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REVIEW

Successful amelioration of oxaliplatin-induced hyperexcitability syndrome with the antiepileptic pregabalin in a patient with pancreatic cancer

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Abstract
Background Oxaliplatin, a platinum derivative used in the treatment of gastrointestinal cancers, has been associated with sensory neuropathies and, more infrequently, a neuromyotonia-like hyperexcitability syndrome. We present a case of hyperexcitability syndrome that developed during the treatment of pancreatic cancer with oxaliplatin and gemcitabine (GEMOX) that was successfully treated with pregabalin.
Case presentation A 54-year-old woman was undergoing chemotherapy with gemcitabine and oxaliplatin (GEMOX) for stage II-B pancreatic adenocarcinoma. On the third day of her fourth cycle, she presented with twitching of eyelids and tremors of hands. This twitching started bilaterally on the eyelids, followed by teeth jittering, hand shaking, and slurring of speech. A thorough neurological exam revealed no abnormalities except increased tone of both hands—she had difficulty opening her hand after closing it for a hand-grip. She was given a dose of 1 g of IV magnesium sulfate and 1 g of IV calcium gluconate, and 50 mg of IV diphenhydramine. In addition to reassurance, pregabalin was prescribed for these myotonic symptoms at a dosage of 50 mg by mouth three times daily. Improvement occurred in these symptoms within 12 h and she was almost asymptomatic within 72 h.
Conclusion Oxaliplatin causes a unique spectrum of acute neurological toxicities that have not been observed in patients receiving either cisplatin or carboplatin. Clinically, sensory alterations are most prominent, particularly cold-induced and perioral paresthesias. Other symptoms, such as cramps, jaw stiffness, voice changes, ptosis, and visual field changes suggest that motor nerves or muscles may also be involved (hyperexcitability). Hyperexcitability syndrome, distinct from cold-induced paresthesias and sensory neuropathy, is a rare complication of oxaliplatin chemotherapy; and up to date no pharmacotherapy has been successful in treating these symptoms. This is the first report of the successful amelioration of this syndrome with the antiepileptic pregabalin.

Keywords Oxaliplatin · Hyperexcitability syndrome · Myotonia · Colon cancer · Peripheral neuropathy · Sodium channels

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Introduction

Oxaliplatin is an antineoplastic agent currently indicated for use with fluorouracil and leucovorin for the treatment of stages III and IV advanced cancer of the colorectal cancer [1–4]. One of the commonest adverse effects associated with oxaliplatin is peripheral neuropathy. Oxaliplatin causes two types of neuropathy: acute and chronic. Acute neuropathy can begin during the infusion, within minutes to hours, or within 1–2 days of administration, but is usually self-limited, often resolving within days. Common signs and symptoms include paresthesias, hypoesthesias, and dysesthesias, which usually begin in the feet or hands. The neuropathy can also be associated with shortness of breath or difficulty swallowing, but without laryngospasm or bronchospasm. Patients have also experienced an unusual sensation in the tongue, jaw spasms, eye pain, and muscle spasms or cramps, which are sometimes described as stiffness in the

hands or feet or the inability to release the grip. A feeling of pressure in the chest has also been reported. Acute neuropathy may be triggered by exposure to cold temperatures and often returns on retreatment [5, 6]. This acute neuropathy causes a variety of distressing, but transient, symptoms due to peripheral sensory and motor nerve hyperexcitability [7]. This nerve hyperexcitability can manifest as a distinct syndrome that clinically exhibits as neuromyotonia known as Hyperexcitability Syndrome. It is perhaps a rare but also the most important neurological syndrome that warrants immediate dose reduction or drug withdrawal in clinical practice. Neuromyotonia is a rare condition characterized by muscle stiffness, slowed muscle relaxation, and increased sweating, and less commonly paresthesias [8]. It has several causes. It may be autoimmune mediated or associated with neuropathy [9], or a rare side effect of drugs, radiotherapy, or toxins [9–11]. The exact mechanism of neuromyotonia in humans is largely unknown, however it is postulated that either persistent sodium channel activity or decreased potassium conductance can be a mechanism for producing axonal hyperexcitability and repetitive discharges in human nerve cells. Non-inactivating sodium channels in sensory axons are thought to produce the repetitive discharges that underlie paresthesia [12]. Direct autoimmune blockade of voltage-gated potassium channels [13–15] and exposure of sodium channels in para-nodal regions [16] has also been implicated.

