Muscle spasms: an unexpected adverse drug reaction of pemetrexed?

Hendrika J. A. de Rouw, Naomi T. Jessurun, Lucie J. P. Masen-Poos and Hieronymus J. Derijks

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***Abstract*:** In this report we describe a 53-year-old woman with advanced non-small cell lung cancer, treated with pemetrexed and cisplatin combination therapy, followed by pemetrexed monotherapy. The patient developed severe muscle spasms at least twice, shortly after administration of pemetrexed monotherapy. A possible explanation for this observation is that in combination with cisplatin therapy, the patient was hyperhydrated before administration to promote renal excretion and reduce toxicity. Pemetrexed is also renally excreted, which supports the finding that toxicity did not occur when the patient was hyperhydrated. After discontinuation of pemetrexed the symptoms did not reoccur. All aspects of this case point to a possible relationship between pemetrexed and an adverse drug reaction (ADR). We conclude that muscle spasms are a rare, but possibly dose-related ADR of pemetrexed-based therapy.

Keywords: adverse drug reaction, muscle spasms, non-small cell lung cancer, pemetrexed

Introduction

Pemetrexed is a folate antagonist, which is primarily indicated for the treatment of advanced non-small cell lung cancer as monotherapy or in combination with cisplatin. We describe a patient with recurring muscle spasms after administration of pemetrexed monotherapy, an adverse drug reaction (ADR) that has not previously been described. Informed consent was obtained from the patient in advance.

Case description

A 53-year-old woman (weight, 44 kg; body surface area 1.43 m^2) was treated for stage IV non-small cell lung cancer and bone metastases with first-line chemotherapy: 500 mg/m^2 pemetrexed intravenously (i.v.) and 75 mg/m^2 cisplatin i.v. on day 1 of every 3 weeks for four cycles followed by pemetrexed: 500 mg/m^2 i.v. on day 1 of every 3 weeks until progression. The patient was diagnosed with TxN0M1b metastasized lung carcinoma in January 2015 after a bone biopsy, based on immunohistochemistry and imaging. In February she received her first administrations of pemetrexed (700 mg) and cisplatin (110 mg), followed by another three cycles with administration on day 1. She experienced expected side effects such as nausea, vomiting, reduced appetite and weight loss. Computed tomography imaging showed stable disease. Maintenance therapy with 700 mg pemetrexed administered on day 1 every 3 weeks was started in May 2015. After two days from the first administration of the pemetrexed maintenance therapy, the patient was admitted to the emergency department with severe abdominal pain. Upon physical examination, remarkable regular spasms of the abdominal musculature, similar to fasciculation or myoclonus, were observed. There was no sign of infection or any other acute pathology. Laboratory results were within normal ranges (see Table 1). Medicines used prior to the incident were diclofenac, oxycodone, colecalciferol, acetaminophen, omeprazole, folic acid, hydroxocobalamin and hydroxychloroquine [used for lupus erythematosus (LE)]. At the emergency department, the patient received oxazepam 10 mg orally for muscle relaxation, without effect. The patient was discharged and prescribed diazepam 5 mg orally, 1–3 times daily on occasion. Chemotherapy was continued and the patient indicated that she experienced spasms multiple times in the following cycles shortly after administration of pemetrexed, although not as severe as the first incident. In October 2015 the patient was admitted again at the emergency department with similar symptoms

Correspondence to:
Hendrika J. A. de Rouw, PharmD
ZANOB Pharmacy Jeroen Bosch Hospital, 5203 DK ´s-Hertogenbosch, 3406, The Netherlands
n.d.rouw@zanob.nl

Naomi T. Jessurun, PharmD
Netherlands Pharmacovigilance Centre – Lareb, ´s-Hertogenbosch, The Netherlands

Lucie J. P. Masen-Poos, MD,
Department of Pulmonary Diseases, Jeroen Bosch Hospital, ´s-Hertogenbosch, The Netherlands

Hieronymus J. Derijks, PharmD, PhD
ZANOB Pharmacy Jeroen Bosch Hospital, ´s-Hertogenbosch, The Netherlands
Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands

Table 1. Laboratory results.

