Signal

Methotrexate and Muscle Spasm

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Summary

Methotrexate is a drug developed as a structural analogue of folic acid. As a folic acid antagonist, it blocks the synthesis of purines by inhibiting numerous regulatory enzymes. It produces an intense anti-inflammatory action and inhibits cell division. A screening of VigiBase, the WHO global database of individual case safety reports, identified the association of MedDRA Preferred Term (PT) "muscle spasm" with methotrexate. A qualitative analysis was undertaken of forty-seven cases with a completeness score of over 0.70. The similarity of characteristics with respect to time to onset, the biological plausibility, the improvement after drug withdrawal, all support this signal. The muscle spasms could be associated with methotrexate, especially in those patients' on chronic low doses. Prescribers and patients need to be aware that muscle spasms could be present with the use of methotrexate. This adverse reaction could impair the quality of life of patients, especially long-term users with chronic diseases.

Signal

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Restricted

Introduction

Methotrexate was granted US FDA approval in December 1953. Since then, it has been used via oral, intramuscular, intravenous, subcutaneous, intrapleural, and intrathecal routes of administration. Methotrexate acts by the inhibition of enzymes responsible for nucleotide synthesis. It is used for the treatment of several neoplasmic conditions such as acute leukaemia, lymphomas, osteosarcoma, breast cancer, and in autoimmune diseases such as rheumatoid arthritis and psoriasis. Moreover, it is used to treat gestational choriocarcinoma, chorioadenoma, hydatiform mole, and advanced mycosis fungoides.[1,2]

Muscle spasm covers several somewhat overlapping concepts of true spasm and of cramps. Spasms are involuntary muscle contractions. When prolonged and painful, they are often termed cramps. Muscle cramps are sustained, painful contractions of muscle and are prevalent in patients with or without medical conditions. Muscle cramps are common in the general population and can be disabling. This description distinguishes muscle cramps from the other painful muscle disorders that either do not include shortening of the muscle, for example, myositis and myalgia, or that include involuntary shortening of muscle but do not cause pain, for instance, myotonia and tetany.[3] Myalgia and arthralgia are mentioned in the Summary of Product Characteristics (SPC) of methotrexate as rare adverse drug reactions (ADRs).[4,5] Other drugs such as diuretics may cause muscle spasm through dehydration or an electrolyte imbalance, especially hypokalaemia, hypocalcaemia, or hypomagnesemia. Muscle spasm can accompany myopathy, which has been associated with numerous medication classes, including antimalarials and statins. Other medications can cause muscle spasms, including beta-agonists, acetylcholinesterase inhibitors (often used for the treatment of myasthenia gravis), cimetidine, steroids, morphine, penicillamine, cardiotropics, antiretrovirals, and psychotropic medications.[6,7]

Reports in VigiBase

As of May 2020, there were 397 reports for the MedDRA Preferred Term "muscle spasms" associated with methotrexate. However, due to the large number of cases, a completeness score over 0.7 was set for this analysis so as to identify the causality patterns that strengthen the signal. In the present case series, 47 cases were evaluated.

The reports came from eighteen countries, most of them in Europe but also from the Americas, Africa, and Asia. There were thirty female cases and seventeen male. The age was recorded for forty-five patients, ranging from 13 to 87 years (median 57). Thirty-one out of the total were adults. Thirty-six cases (76%) were reported by health professionals (20 by physicians and 16 by pharmacists). Sixteen cases were considered serious mainly under the criterion of other medically important condition (ten cases). The last report was received in March 2020. Thirty-three of the cases had a narrative; the summary of their characteristics is set out in Table 1.

The most frequent therapeutic indication was rheumatoid arthritis (17 cases), followed by psoriasis or psoriatic arthritis.(8) There were also cases with neoplastic indications (6) and with polymyositis, meningitis, and Crohn's Disease (one of each). In thirteen reports the therapeutic indications were not given. Twenty-six patients (55%) received methotrexate by oral administration. There were eight cases in which the parenteral route was used (six intravenous and two intrathecal), and four were subcutaneous. The time to onset was highly variable in the whole group –from one day to six years-. However, a weekly dose administration was reported in twenty-six cases: seventeen by the oral route, four cases subcutaneous, and the administration route was unknown in five. In this subgroup of 26 patients, the time to onset was given in fourteen cases, with a median of 29 days and a range of one day to 18 months. A daily dose was mentioned in five cases, in which the time to onset was the same as the day of administration.

