Saudi Pharmaceutical Journal (2012) **20**, 301–305

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Adverse drug reactions caused by methotrexate in Saudi population

Haya M. Al-Malaq [a], Hussein F. Al-Arfaj [b], Abdurhman S. Al-Arfaj [b,*]

[a] *Clinical Pharmacy Department, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia*
[b] *Division of Rheumatology, Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia*

Received 18 April 2012; accepted 13 May 2012
Available online 19 May 2012

KEYWORDS

Methotrexate;
Adverse drug reactions;
Saudi Arabia

Abstract *Aim:* The aim of this study is to document adverse drug reactions (ARDs) of methotrexate (MTX) in Saudi patients.

Methods: Cross sectional study of adult patients on MTX, attending rheumatology drug monitoring clinics in a university hospital, over a period of 24 weeks. Adverse drug reactions were sought by patient interview, files review and laboratory abnormalities.

Results: Data collected included patients' demographics, diagnoses, co-morbidities, MTX dose and duration, other medications, laboratory abnormalities and adverse reactions, their severity, preventability, and outcome. Out of a total of 593 patients screened, 186 (31.4%) using MTX were interviewed. Most of the patients were female (88.5%). Adverse drug reactions (ADRs) were detected in 61 patients (32.8%). Patients with ADRs took a mean dose of 12.9 mg (2.5–22.5 mg). Ten ADRs (16.4% of total reactions) were preventable; they ranged between severe, moderate and mild. The most common ADRs were gastrointestinal (GI) (52.5%), followed by anemia (8.2%) and chest tightness (6.6%). The duration of the reaction ranged from few hours to 4 years.

Conclusion: In conclusion our patients with adverse reactions were younger, took less medications and had less co-morbidities. Our results were different from those published in the literature relating MTX toxicity.

* Corresponding author. Address: Division of Rheumatology, Department of Medicine, College of Medicine, King Saud University, P.O. Box 240466, Riyadh 11322, Saudi Arabia. Tel.: +966 014672573; fax: +996 01 4671494.
E-mail address: asarfaj@ksu.edu.sa (A.S. Al-Arfaj).

Peer review under responsibility of King Saud University.
doi:10.1016/j.jsps.2012.05.004

ELSEVIER **Production and hosting by Elsevier**

1. Introduction

Methotrexate (MTX) usage extends over 50 years. It is widely used as a disease modifying agent (DMARD) in rheumatoid arthritis (RA) and psoriatic arthritis. Its use is still prevalent even in the era of biological targeted therapy due to its therapeutically augmenting effects. It persisted because of its efficacy, acceptable toxicity profile and low cost (Visser and Van der Heijde, 2009). It is prescribed, alone or in combination with other medications in RA and other connective tissue disorders irrespective of the prognostic feature of the disease (Drugs for Rheumatoid Arthritis, 2009; Saag et al., 2008). However, it is

an anti-foliate drug with toxic effects on all rapidly dividing cells (Al-Niaimi and Cox, 2009). This toxicity ranges from mild gastrointestinal side effects to more severe hematopoietic, hepatic, pulmonary and renal effects (Al-Niaimi and Cox, 2009). In July 2004 the National Patient Safety Agency recorded 137 MTX related incidents in England in the previous 10 years including 25 deaths and 26 cases of serious harm (Al-Niaimi and Cox, 2009; NHS National Patient Safety Agency, 2006). Recent advances in genetic technology have led to the investigation of the gene encoding enzyme in the MTX metabolic pathways as possible determinants of MTX efficacy and toxicity and have suggested it to be race specific (Ranganathan and McLeod, 2006). Studies in Caucasians and African Americans found that genetic variation in MTX intracellular transporter system may be an important determinant in MTX related toxicity. It was suggested that the MTX toxicity profile may be distinct in different racial groups with different genetic background (Ranganathan et al., 2008). This prompted us to study adverse drug reactions in our population which has not been studied before.

