Case report

Reversible myoclonus, asterixis, and tremor associated with high dose trimethoprim-sulfamethoxazole: a case report

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Case Diagnosis: Reversible myoclonus, tremor, and asterixis induced by high dose trimethoprim-sulfamethoxazole.

Case Description: The patient was a 66-year-old male with T9 AIS¹ C quadriplegia secondary to spinal cord compression by a tumor due to large B cell lymphoma. Subsequent to tumor resection and chemotherapy, the patient was discovered to have *Pneumocystis jiroveci* pneumonia (PJP). Once started on high dose trimethoprim-sulfamethoxazole (TMP-SMX) therapy (15.6 mg/kg/day of trimethoprim) for the treatment of PJP, he displayed bilateral upper extremity myoclonic jerks at rest, asterixis, and postural tremor. Symptoms resolved once TMP-SMX therapy was discontinued.

Discussion: Myoclonus, asterixis, and tremor have been linked to high dose TMP-SMX therapy as a toxic side effect. Our patient's symptoms did improve with levetiracetam therapy, but did not fully resolve until TMP-SMX was discontinued.

Conclusions: This is thought to be the first reported case of reversible myoclonus, tremor, and asterixis induced by high dose TMP-SMX in the spinal cord injury population. Early recognition of TMP-SMX induced complications were of key importance as they negatively impacted the rehabilitation process. We also recommend consideration of symptomatic treatment with levetiracetam for the duration of required TMP-SMX therapy as it appeared to mitigate the severity of our patient's movement disorders.

Keywords: Trimethoprim-sulfamethoxazole combination, Myoclonus, Dyskinesias, Tremor, Spinal cord injuries, *Pneumocystis jirovecii*, Pneumonia, *Pneumocystis*, Physical and rehabilitation medicine, Etiracetam

Introduction

Reversible myoclonus is one of the less common side effects that may be induced by high dose trimethoprim-sulfamethoxazole. This is a case report of reversible myoclonus with asterixis and tremor noted in a patient with a spinal cord injury being treated for *Pneumocystis jiroveci* pneumonia.

Case Report

Patient V was a 66-year-old male with a complex medical history including T9 AIS C spinal cord injury secondary to spinal cord compression by tumor from large B cell lymphoma diagnosed in August 2012. He initially presented with bowel and bladder incontinence

that developed after lower extremity weakness, which began insidiously and progressed thereafter. He subsequently underwent tumor resection with T7-T10 laminectomy and 4 cycles of R-CHOP with radiation therapy by late February 2013. He had multiple hospitalizations during this time frame for various complications including pneumonia, supraventricular tachycardia, and multiple urinary tract infections. He arrived at the VA Spinal Cord Injury Service in March 2013 for rehabilitation.

Soon after arrival, in early April, the patient underwent urodynamic studies for neurogenic bladder testing and after a brief episode of fever, was placed on trimethoprim-sulfamethoxazole double strength (180/800 mg) dosed twice daily for eight days for a urinary tract infection. Also of note, he began to have

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an increased oxygen requirement with shortness of breath. CT thorax showed bilateral ground glass opacities, bilateral pleural effusions, and mediastinal adenopathy. PET scan did not show evidence of lymphoma recurrence, but was consistent with pneumonitis and/or chemical-related toxicity. Diagnostic thoracentesis was not revealing, showing only transudative fluid, but bronchoalveolar lavage of the right upper lobe and lingula was significant for positive Direct Fluorescent Antibody for PJP. HIV testing was negative and this finding of PJP was thought to be due to immunosuppression from the previous R-CHOP cycles and long-term use of acyclovir. TMP-SMX Double Strength (160/800 mg) 2 tabs by mouth every 6 hours was started. This dosage provided 15.6 mg/kg/day of trimethoprim for the treatment of PJP. Three days after initiation of therapy, the patient noted painful episodes of upper extremity myoclonic hand movements at rest, worse with stimulation. He also had asterixis and a slight super-imposed high frequency, low amplitude postural tremor that increased with intention.

Metabolic causes of tremor, asterixis, and other movement disorders were ruled out, including electrolyte abnormalities, uremia, hyperammonemia, and elevated thyroid function. The neurology consult service agreed that his symptoms were likely secondary to the high dose TMP-SMX therapy. They did not believe an EEG was necessary due to the close correlation of symptoms with onset of drug treatment.

Before the initiation of TMP-SMX, patient V had been undergoing an acute rehabilitation program with physical therapy sessions three to five times per week. In particular, he had been working on improving his bed mobility, self care skills, and his ability to navigate by power wheelchair. Once the symptoms began, he was unable to participate in therapy for several days due to the frequent occurrence of painful myoclonic jerks. The tremor also caused him to be unable to eat independently.