In twenty-eight reports, methotrexate was the only suspected drug, and in 18 methotrexate was the only medication reported. Regarding other suspected drugs, there were five cases with adalimumab as a co-suspected drug, but in only two cases was methotrexate the last medication introduced, and in the other three the patients were on chronic treatment with methotrexate when adalimumab was introduced. Another co-suspected drug in two cases was etanercept; only one case gave the dates: the patient was a chronic user of methotrexate, and etanercept had recently been administered. Other relevant drugs identified were proton pump inhibitors (PPI), in five cases reported as co-suspected (lansoprazole (1), pantoprazole (2), and esomeprazole

(2)). However, there were eight cases where PPI was reported as a concomitant medication (pantoprazole (4) omeprazole, lansoprazole, and rabeprazole (one each)), but in this group, only four have dates that suggest that the PPI administration came before the ADR and were concurrent with the use of methotrexate. In one case esomeprazole was used after the occurrence of the ADR. Other relevant drugs were non-steroidal anti-inflammatory drugs (NSAIDs), in two cases diclofenac, and in one naproxen. In these three cases, these drugs were considered as concomitant. There was one case with concomitant reporting ibuprofen and esomeprazole in the same timeframe. Three cases mentioned concomitant statins, such as atorvastatin and simvastatin.

In one case, another ADR was a decreased level of calcium and magnesium. In seven cases diarrhoea or vomiting were reported at the same time as muscle spasms. Looking closely at the muscle spasm term, in thirty-one cases the LLT term described were muscle cramps; sometimes the location of the cramps was in a limb, legs, hand, or foot. In sixteen cases the reported LLT were muscle spasms, some of them were described as a cervical or back muscle spasm. The intensity of this ADR was described in one narrative as *"very intense, disabling and painful on the arms or the legs, with frequency variable, 1 to 3 times a day"*. This description is of a 63 year-old male patient, reported by a pharmacist. In this case, methotrexate and pantoprazole were reported as suspected drugs. Other concomitant drugs in the narrative were diltiazem, digoxin, and paracetamol. Methotrexate was first used subcutaneously for rheumatoid arthritis. After roughly six months, the patient presented with muscle cramps, and five months after this methotrexate was changed to the oral route. This patient was reported as not recovered.

Another case worth mentioning for a better understanding of the ADR is a 65 year-old patient, reported by a pharmacist. Muscle cramps occurred at night following administration of methotrexate 15 mg a week for rheumatoid arthritis, with a latency of 14 days after increasing the dose, which was subsequently reduced to 7.5 mg a week. The narrative mentioned that the patient felt better with fewer complaints. Only methotrexate was reported as suspected. The concomitant medications were carbasalate, diclofenac, misoprostol, amlodipine, isosorbide dinitrate, folic acid, metoprolol, alendronic acid, and simvastatin. The patient had never had a muscle disorder in association with simvastatin. The national centre mentioned that the official product information of methotrexate only describes myalgia.

Positive dechallenge was observed in twenty-one cases. The drug was withdrawn in eighteen cases; sixteen out of these eighteen cases mentioned the outcome as recovered, the other two had recovering, and recovered with sequelae. In three cases the dose of the drug was reduced, with the outcome recovered. Sixteen cases out of the total had an individual causality assessment (10 using the Naranjo algorithm and 6 using the UMC/WHO global introspection method). In fifteen cases the reported category was "possible", and one case was described as not assessable by the UMC/WHO method.

Rechallenge was undertaken in eight out of forty-seven cases, and in three there was a positive rechallenge; however, there was no narrative in these reports. The other rechallenge cases gave the outcome as unknown, although these uncovered interesting details. For example a 57 year-old man, whose physician described muscle cramps and increased blood creatine phosphokinase with the use of methotrexate and lansoprazole. In the narrative, the physician wrote: *This patient is being followed for non-erosive rheumatoid arthritis. Treatment with methotrexate 10 mg/week was introduced in February. The patient reports from the start of his treatment disabling muscle cramps preventing any sporting activity. He has also been treated with lansoprazole since February. This patient was also on hydrochlorothiazide- irbesartan, stopped in November of the same year, but without improvement in muscle symptoms.* It is worth noting that the rechallenge had an unknown outcome. However, with the dates given in the original report, it is possible to deduce that the rechallenge was without the lansoprazole, because at the beginning in February the patient was exposed to both drugs, but for the rechallenge, only methotrexate was reintroduced.