2. Methods

2.1. Subjects and methods

This is a cross sectional study conducted in a tertiary hospital (King Khalid University Hospital, Riyadh). This hospital has a very active rheumatology service with a busy practice covering hundreds of patients attending specialized clinics for monitoring of anti-rheumatic drugs and their adverse drug reactions. We included all adult patients (age more than 16 years) attending rheumatology drug monitoring clinics for a period of 24 weeks. The study was approved by the Institutional Review Board, at College of Medicine and King Khalid University hospital, King Saud University, Riyadh and was conducted in accordance with the Declaration of Helsinki. We collected patients' demographics, diagnoses, other co-morbidities, especially those reported to influence the risk of developing toxicities in previous studies namely; alcohol intake, impaired renal function, hypo-albuminemia, human immunodeficiency virus infections (HIV), hepatitis B infections, lung abnormality on chest X-ray, obesity and diabetes. We also recorded MTX dose, duration, other medications use, laboratory abnormalities. Adverse reactions were documented and their severity, preventability, duration and outcome were noted. Both the World Health Organization (WHO) and American Food and Drug Administration (FDA) definitions were used to describe the adverse drug reaction. WHO defines Adverse Drug Reaction (ADR) as "a response to a drug which is noxious and unintended, and which occurs in doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function" (International Drug Monitoring, 1969). FDA defines adverse event as any untoward medical occurrence associated with the use of a drug in humans" (FDA, 2010). An adverse effect was defined as "severe" when the drug was permanently stopped, "moderate" when the drug was temporarily stopped or the dose was adjusted and "mild" when no action was taken (Van Jaarsveld et al., 2000). The ADRs were detected by patient interview, file review and laboratory abnormalities. If an adverse drug reaction was suspected, a form was filled which was designed by combining the British National Formulary and Med Watch volunteer reporting system (Appendix I) (British National Formulary, 2010; FDA, 2011). Since the reported events could be related to the illness itself or to other drugs that most patients used, a causal link was identified by using Narinjo scale ($\leqslant 0$ doubtful; 1–4 possible; 5–8 probable; $\geqslant 9$ definite) for assessing the probability of the reaction and McDonnell preventability questionnaire for the preventability of the reaction (Appendices II and III) (Naranjo et al., 1981; McDonnell and Jacobs, 2002).

2.2. Statistical analysis

All patients who entered the study were classified into two groups, those with ADRs, and those with no ADRs. Data were coded and entered into statistical package for social

Table 1 Comparison between ADRs group and no ADRs group.

	ADRs group (n = 61)	No ADRs (n = 125)	P-value
Age (mean ± SD)	45.89 ± 11.7	51.51 ± 14.26	0.008*
Number of medications (mean ± SD)	5.4 ± 1.7	5.89 ± 2.14	0.145
Sex			
Male	7 (11.5%)	20 (16.0%)	0.411
Female	54 (88.5%)	105 (84.0%)	
Co morbidities	22 (41.5%)	68.5%)	0.001*
Folic acid			
Yes	47 (90.4%)	119 (96.7%)	0.09
Diagnosis	(n = 53)	(n = 124)	
Rheumatoid arthritis	38 (41.0%)	97 (78.2%)	
Systemic lupus erythematosus	3 (5.7%)	4 (3.2%)	0.572
RA & SLE (overlap)	3 (5.7%)	2 (1.6%)	
Psoriatic arthritis	3 (5.7%)	7 (5.6%)	
Others	6 (11.3%)	14 (11.3%)	

* Significant, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus.

Table 2 Diagnoses compared between ADRs group and No ADRs group.

	ADRs group		No ADRs	
	Male	Female	Male	Female
RA	3	35	15	82
SLE	0	3	0	4
RA & SLE overlap	0	3	0	2
Psoriatic arthritis	2	1	3	4
Wegener's granulomatosis			0	1
JCA	0	1	0	2
Ankylosing Spondylitis			0	2
Henoch Schonlein purpura			0	1
Scleroderma			0	1
Polymyositis	0	1		
Adult-onset Still's disease			1	0
Others		4	1	5
Total	5	48	20	104

RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, JCA = Juvenile chronic arthritis.

Table 3 Types of ADRs.

Type of ADR	No	%
GI	32	52.5
Anemia (Hb < 10 mg/dl)	5	8.2
Chest tightness	4	6.6
Fatigue	3	4.9
Alopecia	3	4.9
Urinary symptoms	2	3.3
Infection	2	3.3
Elevated liver enzymes (>2 times the normal)	1	1.6
Feels depressed	2	3.3
Increased stiffness	1	1.6
Photosensitivity	1	1.6
Pulmonary fibrosis	1	1.6
Hyperglycemia	1	1.6
Oral ulcer	1	1.6
Dry mouth	1	1.6
Back pain	1	1.6
Total	61	

GI = gastrointestinal.

science (SPSS) version 17. These two groups were compared using student's t test for continuous variables; chi square and Fisher's exact test for categorical variables. A p value of less than 0.05 was considered significant.

