Adverse consequences of low-dose methotrexate medication errors: data from French poison control and pharmacovigilance centers

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Abstract

Objective: The objectives of this study are to carefully describe the context of methotrexate medication errors, to details medical consequences and management approaches, and to determine the rate of fatal outcome.

Methods: Data on methotrexate medication errors were obtained from the French network of Poison Control and Pharmacovigilance Centres which collected and documented reported drug-induced adverse effects. Cases were included if the intake was more than 2-fold the intended weekly dose or a weekly cumulative dose ≥ 30 mg and a follow-up of at least 4 days after the last dose. Data were analysed for demographics, treatment indication, prescribed dose, drug interactions, clinical complications and medical outcomes.

Results: Seventy four patients were included. The causes of methotrexate errors resulted from an erroneous prescription renewal (23.3%), incomprehensiveness of the weekly schedule by patients or at-home caregivers (56.2%) and administration of a wrong dose by a health care professional (20.5%). Of the 70 patients who took methotrexate daily, the mean daily dose received over the whole duration of the error was 9.6 ± 4.1 mg (range 2.5-22.5) with a mean duration of the error of 11.7 ± 12.2 days (range 2 to 90). Thirteen (18%) patients remained asymptomatic and 61 (82%) developed complications of which 46 (62.2%) were severe. Nine (14.8%) patients died within 11 to 45 days after the first dosing error. Compared to patients with no or mild symptoms, those with severe symptoms were more likely to be older (75.6 ± 10.8 *vs*. 69.5 ± 12.9 years) and to be exposed to a higher cumulative dose (94.8 ± 46.2 vs. 68.0 ± 45.7 mg).

Conclusions: This study confirms that dosing errors with methotrexate can be lethal and persisted despite several warnings from drug agencies. Further measures are awaited from the European Medicine Agency.

Keywords: methotrexate, medication error, drug toxicity, mortality

1. Introduction

Oral methotrexate (MTX), a folic acid analog that competitively inhibits folic acid reductase, is indicated in a variety of chronic inflammatory diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, resistant psoriasis and psoriatic arthritis. It is also sometimes used off-label for maintenance of remission in Crohn's disease [1] or in serious vasculitis [2], but with few evidence of efficacy from randomized clinical trials. Although some rare but severe adverse effects such as bone marrow suppression with pancytopenia or hepatic injury have occurred with low-dose methotrexate therapy, its efficacy and safety in the setting of rheumatoid arthritis is not questioned [3].

The weekly dose of MTX varies from 5 mg to 25 mg. A 50% reduced dose is recommended when the creatinine clearance is decreased to 20-50 ml/min, while MTX is contra-indicated in severe renal insufficiency. According to EULAR recommendations and a systematic review of clinical trials, systematic folate supplementation is highly recommended to reduce MTX adverse effects in patients treated for rheumatoid arthritis [4,5]. Besides, the unusual weekly schedule exposes to potential medication errors. Consequently, analysis of data from poison control centers or spontaneous cases reported to national drug agencies have warned on the consequences of oral MTX medication error [6-8] and the French Drug Agency produced two consecutive Dear Doctor Letters (DDL) in July 2011 [9] and November 2016 [10] to inform health professionals on the risks of severe adverse effects and deaths following methotrexate medication errors.

The objectives of this study were to describe the consequences of medication errors involving low-dose oral MTX, to identify factors associated with severe outcome and to evaluate the mortality incidence rate.

2. Methods

Medication errors involving oral MTX and reported between 1st January 2007 and 31st October 2013 to the French networks of poison control centres (PCCs) or pharmacovigilance centres (PVCs) were

analysed. The French network of PCCs comprises 9 centres and the PVCs network is based on 31 centres. Both are located in university hospitals with their own databases. The data system of PCCs depends on the French governmental agency dealing with sanitary safety in food, the environment and at work. The data system of PVCs is located within the French Drug Agency. Although separate centres, PCCs and PVCs regularly communicate, either directly or through their respective agencies. Interestingly, these two sources provided complementary data. For the purpose of this study, each centres were contacted and all agreed to participate. Due to the retrospective and non-interventional design of this study the approval of the local Ethics Committee was not necessary.

