so patient was isolated and treated appropriately. On day 1 of hospitalization his white blood cells count was 1500 cells/Cumm of blood On day 3 it decreased to 340

cells/Cumm. From day 4 to day 6 it was around 500 cells/Cumm, it gradually increased to 1200, 3700, 6500 on day 7, 8 & 9 respectively on treating with granulocyte colony stimulating factor 'filgrastim'.

Day	1	3	4	5	6	7	8	9
Hb	11.6	10.1	10.4	9.5	12.1	12.4	11.5	12.0
WBC	1500	340	600	560	520	1200	3.7	6.5
RBC	4.2	3.2	3.3	3.08	4.09	4.0	3.5	3.7
Pt	20,000	<10.000	25,000	20,000	25,000	35,000	70,000	93,000
DLC	NP due to low count	NP due to low count	NP due to low count	NP due to low count	NP due to low count	N-55 L-29 M-08 E-08 B-00	N-67 L-20 M-11 E-02 B-00	N-79 L-12 M-08 E-01 B-00
Na	134	137	135	130	130	127		
k	3.2	2.9	2.2	2.4	2.6	2.0		
Cl	99	95	94	97	106	94		

Patient was treated with Leucovorin which is a folic acid analog used to counteract the toxic effects of MTX. Dose of leucovorin on day 1 & 2 was 25mg in 100ml NS over 1hr, On day 3 30mg in 100ml NS over 1hr and on day 4, 5 & 6 50mg in 100ml NS over 1hr. Filgrastim 300mcg; Sc; stat was given on day 3, 4 & 5 for Myelosuppression, it is a human granulocyte colony stimulating factor (G-CSF) which acts on hematopoietic cells by binding to specific cell surface receptors and regulating neutrophil production, progenitor proliferation and differentiation. It also has effects on some end cell functional activation including phagocyte activity, cellular metabolism and antibody dependent killing. Other supportive treatments include Sodium bicarbonate which is an alkalizer It works by increasing the pH of blood and urine, thereby correcting metabolic acidosis and also helps in removing toxic substance from the body; Antibiotics like piperacillin tazobactam which is an extended-spectrum penicillin antibiotic was given from day 1 to 9 and clindamycin from day 4 to 7, as prophylactic treatment to prevent infections and was treated with anti hypertensives, folic acid and multi vitamin.

Gradual decrease in signs and symptoms was seen, all vitals were stable at the time of discharge on day 10. Patient and his care takers were counseled about the medication, its dose, dosage and route of administration.

II. Discussion:

Reduction in drug toxicity can be achieved by following proper management strategies which includes; excessive hydration, urine alkalinization, counteracting the toxic effect of drug using antidote and by following other extracorporeal methods such as HD, continuous renal replacementtherapy (CRRT) and haemoperfusion. CRRT includes 3 primary variants: CVVH, continuous venovenous haemodialysis (CVVHD),and continuous venovenous haemodiafiltration (CVVHDF).

Hydration:

More than 90% of methotrexate is eliminated by the kidneys.[25] The use of fluids to promote high urinary flow rates and alkalinize the urine protects the kidney from injury during treatment with high dose MTX.[26] Fluids resuscitation may be required to reverse volume depletion from gastrointestinal losses. Intravenous crystalloids sufficient to maintain brisk diuresis (60 mL/hour) are also critical to maximizing methotrexate elimination.[27]

Urine Alkalinization:

Urine alkalinization further improves urinary elimination of MTX[27] Methotrexate and its metabolites, including 7-OH-methotrexate and 4-deoxy-4-amino-*N*-10-methylpteroic acid (DAMPA), are poorly soluble at an acidic pH. An increase in urine pH from 6.0 to 7.0 increases the solubility of methotrexate and its metabolites by five- to eightfold, and alkalinization is imperative to reduce intratubular crystal formation (precipitation).[28, 29] Methotrexate's urinary precipitation is minimized in alkaline urine: at pH 7.5 MTX is 10 times more soluble than at pH 5.5[30, 31] . The beneficial

effects of alkaline diuresis are seen even in patients with preexisting renal dysfunction.[32] Therefore, intravenous sodium bicarbonate should be routinely given in addition to aggressive hydration to maximize urinary solubility.[33]

Antidote:
Leucovorin (5-formyl-FH4, folinic acid, citrovorum factor, calcium folinate) was first identified in 1948 as a required growth factor for deficient *Leuconostoc citrovorum* species.[34] Within 2
years it was reported to successfully reverse aminopterin and MTX toxicity, which had previously resisted folate rescue.[35] For more than 30 years, leucovorin rescue has been a cornerstone of HDMTX treatment.[36] leucovorin effectively neutralizes the effects of methotrexate.
Supportive Treatment:
Concomitant folic acid supplementation alongside methotrexate has been shown to reduce the incidence of gastrointestinal side effects, liver dysfunction, and improve continuance of treatment.[37].
Withdrawal of other potential nephrotoxins.

III. Conclusion:

Mtx plays a major role in the treatment of RA but if used irrationally, troublesome adverse effects may be noted. Patient/caretaker should be thoroughly informed about dosing, the potential risk associated with its long term use and the symptoms associated with its overdose. Patients on MTX therapy should be regularly monitored with liver function tests, renal function tests and CBC to identify myelosuppression. primary care physicians should be very careful and aware of these complications and recommendations, because the majority of these serious complications can be detected on time and even prevented if monitored.

Conflicts of interest:
There are no conflicts of interest.

Patient consent:
The patient was informed about the case report and patient's queries were resolved. The patient gave full consent to report the details of his condition in the case report.

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