3. Results

A total of 593 patients visited the outpatient rheumatology drug monitoring clinic during the 24 week study period,186 patients (31.4% of total patients) were taking MTX. There were 159 females (85.5%) and 27 males (14.5%) (Table 1). The mean dose of MTX was 12.9 mg/week (2.5–22.5) mg of methotrexate. The routes of administration were subcutaneous in one patient, intramuscular in two and the rest via oral route with a mean therapeutic duration of 4.9 years. Out of 181 patients using MTX, 61 patients (32.8%) experienced at least one adverse event 10 (16.4%) of ADRs could be preventable according to McDonnell preventability questionnaire. Twelve (19.7%) of the events were severe and resulted in drug discontinuation. Five (8.2%) were moderate. Out of these moderate ADRs, one resulted in dose separation, 1 resulted in reducing the dose and 3 in more frequent monitoring and follow up, the rest were classified as minor and resulted in no alteration of therapy. The duration of the reaction ranged from few hours after drug ingestion to 4 years.

One hundred and seven patients had other co-morbidities (32 patients had hypertension, 32 diabetes mellitus, 55 other bone and endocrine disorders). Patients with co-morbidities in the ADR group were 22, and non ADR group were 85 with a difference in favor of the non ADR group ($p = 0.001$). Most of the patients in the ADR and non ADR group took folic acid with no significant difference between the two groups ($p = 0.09$). The analysis of patient's age between the two groups showed that the patients with ADRs were younger than those with no ADRs ($p = 0.008$). Patients with risk factors for toxicity include 32 patients with diabetes mellitus (2 in the ADR group and 30 in the non ADR group), 1 patient with renal impairment in the non ADR group, one report of hepatitis B infection in the non ADR group, two reports of positive PPD (purified protein derivative) one in the ADR group and the other in the non ADR. There was no difference between male and female ratio in the two groups and in the number of other medications usage. In most patients (41%) (Table 2) MTX was being used to treat RA with no significant difference between the two groups ($p = 0.734$).

Causality assessment revealed that no reactions were certain or definite, 9 were probable and 52 were possible reactions. All included ADRs occurred after receiving methotrexate. Most common ADRs were gastrointestinal in nature (52.5%) (Table 3) ranging from mild abdominal discomfort to severe vomiting: vomiting in 1 (1.6%), diarrhea 1 (1.6%), oral ulcer 1 (1.6%), nausea 6 (9.8%) and the rest were non-specific abdominal discomfort (37.7%). Other common types of ADRs included chest tightness (6.6%), anemia (8.2%), fatigue (4.9%), and alopecia (4.9%).

4. Discussion

Despite the introduction of new biological agents, MTX monotherapy or in combination with other drugs is still considered an anchor treatment of many connective tissue disorders (Katchamart et al., 2009). It is also considered to be the most tolerable in long term therapy (Grove et al., 2001). Monitoring is the key to minimize drug toxicity. This is the main aim of the drug monitoring clinics in the study hospital. Risk factors for MTX toxicity include alcohol intake, impaired renal function, hypo-albuminemia, HIV infections, hepatitis B infections, lung abnormality on chest X-ray, obesity and diabetes (Visser et al., 2009). In our study these did not seem to lead to increased incidence of ADRs. Our rate of non compliance as a preventability factor (16.4%) was less than what was reported in the literature (22.7%). In our study the number of patients with other co-morbidities were greater in the non-ADR group with significant difference ($p = 0.001$). Methotrexate dose was less than that reported in the literature (17–20 mg/week) which may have contributed to reduction in

toxicity, but it is higher than what is recommended by the Japanese (8 mg/week) (Visser and Van der Heijde, 2009; Kay and Westhovens, 2009). Almost all patients (166 of 186; 89.2%) took folic acid therapy which is known to decrease the toxicity of MTX especially GI side effects (Prey and Paul, 2009). Anemia encountered here was most likely not due to MTX as it was not the type associated with MTX toxicity, namely megaloblastic (Jones and Patel, 2000). Myalgia was reported by one patient (1.6%) in our study. This complaint has been reported in 20–30% of MTX treated patients (Jones and Patel, 2000). People with ADRs were younger ($p = 0.008$) which is different from what is published in the literature (Al-Malaq et al., 2008). Withdrawal or spontaneous stopping of the drug was mainly seen in patients who took combination therapy. Most common adverse effects were gastrointestinal (52.5%) in nature similar to other studies (53%), but higher than in an Indian study (21%) (Van Jaarsveld et al., 2000; Bahroo and Baba, 2006). These included nausea, vomiting, diarrhea, oral ulcer and unspecific abdominal discomfort. Toxicity leading to the discontinuation of the drug comprised 17% of ADRs which was higher than that reported in literature (Van Jaarsveld et al., 2000). No adverse effects could be named as being definitely associated with MTX according to Narenjo scale (Naranjo et al., 1981). However no adverse effects were irreversible or lethal.