Medication errors reported in patients treated with oral MTX were extracted from both databases. Because of the narrow safety margin of prolonged oral MTX treatment with 30 mg per week regarded as the highest tolerable dosage [11], our inclusion criteria were intake of more than 2-fold the intended weekly dose (data extracted from the narrative of the reported case) or a weekly cumulative dose ≥ 30 mg. According to the short half-life of MTX [12], a follow-up of at least 4 days after the last MTX dose was required in asymptomatic patients. Data were analysed for demographics, indication, prescribed MTX dose, concomitant folic acid intake, clinical complications and medical outcomes. A particular attention was paid to concomitant treatments that have been suggested to interact with high-dose intravenous MTX, e.g. non-steroidal anti-inflammatory drugs, penicillins and proton pump inhibitors, although the clinical relevance of such interactions with low-dose MTX has not been substantiated by the most recent available evidence |13].

Baseline renal function was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and classified into 5 stages [14]. The severity of complications was coded according to the Common Toxicity Criteria for Adverse Events (CTCAE, version 4.03) with severity considered when at least one score among mucitis, haematological, hepatic or renal adverse consequences was graded ≥ 3. The types of error (prescription, dispensation, administration), the persons involved in the error and the sites the error happened were also recorded. When serum levels of MTX were available, only those assessed within 96 hours after the last intake were

considered. If necessary, additional clinical or biological information were requested from the centre which collected initial data.

For statistical analysis, qualitative variables (including ordinal variables) are expressed as frequency (percentage) and continuous variables as mean and standard deviation. Categorical data were compared by chi square test or Fisher exact test and continuous data by the Student t test or the non-parametric Wilcoxon test when the variable of interest was not normally distributed. We conducted a logistic regression analysis with manual backward selection based on P-values to identify which set of variables were independent predictors of sever outcome. Data were analyzed by the R statistical software (www.R-project.org).

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3. Results

A total of 174 MTX medication errors were retrieved during the 7 years-follow-up by both centres (128 from PCC and 46 from PVC). Of these, 74 (42.5%) were included after review and agreement by two senior physicians (Anne Marie Patat and Thierry Vial). Causes of exclusion were duplicates between centres in 16 cases, a cumulated dose < 30 mg over one week in 23, isolated medication error in an untreated patient in 9, unconfirmed medication error in 8, unintentional and isolated intake in 5 children, and insufficient data or an unknown outcome in 39.

Baseline characteristics of the patients and circumstances of the error are summarized in Table 1. Eleven (14.9%) patients had a previous moderate or severe alteration of the renal function. Most were treated for rheumatoid arthritis, related rheumatic inflammatory disorders or psoriasis. In 38 (51.4%) patients, the treatment was prescribed for more than 6 months whereas 26 (35.1%) started MTX recently (unknown in 10).

The source of the error was clearly identified in 73 cases and resulted from an erroneous prescription renewal by the general practitioner (5.5%) or by the time of hospitalisation in a non-rheumatic unit or transfer in a nursing home (17.8%), administration of the wrong dose due to an

incomprehensiveness of the weekly schedule by the patients or at home by caregivers (54.8%), by hospital nurse (6.8%) or the nursing home staff (13.7%) at the time of transfer, and from self-medication in one patient. None of the errors were due to pharmacist dispensing. The medication error resulted in taking a daily dose instead of a weekly dose in 70 patients (94.6%) while 4 other patients mistakenly took 50 to 100 mg MTX as a single dose. Of the 70 patients who took methotrexate daily, the mean daily dose received over the whole period of the error was 9.6 ± 4.1 mg (range 2.5-22.5) and the mean duration of the error was 11.7 ± 12.2 days (range 2 to 90). The distribution of dose and duration of the error is indicated on figure 1. Medication errors were identified from symptoms highly suggestive of MTX toxicity in 49 (66.2%) of patients, directly by the patient or the medical staff in 20 (27%) and on a systematic blood cell count in 2 (2.7%) (unknown in 3).