These symptoms have been treated with partial success with the use of anti-convulsant drugs like phenytoin and carbamazepine in some patients [17, 18]. We previously published our experience with carbamazepine in patients who were treated in a phase I study designed to establish the maximum-tolerated dose of capecitabine given with oxaliplatin (XELOX). As an exploratory analysis, we performed detailed neurological examination, needle electromyography (EMG), and nerve conduction studies (NCS) before and the day after oxaliplatin in a subset of 13 patients. Carbamazepine therapy was tried in 12 additional patients to determine whether the neurologic effects might be relieved. In this study, all patients experienced acute, reversible neurotoxicities with oxaliplatin. In addition to commonly seen symptoms including paresthesias, dysesthesias, cold hypersensitivity, jaw pain, eye pain, pain in the arm used for drug infusion, ptosis, leg cramps, visual/voice changes, signs of hyperexcitability were also noticed in the serial EMG and NCS in motor nerves after oxaliplatin. In patients who achieved therapeutic levels, carbamazepine did not alter the clinical or electromyographic abnormalities. Therefore, we concluded that carbamezepine, which provides symptomatic relief in acquired neuromytonia, did not seem to be beneficial. Addition of gabapentin to a modified FOLFOX regimen did not reduce oxaliplatin-induced neurotoxicity in a recent study published by Mitchell [19]. Patients with chemo-naïve metastatic colorectal cancer were recruited sequentially to two cohorts: first cohort received a modified FOLFOX6 (fluorouracil/leucovorin/oxaliplatin) regimen alone with oxaliplatin 100 mg/m^2 every 2 weeks (mFOLFOX; $n = 40$), and the second cohort received the addition of gabapentin (mFOLFOX + G; $n = 41$). Gabapentin commenced at 300 mg daily, increasing to a maximum of 600 mg three times daily to decrease neurotoxicity. Doses of gabapentin were increased in 31 of 41 patients, with 39% of patients receiving > or = 900 mg daily. The median relative dose intensity of oxaliplatin and requirement for dose reductions or delays because of neurotoxicity were similar in the two cohorts. There was no grade 4 neurotoxicity. Whereas grade 3 neurotoxicity was observed in 10% of patients treated with gabapentin versus 21% of patients treated with mFOLFOX alone, there was no statistically significant difference in the severity of neurotoxicity between the two cohorts ($P = 0.89$) or the time to recover from grade 2/3 neurotoxicity ($P = 0.97$). There were also no significant differences in non-neurological toxicity or anti-tumor efficacy between the two cohorts. This study does not support a role for gabapentin in reducing the incidence or severity of oxaliplatin-induced sensory neurotoxicity.

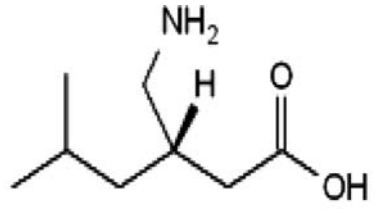
Pregabalin, like gabapentin, is an amino acid derivative of gamma-amino butyric acid, it is pharmacologically active *S*-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid, and has a similar pharmacological profile to gabapentin (Fig. 1) [20, 21]. Pregabalin has been shown in studies to provide equivalent efficacy to gabapentin, however, at much lower doses [22]. Because lower dosages can be used to treat neuropathic pain, it is likely that pregabalin will be associated with fewer dose-related adverse events. Part of the reason why pregabalin requires a lower dosage is that it has a much higher bioavailability (90 vs. 33–66%) and a rapid absorption (peak 1 h). Also, plasma concentrations increase linearly with increasing dose [23]. This is not true with gabapentin. Gabapentin is slowly absorbed (peak 3–4 h post-dose) and more importantly, plasma concentrations have been found to have a non-linear relationship to increasing doses. Since pregabalin has been found to have distinct pharmacokinetic advantages over gabapentin, and the efficacy of treating the neuropathic symptoms with gabapentin has not been completely successful [19], we opted to treat our patient with pregabalin for hyperexcitability secondary to oxaliplatin that was being administered to her for the treatment of her pancreatic cancer.