No studies in Saudi or Arab patients have measured MTX toxicity alone. Methotrexate was not mentioned in the few studies done in Arab patients except one which mentioned that side effects from analgesics and anti rheumatics were among most common causes of ADRs, with a prevalence of 6.7% of total reported ADRs and general preventability was 60%, and patients were young, took more medications and were often females (Al-Malaq et al., 2008; Ahmed, 1997; Major et al., 1998).

A main limitation of this study is that most ADRs are subjective and almost all the patients took other medications, also the study is open in nature and both the researcher and the patient know that the drug used is MTX which could lead to over reporting of the side effects.

We recommend a patient safety booklet to document any changes in MTX dose or in the side effects profile as recommended by previous studies (Al-Niaimi and Cox, 2009). Application of diagnosis and monitoring data base (DIAMOND) program, in which data is entered by a specialized rheumatology nurse to act as a communication tool between medical and nursing staff. A telephone helping system could also be used to keep patient compliant with all DMARDS including MTX in the face of minor symptoms that might otherwise result in unnecessary discontinuation (Grove et al., 2001).

In conclusion 32.8% of Saudi patients using MTX experienced at least one ADR. Most common ADRs reported were GI. ADRs occurred in younger patients, in patients taking less medications and in those who had less co-morbidities. Our results are different from those published in the literature regarding MTX toxicity. A prospective study in our population may help clarify these differences.

Acknowledgments

We would like to convey special thanks to Dr. Najma Khalil for reviewing the text and Mr. Amir Marzouk for statistical help (College of Medicine Research Centre, King Saud University, Riyadh).

Appendix.

A.I. Form

Patient information

File #:_____

Age: _____ **Years** **Sex:** **M** **F**

Suspected drugs

Drug Name:_MTX **Rout:**_____ **Dosage:**_____

Date Started:_____ **Date Stopped:**_____

Prescribed For:_____

Suspected reaction

_____

_____

Date Reaction Started:_____**Date Reaction Stopped:**_____

Outcome from the reaction

○**Death** ○**Life threatening** **Hospitalization** **Other**

Comments:

Possible cause of reaction

_____

Type of reaction

○preventable ○ not preventable ○other

Comments:

Reaction is confirmed by

Disease activity at time of reaction

Severity assessment

○**sever** ○**moderate** ○**mild**

Other Drugs (including Self-medication and herbal remedies)

Drug	**Rout**	**Dose**	**Prescribed For**
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

Reporter details

Physician **Pharmacist** **Other**

Other relevant information (including medical history, known allergies, pregnancy and other congenital abnormalities)

_____

_____

.

A.II. Narenjo Algorithm

To assess the adverse reaction you should answer the following questionnaire and give a score				
		Yes	No	Don't know
1	Are there previous conclusive reports of this reaction?	+1	0	0
2	Did the adverse event appear after the suspected drug was administered?	+2	−1	0
3	Did the adverse reaction improved when the suspected drug was discontinued or a specific antagonist was administered?	+1	0	0
4	Did the adverse reaction reappear when the drug was re-administered?	+2	−1	0
5	Are there alternative causes that could on their own cause the reaction?	−1	+2	0
6	Did the reaction reappear when placebo was given?	−1	+1	0
7	Was the drug detected in the blood or other body fluids in concentrations known to be toxic?	+1	0	0
8	Was the reaction more sever when the dose was increased or less severe when the dose was decreased?	+1	0	0
9	Did the patient have a similar reaction to the same or similar drugs at any previous exposure?	+1	0	0
10	Was the adverse event confirmed by any objective evidence?	+1	0	0
Total score ⩾9 Definite; 5–8 probable; 1–4 possible; ⩽0 doubtful				

Naranjo et al. (1981).