Levetiracetam (dosed at 6.1 mg/kg twice daily) was trialed, and allowed for a mild to moderate decrease in the frequency of episodes of tremor and myoclonic jerks. This allowed for increased tolerance to therapy sessions, up to three per week. He also regained the ability to eat independently with setup assistance. Despite this mitigation in symptoms, he was downgraded from requiring minimum to moderate assistance in power wheelchair navigation in open spaces and from moderate to maximum assistance in tight spaces.

After 3 weeks of high dose TMP-SMX, he was down-titrated to single strength TMP-SMX daily for PJP prophylaxis (1.9 mg/kg/day). Three days later, his

abnormal movements resolved, no longer requiring levetiracetam. His functional abilities, as seen in therapy, returned to baseline over the next week and began to improve once more. He reached a modified independent level for power wheelchair navigation on the second week. The prophylactic dose of TMP-SMX was stopped after two weeks because of thrombocytopenia.

Discussion

Adverse reactions to standard dosages of TMP-SMX occur in roughly ten percent of patients and typically involve the gastrointestinal tract and skin. However, myoclonus, intention tremor, and asterixis have been rarely cited as reactions, and linked to high dose therapy as a reversible neurotoxic side effect.²⁻⁴ Our patient's neurologic symptoms did improve with levetiracetam therapy but did not resolve until TMP-SMX dosage was stopped. During the three weeks of high-dose therapy, the patient's ability to take part in, and progress in therapies was significantly impacted.

The type of myoclonus exhibited by our patient did not appear to be associated with seizure disorder. It was spontaneous and not reflexive. He maintained full consciousness during episodes. The tremor that he had was postural, but sometimes, it also occurred at rest. Metabolic causes of movement disorders were also screened for but not detected.

There have been several other case reports involving similar symptoms for patients on high dose TMP-SMX.²⁻⁴ All were receiving high dose TMP-SMX for infection in the setting of immunocompromise. Symptoms described, as well as onset and resolution patterns in relation to dosage of TMP-SMX were similar to those of patient V. Please see Table 1 below for a comparison between cases.

We believe patient V's case lends valuable material for discussion for several reasons. One is that we were able to track his functional performance in therapy. Due to his spinal cord injury and other medical problems, the addition of an upper extremity movement disorder posed a severe insult to his already compromised health and functional status.

Also, we were able to mitigate his symptoms somewhat, using levetiracetam. Symptomatic treatment was attempted previously in a case report of patient with an exacerbation of posthypoxic action myoclonus during high dose TMP-SMX treatment for PJP.² Therapeutic agents included a combination of valproic acid and piracetam. However, the severe exacerbation of the original action myoclonus was not controlled. Thus, Patient V's treatment was unique. His functional status was not returned to baseline but he was able to

Table 1 Case comparison

Case	Movement Disorder Symptoms	Onset	Trimethoprim Dose (mg/kg/day)	Reason for TMP-SMX	Time to Resolution	Mitigation of Symptoms
Patient V	myoclonus, asterixis, and postural tremor	2–3 days	15.6	PJP after chemotherapy-induced immunosuppression for large B cell lymphoma	3 days	Symptoms mitigated by levetiracetam to allow tolerance of physical therapy
Jundt ²	exacerbation of posthypoxic action myoclonus	day 2	19.2*	PJP after chemotherapy-induced immunosuppression for non-Hodgkin's lymphoma	2 days	Symptoms not controlled by valproic acid or piracetam until downtitration of TMP-SMX
Dib ³	diffuse multifocal myoclonus and bilateral asterixis	day 4	20	Nocardia pneumonia after chemotherapy-induced immunosuppression for acute myelogenous leukemia	4 days	None discussed
Van Gerpen ⁴	high frequency low amplitude postural tremor, greater in the upper extremities	day 3	960 mg/day**	PJP in the setting of AIDS	3 days	None discussed

*Calculated 0.166667 (fraction of TMP in TMP-SMX) * 115 mg/kg/day (dose of combined TMP-SMX) = 19.2 .

**Patient weight and mg/kg/day dose not provided.

participate in therapy. Therefore, muscle mass and cardiovascular conditioning were not lost while he would have missed therapy sessions. Once the high dose TMP-SMX course was complete, he was able to quickly return to his baseline and then go on to improve upon that level within two weeks.

Conclusions

High dose TMP-SMX is a cause of reversible movement disorders, including myoclonus, tremor, and asterixis.

This case report is one of the first to our knowledge to document TMP-SMX related myoclonus, tremor, and asterixis in a patient with SCI. We believe high dose TMP-SMX therapy should be monitored with great care in patients with SCI as these adverse reactions can cause a much greater functional impact when compared to able bodied patients. We also posit a trial of levetiracetam for the mitigation of these movement disorders in appropriate patients, where a high dose TMP-SMX course cannot be avoided, as it showed a positive effect in this case.

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Disclaimer statements

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