Only 13 (17.6%) patients remained asymptomatic during the follow-up. They had ingested a mean dose of 7 ± 4.4 -fold (range 2-20) the intended dose for a mean cumulative dose of 68.3 ± 52.6 mg (range 25-225). Clinical and/or biological effects attributable to MTX were observed in 61 (82.4%) patients. Adverse events occurred within a mean of 11.7 ± 12.7 days (range 2-90) after the first dosing error (unknown in 1). Table 2 summarizes the type and severity of clinical or biological symptoms. Overall, 14 (18.9%) patients experienced mild-to-moderate adverse effects and 46 (62.2%) had severe (≥ grade 3) complications. The exact grade of severity was not assessable in one patient who experienced only fever and mucositis. The mean time to onset of symptoms ≥ grade 3 was 12.5 ± 13.6 days with only as few as 3-4 consecutive days of MTX administration in 5 patients (3 with pancytopenia, 1 with severe thrombocytopenia and 1 with severe mucositis). Serum levels of MTX assessed within 48 hours after the last MTX intake in 12 patients were below the limit of detection in 11 and higher than the toxic dose in one (0.26 µM at H14).

Initial management of the error consisted of surveillance at home or general practitioner consultation for 20 (27%) patients, including 8 poorly symptomatic patients, and hospitalization for

54 (73%) patients of whom 7 remained paucisymptomatic and 3 had no symptoms. Eight of the 28 patients with no symptoms or low grade of severity (≤ 2) only received additional folinic acid. The 46 patients who had severe toxicity received standard treatment including supportive care with intravenous fluids and administration of antibiotics or antifungals. In addition, 35 received folinic acid, 19 granulocyte-colony stimulating factor infusion and 23 underwent platelet or blood transfusions. Fourteen received the last 3 treatments. Of the 61 symptomatic patients, 45 (73.8%) fully recovered within a median of 10 days (range 5-45, calculable for 41 patients), 9 (14.8%) died, and the long term outcome was unknown in 7 (11.5%) patients who had only limited complications that initially improved

The 9 deaths occurred within a mean of 23.4 ± 10.4 days (range 11-45) after the first occurrence of the medication error. The median age of these patients was 84.7 ± 6.6 years (range 71-94) and the mean cumulative dose received was 90.6 ± 39.6 mg (range 40-150). The duration of MTX dosing error ranged from only 4 to 16 days. All of them experienced severe haematological disorders (grade 3 in one and grade 4 in 8) and 2 also had serious liver injury. All died from severe sepsis. Of these 9 patients, the medication error occurred in a hospital in 6 cases or in nursing house in 2. The overall rate of death was 12.2% (CI: 5.7-21.8). As the probability of over-reporting the most severe cases to PVC, we separately examined the death rate observed by PCCs which collected data prospectively at the time of toxicological advice and at the time of follow-up. Among 37 cases, 3 deaths were reported (incidence rate 8.1%; CI 1.7-21.9).

When compared to patients with no or mild symptoms, those who experienced severe complications were significantly older (75.6 ± 10.8 vs. 69.5 ± 12.9 years) and more likely to have been exposed to a higher cumulative dose (94.8 ± 46.2 vs. 68.0 ± 45.7 mg) (table 3). There was also a trend toward more frequent concomitant proton pump inhibitor exposure in the severe group. Multivariate adjustment showed that age and cumulative dose were independent predictor of severe complications.