A.III. Factors that determine the preventability of ADR

If the answer is yes to any of these questions the ADR is considered preventable
Was the drug involved in the ADR not considered appropriate for the patient's clinical condition?
Were the dose, route, and frequency of administration not appropriate for the patient's weight and disease state?
Was required therapeutic drug monitoring or other necessary laboratory test not performed?
Was there a history of allergy or previous reaction to the drug?
Was a drug interaction involved in the reaction?
Was a toxic serum drug concentration documented?
Was poor compliance involved in the reaction?

References

Ahmed, M el-B., 1997. Drug-associated admissions to a district hospital in Saudi Arabia. Clin. Pharmacol. Ther. 22, 61–66.

Al-Malaq, H.M., Al-Aqeel, S.A., Al-Sultan, M.S., 2008. Adverse drug reactions related hospitalization identified by discharge ICD-9 codes in a university hospital in Riyadh. Saudi Med. J. 29, 1145–1150.

Al-Niaimi, F., Cox, N.H., 2009. Methotrexate safety: from prescribing to labelling. Br. J. Dermatol. 160, 1345–1346.

Bahroo, A.M., Baba, A.N., 2006. Adverse effects of low dose methotrexate in patients with rheumatoid arthritis. IJPMR 17, 21–25.

British National Formulary, 2010. 60 ed. MHRA.

Drugs for Rheumatoid Arthritis, 2009. Treat. Guidel. Med. Lett. 7 (81), 37–46.

FDA, 2010. Guidance and Compliance Regulatory Information.

FDA, MedWatch, 2011. Voluntary Drug Reporting Form [3500].

Grove, M.L., Hassell, A.B., Hay, E.M., Shadforth, M.F., 2001. Adverse drug reactions to disease modifying anti-rheumatic drugs in clinical practice. Q. J. Med. 94, 309–319.

International Drug Monitoring, 1969. The role of the hospital. World Health Organ. Tech. Rep. Ser. 425, 5–24.

Jones, K.W., Patel, S.R., 2000. A family physician's guide to monitoring methotrexate. Am. Fam. Physician 62, 1607–1612, 1614.

Katchamart, W., Trudeau, J., Phumenthum, V., Bombardier, C., 2009. Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying anti-rheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis. Ann. Rheum. Dis. 68, 1105–1112.

Kay, J., Westhovens, R., 2009. Methotrexate: the gold standard without standardisation. Ann. Rheum. Dis. 68, 1081–1082.

Major, S., Badr, S., Bahlawan, L., et al., 1998. Drug-related hospitalization at a tertiary teaching center in Lebanon: incidence, associations, and relation to self-medicating behavior. Clin. Pharmacol. Ther. 64 (4), 450–461.

McDonnell, P.J., Jacobs, M.R., 2002. Hospital admissions resulting from preventable adverse drug reactions. Ann. Pharmacother. 36, 1331–1336.

Naranjo, C.A., Busto, U., Sellers, E.M., et al., 1981. A method for estimating the probability of adverse drug reactions. Clin. Pharmacol. Ther. 30, 239–245.

NHS National Patient Safety Agency, 2006. Patient Safety Alert 13. Improving Compliance with Oral Methotrexate Guidelines..

Prey, S., Paul, C., 2009. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. Br. J. Dermatol. 160, 622–628.

Ranganathan, P., McLeod, H.L., 2006. Methotrexate pharmacogenetics: the first step toward individualized therapy in rheumatoid arthritis. Arthritis Rheum 54, 1366–1377.

Ranganathan, P., Culverhouse, R., Marsh, S., et al., 2008. Methotrexate (MTX) pathway gene polymorphisms and their effects on MTX toxicity in Caucasian and African American patients with rheumatoid arthritis. J. Rheumatol. 35, 572–579, 628.

Saag, K.G., Teng, G.G., Patkar, N.M., et al., 2008. American College of Rheumatology 2008 recommendations for the use of non-biologic and biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 59, 762–784.

Van Jaarsveld, C.H., Jahangier, Z.N., Jacobs, J.W., et al., 2000. Toxicity of anti-rheumatic drugs in a randomized clinical trial of early rheumatoid arthritis. Rheumatology (Oxford) 39, 1374–1382.

Visser, K., Van der Heijde, D., 2009. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of literature. Ann. Rheum. Dis. 68, 1094–1099.

Visser, K., Katchamart, W., Loza, E., et al., 2009. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E initiative. Ann. Rheum. Dis. 68, 1086–1093.