Case report

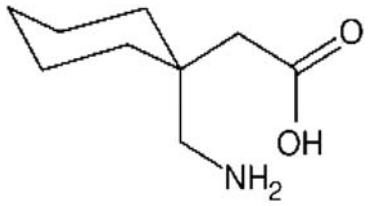
A 54-year-old white female, with history of diabetes mellitus, anxiety disorder and hypothyroidism, presented to her

Table 1 Sequence of events following GEMOX on day 3 and development and resolution of hyperexcitability syndrome

Week #1 of chemotherapy						Started pregabalin				
Symptoms	Mon 5th	Tue 6th	Wed 7th	Thu 8th	Fri 9th AM	Fri 9th PM	Sat 10th AM	Sat 10th PM	Sun 11th AM	Sun 11th PM
Eyelid myokemia	No	Yes	Yes	No	No	No	No	No	No	No
Teeth clattering	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Arms shaking	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Arms burning sensation	No	No	No	No	No	No	Yes	Yes	No	No
Hand tremor	No		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hands spasm	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Leg shaking	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Calves Spasm	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Slurry speech	No	Yes	No	No	No	No	No	No	No	No
Whole body shaking	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No



Pregabalin
(*S*)-3-(aminomethyl)-5-methylhexanoic acid



Gabapentin
2-[1-(aminomethyl)cyclohexyl]acetic acid

Fig. 1 Pregabalin is a 3-substituted analogue of gamma-amino butyric acid (GABA)

primary care physician with itching in early 2005. Since she also had jaundice and diarrhea, the primary care physician referred her to a gastroenterologist who obtained a CT scan of the abdomen and pelvis which revealed a pancreatic mass that involved the gastro duodenal artery without any evidence of distant metastasis. Subsequently, endoscopic ultrasound (EUS), showed a hyperechoic mass of 2.3×2.3 cm in size inside the head of the pancreas that involved the common bile duct which was dilated. The biopsy via EUS was positive for malignancy. She finally underwent a Whipple's procedure, and the biopsy revealed an infiltrative ductal adenocarcinoma $1.5 \times 1.0 \times 1.0$ which was staged at T1N1Mx stage II-B. She was started on gemcitabine and oxaliplatin (GEMOX) at doses of 1,000 mg/m^2 over 100 min on day 1 and 100 mg/m^2 over 2 h on day 2 respectively. On the 28th day, the patient complained about "shaking hands" after her chemotherapy. At that time her neurological examination was normal. Since she also had an anxiety disorder, it was decided to closely observe her and continue the anti-anxiety medications and chemotherapy.

On the third day of her fourth cycle (2 months after the initiation of chemotherapy), she presented with twitching of eyelids and hands that accompanied the chemotherapy, in addition to shaking of hands that she had experienced earlier with the previous oxaliplatin infusions. This twitching started on the eyelids bilaterally, and was followed by teeth jittering, hand shaking, and slurring of speech. She had never experienced such a symptom before and had no known inheritable neuromuscular disease in the family. These symptoms caused severe emotional distress to the patient (Table 1 indicates the symptom sequence following the gemcitabine/oxaliplatin regimen). A thorough neurological exam revealed no abnormalities except increased tone of both hands—she had difficulty opening her hand after closing them for a hand grip to shake hands (Fig. 2 depicts the patient's hand at the time of presentation). Her cardiovascular examination was unremarkable and so was the electrocardiogram done earlier. At that time, patient's medications included citalopram, lorazepam, glipizide, levothyroxine, lansoprazole, propoxyphene and a pancreatic enzyme preparation.