4. Discussion

Besides the large number of cases available for complete evaluation, the strength of our study is to provide detailed clinical and biological data on the consequences of MTX medication errors. While the most frequent cause of the error was due to the patient (53.4%), a concerning number resulted from erroneous prescription renewal by a non-specialist and error in administration due to a nurse during a hospital stay or in a nursing room. Severe complications were observed in 62% of patients with age and the cumulative dose over the period of the error significantly associated with the most severe outcomes. Although it has been shown that severe MTX toxicity from low-dose exposures correlates with renal impairment [12], our study was unable to find a significant role of altered renal function in the severity of MTX intoxication. Even very short term duration of the error was associated with severe outcome or death. The incidence rate of death was 12.2% (CI: 5.7-21.8) and 8 of these 9 cases resulted from an error of health care professionals.

Whereas the consequences of accidental or intentional single intake of high-dose oral MTX are limited to minor symptoms [7], the risks of MTX toxicities after repeated medication errors by the oral route is very worrying and listed in the never events list [15]. Since the early 90's, a number of publications reported severe or fatal outcomes that were often due to prescription errors by non-rheumatic physicians [16-18]. Later on and based on large series, many countries such as Australia [6], Denmark [19], Spain [8] and USA [20] mentioned a dramatic death rate ranging from 5.2% to 24% after MTX dosing errors. In our study, the overall death rate of 12.2% was exactly within this range. Also important here is that severe cases can occur after only 3 consecutive days of medication error, as reported by others [6], and death after a little as a cumulative dose of 40 mg. Eight of the nine deaths were observed in patients who received MTX for more than 6 months before the error, strongly suggesting that the risk of fatalities is higher in these patients.

Causes and locations of the errors depend on the countries. Based on reports submitted to the FDA, causes were attributable to the prescribers (37% of cases), the patient (20%), a dispensing error (19%) or a health care professional (17%) in US [20]. Another nationwide study based on 4 Danish

national databases found prescribers, nurses and patients or its relatives as the main persons who made the errors in 40.5%, 27.7% and 11% of cases, respectively [19]. By contrast data from Spain evidenced the patient (68.1%) or an error in the prescription process (19.1%) as the most common causes [8]. Overall, this suggests that patient's and non-specialist physician education on the proper use or prescription still remain a key way to reduce MTX errors. Also disturbing from our series is the relatively frequent occurrence of errors in a nursing home (16.2%) or during a hospitalization in non-rheumatologic departments (23%). Such a high incidence was also found in the Danish study with respective rates of 11.6% and 32.4% [19]. Once again this underlined insufficient knowledge on the particular schedule of oral MTX administration by the nursing staff or non-specialized physicians.

Following an accumulating number of MTX medication errors, a leaflet from the French Drug Agency was posted in July 2011 to ensure that patients, pharmacists and non-rheumatologic prescribers are aware of the risks of extra MTX dose [9]. In our survey, the annual number of cases reported in the 36 month-period following these warnings was stable compared to the period 2007-2010 (8-13 cases per year). Therefore, the Agency extended this information in November 2016 to nurses and nursing home [10]. A number of public institutions from other countries exposed to similar problems have also largely communicated [21-23]. Interestingly, a corporate-wide initiative conducted in nursing homes clearly showed that modifying the dispensing system and medication use processes that forced a mandatory second clinical review of all MTX orders during the pharmacist verification process completely eradicated MTX medication errors [24]. Finally, the European Medicines Agency recently started a review of the risk of dosing errors with methotrexate in order to identify the causes and to elaborate preventive measures [25].

Treatment of MTX overdose after repeated oral dosing error is not established, but folinic acid use is warmly recommended in any symptomatic patients. Because the chemotherapy normogram for acid folinic acid rescue is of no value because serum MTX concentrations are generally below the limit of quantification at the time of determination in these patients, we pragmatically suggest a starting dose of 25 mg folinic acid to continue as long as the neutrophil count is lower than $1x10^9$/L.

Our study confirms that MTX medication errors still occurred despite repeated warnings. Even short-error duration with low-dose oral MTX may result in sometimes life-threatening toxicity. The number of events observed in nursing home or non-rheumatic hospital department is of particular concern, indicating that many of these errors take place during transition cares. Improving education and warnings when prescribing and dispensing low-dose methotrexate are paramount. Prescribers should therefore ensure that the patient and/or their caregiver clearly understand the dosing scheme while pharmacists should also contribute by underlining clear instructions on dosage and encouraging patients to read the Product Information Leaflet.