	May 2015	October 2015	Reference values
Creatinine	64	63	50–100 µmol/l
eGFR	>60	>60	>60 ml/min
Urea	6.5	6.9	2.5–6.5 mmol/l
Sodium	138	137	135–145 mmol/l
Potassium	3.7	3.5	3.5–5 mmol/l
Chloride	105	Not tested	96–107 mmol/l
Phosphate	Not tested	0.8	0.8–1.5 mmol/l
Magnesium	0.81	0.64	0.7–1.0 mmol/l
Calcium	2.19	2.16	2.20–2.65 mmol/l
Calcium corrected*	–	2.41	2.20–2.65 mmol/l
Albumin	Not tested	30	35–50 g/l
CRP	<3	7	0–8 mmol/l
CK	Not tested	152	0–170 mmol/l

CK, creatine kinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.
*corrected calcium according albumin levels.

of vigorous tensed and painful abdominal musculature. Before this visit to the emergency department, the patient took diazepam 5 mg orally and oxycodone 5 mg orally, both twice (besides her standard twice daily 20 mg oxycodone prolonged release tablets), but the symptoms persisted. At the emergency department the patient received two administrations of morphine 5 mg i.v. and diazepam 5 mg i.v. The patient's symptoms improved slightly for a short period of time. Laboratory results were within normal range (see Table 1). Other medicines used prior to this incident were indometacin, pregabalin, folic acid, hydroxocobalamin, macrogol and electrolytes, oxycodone, diazepam, colecalciferol, acetaminophen, omeprazole and hydroxychloroquine. Differences in medication used compared with the first incident included her pain medication (indometacin and pregabalin) and laxative use. The patient stayed in the hospital for further observation. The spasms persisted for about 36 h. The pain was under control with morphine continuous infusion (1.5 mg/h), but this dose resulted in a morphine intoxication (diagnosed by an anaesthesiologist based on symptoms), which prolonged her stay in the hospital for a total of 12 days. After the spasms disappeared, the patient experienced severe myalgia. After 10 days from admission the patient indicated she was painless. The patient continued her chemotherapy. Granisetron and dexamethasone were used as an anti-emetic co-medication on the same day as administration of chemotherapy. To exclude granisetron as a suspect for the ADR, it was replaced by aprepitant orally (125 mg, 80 mg, 80 mg, on day 1, 2, and 3 of chemotherapy, respectively) in the following cycle. Nevertheless, the patient reported that the muscle spasms reoccurred after administration of pemetrexed. Due to further progression of disease, chemotherapy was discontinued in November 2015. The symptoms did not reoccur.

Discussion

There are several observations that indicate causality between the occurrence of muscle spasms and pemetrexed use in this patient. Upon start of pemetrexed monotherapy the symptoms occurred within 2 days, but also diminished after a short period of time (1–2 days). Subsequently, spasms occurred in the following cycles after administration of pemetrexed (positive rechallenge). A physician twice objectified the ADR. The discontinuation of pemetrexed, with subsequent absence of the symptoms (a positive dechallenge), suggests possible causality. Granisetron was ruled out as another possible suspect, leaving no other potential drugs.

A possible mechanism of action is that antifolate compounds interfere with pyrimidine and purine synthesis through inhibition of several enzymes, causing a folic acid and vitamin B12 deficiency [Rossi *et al.* 2009; Hanauske *et al.* 2001]. Such deficiencies often result in neurological symptoms; thus the muscle spasms could theoretically have a neuromotor component. The predicted ADRs due to these deficiencies are (partly) preventable by vitamin supplementation. Our patient received

folic acid and hydroxocobalamin, which makes this explanation more unlikely [Rossi *et al.* 2009; Hanauske *et al.* 2001; Scagliotti *et al.* 2003].

It is remarkable that there were no symptoms when pemetrexed was used in combination with cisplatin. The symptoms only occurred while the patient received pemetrexed monotherapy. A possible explanation for this observation is that in combination with cisplatin therapy, the patient was hyperhydrated before administration to promote renal excretion to reduce cisplatin toxicity. Like cisplatin, pemetrexed is also renally excreted (for 70–90%) [Hanauske *et al.* 2001]. Possibly, hyperhydration not only had a positive effect on the excretion of cisplatin, but also on pemetrexed clearance resulting in reduced toxicity. In addition, the patient was in a cachectic state. This suggests that the ADR was probably dose-related. No pemetrexed serum levels were measured.