Another case with rechallenge was a 33 year-old woman, reported in a study by a physician. Her ADRs were pain, muscle spasm, and tetany. The suspected drugs were methotrexate and adalimumab (both subcutaneous, weekly) and opipramol (daily, oral). The medical history included former smoking, adiposity, allergic bronchial asthma, depression, onychomycosis,

gonalgia both-sided, and psoriasis arthropathic. The starting date for methotrexate was in January and for the adalimumab in March of the same year. The muscle cramps began on April 30th and the tetany on May 4th. The patient showed complete tetany of the right leg, which was not resolved by administration of tetrazepam. The case was reported as rechallenge with an unknown outcome.

Literature and labelling

The main risks with the use of methotrexate are related to haematological toxicity, and imbalance of immunity with the presence of infections. However, neither the SPC in the US nor in Europe describe muscle spasm or cramps as ADRs. Myalgia, arthralgia, osteonecrosis, and osteoporosis are listed as musculoskeletal ADRs.

Moreover, methotrexate has several cautions regarding potential interactions with other drugs. There is a warning regarding the concomitant use with NSAIDs, because it has been found to decrease the tubular secretion of methotrexate and possibly to increase its toxicity. Likewise, there is a precaution in the concomitant use of omeprazole and pantoprazole (methotrexate elimination possibly reduced).[5] However, there are no warnings regarding concomitant use of statins or adalimumab, or other drugs that can cause musculoskeletal complaints.

Regrettably, in the literature there are no case reports about muscle cramps, though there are two regarding musculoskeletal ADRs. One describes two cases of acute diffuse muscular pain following initiation of weekly low dose oral methotrexate in rheumatoid arthritis (women 70 and 49 years old).[8] The other literature report concerns a 59-year-old man with a folliculotropic cutaneous T-cell lymphoma taking low dose pulse methotrexate (15 mg intramuscularly, once a week), at the same time as being treated with pantoprazole (20 mg/day, orally); after the first injection of methotrexate he presented with generalized myalgia and bone pain. The symptoms recurred over the following four methotrexate cycles. Pantoprazole was replaced by ranitidine and the muscle symptoms disappeared. This report mentions a positive rechallenge, during which a laboratory test showed an elevation in the serum concentration of the 7-hydroxymethotrexate, which the authors interpreted as an interaction in renal elimination, rather than a metabolic interaction.[9]

Discussion

Muscle spasms or cramps may sometimes overlap with myalgia, and myalgia has already been identified as an ADR. Nevertheless, this series presents a group of patients who suffer from spasm or cramp, with most cases reported by physicians. For that reason, it is plausible to think the muscle spasm or cramp is a worrisome clinical event that may not allow daily activities for some patients.

Methotrexate inhibits the aminoimidazole caboxamide ribonucleotide transformylase (AICART). Inhibition of AICART leads to the accumulation of AICART ribonucleotide, which inhibits adenosine deaminase, leading to an accumulation of adenosine triphosphate and adenosine in the extracellular space, stimulating adenosine receptors. This action is well-known as the basis of the anti-inflammatory properties, however, this acts on the skeletal muscle by the adenosine monophosphate-activated protein kinase (AMPK). Hence, the potential action of the methotrexate on the skeletal muscle is a concern. Recent research suggests that methotrexate could reduce the threshold for AMPK activation by AICART. On the other hand, AMPK has recently emerged as a novel target for the treatment of pain, with the exciting potential for disease modification. AMPK activators inhibit signalling pathways that are known to promote changes in the function and phenotype of peripheral nociceptive neurons and promote chronic pain.[2,10–12]

The medical literature suggests that muscle spasms could be associated with peripheric neuropathy and hypothyroidism, clinical conditions not identified in this case series due to the intrinsic limitations of spontaneous reporting. Other causes could be electrolyte imbalances; one case mentioned imbalances in calcium and magnesium. It is well known that hypokalaemia could be associated with muscle cramps or other muscle complaints; however, there were no cases with hypokalaemia.

The concomitant drugs found in the cases raise concerns about an incomplete profile of methotrexate interactions. Some drugs, such as adalimumab, or statins, could be strongly associated with the muscle ADRs; however, it is not possible to rule out the suspected role of methotrexate as it fits the same timeframe. Also, since other drugs such as NSAIDs and PPI can decrease renal elimination and the

tubular secretion, this statement is supported in an animal model and some pharmacokinetics studies. Some studies have analysed this interaction in low and high doses of methotrexate. Their conclusions are similar; the relevance of the elevation in methotrexate concentration as a consequence of the interaction has a low clinical impact; however, they emphasize the importance of a careful risk-benefit balance before deciding on use, and of the necessity of a follow-up, especially in chronic users of methotrexate.[5,13,14]

Conclusion

Muscle spasms or muscle cramps are not currently mentioned in the SPC, and this ADR could have an impact on the quality of life of patients undergoing treatment with methotrexate. Patients, as well as physicians, should be aware of these ADRs to avoid a reaction that could affect the quality of life of patients. For this reason, it is reasonable to consider an in-depth clinical analysis when the patient mentions these complaints, especially those patients on low doses.