Disclosure of interest

The authors declare that they have no competing interest

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Table 1. Characteristics of the 74 patients and circumstances of the error

Gender (Female:male)	55:19
Age (years), mean ± SD (24)	73.3 ± 11.9 (44-94)
Usual renal function (%)	
- Stage 1	30 (40.5)
- Stage 2	16 (21.6)
- Stage ≥ 3	11 (14.9)
- Unknown	17 (23.0)
Treatment indication (%)	
- Rheumatoid arthritis or related diseases	58 (78.4)
- Psoriasis	4 (5.4)
- Other inflammatory or autoimmune diseases	10 (13.5)
- Unknown	2 (2.7)
Type of error (%)	
- Administration	55 (74.3)
- Prescription of the wrong dose or treatment schedule	17 (23)
- Self-medication	1 (1.4)
- Unknown	1 (1.4)
Site of the error (%)	
- At home due to the patient or a nurse	45 (60.8)
- Retirement community	12 (16.2)
- During hospitalization in a non-rheumatologic department	17 (23.0)

Table 2. Type and severity of clinical or biological symptoms observed in 60 symptomatic patients*

Severity**	Type of symptoms (n=106)***			
	Mucositis	Decrease in blood cell count	Renal function abnormal	Increased hepatic enzymes
≤ 2	14	8	13	8
3	13	10	3	4
4	2	28	0	3
Total	29 (27.4%)	46 (43.4%)	16 (15.1%)	15 (14.2%)

* The exact grade of severity was not assessable in one patient who experienced fever and mucositis

** Severity was assessed using the NCI CTCAE v4.03 (death are excluded from this table)

*** As more than one symptom may be observed in the same patient, the total number of adverse effects was 104

Table 3. Main characteristics of patients, treatment, renal function, ingested dose and concomitant treatment in asymptomatic or poorly symptomatic patients and patients with severe complications

Characteristics	Patients asymptomatic or without severity criteria (n=28)	Patients with severity criteria (grade ≥ 3) (n=46)	p
Female, n (%)	22 (78.6)	33 (71.7)	NS
Mean age ± SD (years)	69.5 ± 12.9	75.6 ± 10.8	< 0.05
Mean Body Mass Index ± SD	26.5 ± 5.9 (n=14)	24.4 ± 6.0 (n=33)	NS
Creatinine clearance ≥ stade 3, n (%)	3 (16.7) (n=18)	8 (17.4) (n=40)	NS
Type of error and person involved, n (%)* - *Administration* - Patient or caregiver - Hospital nurse or nursing home staff - *Prescription* - General practitioner - Hospital or nursing home practitioner	n= 27 19 (70.4) 5 (18.5) 1 (3.7) 2 (7.4)	n = 45 22 (48.9) 9 (20) 3 (6.7) 11 (24.4)	 NS
Mean duration of the error ± SD (days)	7.9 ± 8.0	13.1 ±13.8 (n=45)	< 0.005
Mean cumulative dose ± SD (mg)	68.0 ± 45.7	94.8 ± 46.2 (n=45)	< 0.05
Chronic MTX treatment, n (%)	10 (52.6) (n=19)	28 (60.9) (n=46)	NS
MTX continuation for more than 2 days after first suggestive symptoms of toxicity in symptomatic patients, n (%)	2 (20) (n=10)	8 (20) (n=40)	NS
Regular folic acid supplementation before medication error, n (%)	8 (50) (n=16)	16 (42.1) (n=38)	NS
Concomitant PPI treatment	3 (20) (n=15)	18 (47.4) (n=38)	NS

MTX: methotrexate; NS: non significant; PPI: proton pump inhibitor

* full data available for 72 patients

Figure 1. Dose and duration of 68 methotrexate dosing errors

Six of the 74 cases are not included because the error was unique or its duration was unknown