It should be noted that there was concomitant use of the non-steroidal anti-inflammatory agents (NSAIDs) diclofenac and indometacin respectively, during the entire period of chemotherapy. Both NSAIDs and pemetrexed can negatively influence renal function. In combination both can contribute to higher pemetrexed blood levels, and thus toxicity, shortly after administration. However, the patient's serum creatinine levels were within the normal range and there was no indication that renal dysfunction contributed to the toxicity of pemetrexed in our patient.

There are some other, nonmedication-related factors to be considered as a possible cause for the muscle spasms. Firstly, electrolyte unbalance (magnesium and calcium) can cause muscular symptoms. As showed in Table 1, lab results were within the normal range, providing that the calcium value was corrected for the albumin level. Secondly, this patient suffers from LE. Muscle pains are a known symptom of LE. While these symptoms are often described as pain and weaknesses, not as spasms, and in this case the spasms were cycle-related, LE was not likely to be the cause in our patient.

A literature search shows no publications with comparable cases, but further research reveals two case reports of pemetrexed-related life-threatening rhabdomyolysis. No possible mechanism for the ADRs was given [Huang *et al.* 2012; Ceribelli *et al.* 2006]. There are more previously nondescribed cases of muscle spasm associated with pemetrexed and methotrexate. Methotrexate is another folate antagonist used for the treatment of acute lymphoblastic leukaemia and rheumatoid arthritis. The World Health Organization (WHO) VigiBase™ database contains 14 reports of muscle spasms associated with the use of pemetrexed, and 129 reports of muscle spasm associated with the use of methotrexate [World Health Organization, 2016a]. The reports of these cases suggest that muscle spasms occur more often and support the causality between the occurrence of muscle spasms and the use of pemetrexed. When using the WHO Causality Assessment System [World Health Organization, 2016b], we can classify the causality of this ADR as 'probable/likely', with the addition of a possible pharmacological explanation.

Conclusion

This is the first case-report of muscle spasms associated with the use of the folate antagonist pemetrexed. The short latency time, recovery on withdrawal, positive rechallenge and dechallenge, exclusion of other suspected drugs and the fact that it was objectified by a physician together with the other reported cases of muscle spasms associated with antifolate drugs, all point to a possible relationship between pemetrexed and the observed muscle spasms. Clinicians should be aware that muscle spasms are a rare, but possible, dose-related ADR of pemetrexed-based therapy, which should be recognized as such.

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References

Ceribelli, A., Cecere, F., Milella, M., Facciolo, F., Gelibter, A. and Cognetti, F. (2006) Severe rhabdomyolysis associated with pemetrexed-based chemotherapy. *Lancet Oncol* 7: 353.

Hanauske, A., Chen, V., Paoletti, P. and Niyikiza, C. (2001) Pemetrexed disodium: a novel antifolate clinically active against multiple solid tumors. *Oncologist* 6: 363–373.

Huang, M., Tsai, J., Shen, M., Chou, S. and Yang, C. (2012) Pemetrexed as a possible cause of severe rhabdomyolysis in the treatment of lung cancer. *Lung Cancer* 76: 491–492.

Rossi, A., Ricciardi, S., Maione, P, de Marinis, F. and Gridelli, C. (2009) Pemetrexed in the treatment of advanced non-squamous lung cancer. *Lung Cancer* 66: 141–149.

Scagliotti, G., Shin, D., Kindler, H., Vasconcelles, M., Keppler, U., Manegold, C. *et al.* (2003) Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. *J Clin Oncol* 21: 1556–1561.

World Health Organization (2016a) The database of the World Health Organization Collaborating Centre for International Drug Monitoring (VigiBase™). Available at: https://tools.who-umc.org (accessed 29 January 2016).

World Health Organization (2016b) The World Health Organization – Uppsala Monitoring Centre Causality Assessment System. Available at: http://who-umc.org/Graphics/24734.pdf (accessed October 2016).