References

1. Cipriani P, Ruscitti P, Carubbi F, Liakouli V, Giacomelli R. Methotrexate in rheumatoid arthritis: Optimizing therapy among different formulations. Current and emerging paradigms. Vol. 36, Clinical Therapeutics. Excerpta Medica Inc.; 2014. p. 427–35.

2. Inoue K, Yuasa H. Molecular basis for pharmacokinetics and pharmacodynamics of methotrexate in rheumatoid arthritis therapy. Drug Metab Pharmacokinet. 2014;29(1):12–9.

3. Jansen PHP, Gabreëls FJM, van Engelen BGM. Diagnosis and differential diagnosis of muscle cramps: A clinical approach. J Clin Neuromuscul Dis. 2002;4(2):89–94.

4. Methotrexate 2.5 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2020 May 13]. Available from: https://www.medicines.org.uk/emc/product/511/smpc

Table 1. Summary characteristics of 47 cases in VigiBase of muscle cramps in association with methotrexate with a completeness score over 0.70

Characteristic	47 cases with completeness score over 0.70
Age (mean / range)	53 years / 13-87
Patient sex distribution	30 females / 17 males, ratio 2:1
Top Ten countries	Netherlands (15), France (6), Canada (5), Australia (2), Republic of Korea (2), Sweden (2), Croatia (2) Germany (2), Italy (2), Costa Rica (1)
Reporter types	Physician (26), Pharmacist (10), Consumer (7), Other Health Professional (4)
Single suspect drug	28 reports (59%)
Single reported drug	18 reports
Time-to-onset	1 day to 6 years
The action taken with the drug /outcome	25 cases with drug withdrawn / 16 recovered, 1 recovered with sequelae, 1 in recovering, and 1 outcome unknown. 4 cases with dose reduced / 3 recovered and 1 not recovered. 12 cases with the drug not changed / 3 recovered, 1 recovered with sequelae, 7 not recovered and 1 outcome unknown. 6 drug action unknown / 3 recovered and 3 outcomes unknown

5. DailyMed - METHOTREXATE- methotrexate sodium tablet [Internet]. [cited 2020 May 13]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8f1260de-b60c-4f0e-8af6-0e957b0a281b

6. Stamford B. Muscle Cramps. Phys Sportsmed. 1993;21(7):115–6.

7. Miller TM, Layzer RB. INVITED REVIEW MUSCLE CRAMPS. Muscle Nerve [Internet]. 2005 [cited 2020 May 18];32:431–42. Available from: www.interscience.wiley.

8. Eames P, Jones AC. Acute diffuse muscular pain following initiation of methotrexate therapy [2]. Vol. 53, Annals of the Rheumatic Diseases. BMJ Publishing Group; 1994. p. 478–9.

9. Tröger U, Stötzel B, Martens-Lobenhoffer J, Gollnick H, Meyer FP. Drug points: Severe myalgia from an interaction between treatments with pantoprazole and methotrexate. Vol. 324, British Medical Journal. BMJ Publishing Group; 2002. p. 1497.

10. Dolinar K, Jan V, Pavlin M, Chibalin A V., Pirkmajer S. Nucleosides block AICAR-stimulated activation of AMPK in skeletal muscle and cancer cells. Am J Physiol - Cell Physiol. 2018 Dec 1;315(6):C803–17.

11. Asiedu MN, Dussor G, Price TJ. Targeting AMPK for the Alleviation of Pathological Pain. Vol. 107, EXS. NIH Public Access; 2016. p. 257–85.

12. Pirkmajer S, Kulkarni SS, Tom RZ, Ross FA, Hawley SA, Hardie DG, et al. Methotrexate promotes glucose uptake and lipid oxidation in skeletal muscle via AMPK activation. Diabetes. 2015;64(2):360–9.

13. Reeves DJ, Moore ES, Bascom D, Rensing B. Retrospective evaluation of methotrexate elimination when co-administered with proton pump inhibitors. Br J Clin Pharmacol. 2014;78(3):565–71.

14. Hall JJ, Bolina M, Chatterley T, Jamali F. Interaction Between Low-Dose Methotrexate and Nonsteroidal Anti-inflammatory Drugs, Penicillins, and Proton Pump Inhibitors: A Narrative Review of the Literature. Ann Pharmacother. 2017;51(2):163–78.

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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