Intravenous infusions of 1 g of magnesium sulfate and 1 g of calcium gluconate along with diphenhydramine 50 mg were administered (these salts were also given on the day of administration of chemotherapy). In addition, pregabalin was prescribed for these myotonic symptoms at a dosage of 50 mg three times daily. Dramatic improvement occurred in these symptoms within 12 h of taking pregabalin (patient's husband updated us via multiple emails)

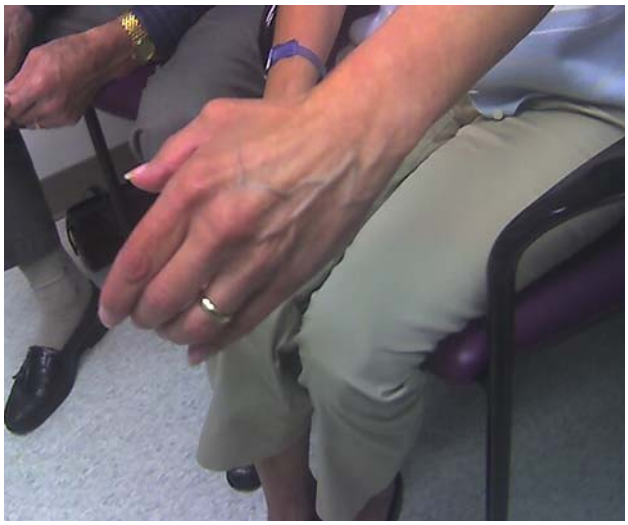


Fig. 2 Inability to release grip in the left hand of the patient after infusion of oxaliplatin

Fig. 3 Relaxed tone of left hand after treatment with pregabalin

and she was almost asymptomatic within 72 h (Fig. 3). The patient deferred to get nerve conduction velocity studies and electromyogram since she clinically improved. Oxaliplatin was removed from her chemotherapy regimen and replaced with gemcitabine–capecitabine. She did not have any relapse of those symptoms and pregabalin was stopped after a total of 4 months. Currently, she off pregabalin and remains asymptomatic neurologically.

Discussion

Acquired neuromyotonia is a rare disorder where hyperexcitability of peripheral motor nerves leads to incapacitating muscle twitching, cramps, myotonia, pseudomyotonia (slow muscle relaxation after forceful contraction) and mild weakness [24]. The muscle cramping may be prominent and can be accompanied by excessive sweating and weight loss [25]. Most cases are sporadic, but drug induced cases have been reported. This may be related to the autoimmune mechanism where the auto antibodies are usually detected against the voltage-gated potassium channel [26].

Our patient, unfortunately, developed this syndrome during her treatment with GEMOX (gemcitabine and oxaliplatin) for pancreatic cancer, and she distinctly felt exacerbations of her symptoms during oxaliplatin infusions. She was not suffering from any autoimmune or genetic disease, nor was she taking any other medication that would predispose her for this condition. Up to date, no effective therapy is available that would completely cure these neuromyotonic symptoms. Gabapentin has been used to alleviate the symptoms with partial success [19]. Due to nearly same mechanism of action but superior pharmacokinetics, pregabalin was used on this patient for the treatment of her neuromyotonic symptoms, especially for the abnormal tonicity in her hands. Surprisingly, the symptoms started to improve within few hours of starting pregabalin, with complete resolution in 72 h of starting this medication (and stopping oxaliplatin). This case report shows the use of pregabalin to treat the neurotoxicity of oxaliplatin rapidly and successfully.

In addition to sensory neuropathy associated with oxaliplatin, motor symptoms, including cramps, jaw stiffness, voice changes, ptosis, and visual field changes have also been reported [27]. The electrophysiologic studies reported by our group provide evidence that oxaliplatin produces hyperexcitability of the motor nerves [28]. These acute electrophysiologic findings after oxaliplatin are the same as are seen in neuromyotonia. Clinically, neuromyotonia is a rare condition characterized by muscle stiffness, slowed muscle relaxation, and increased sweating, and less commonly paresthesias. Slowed muscle relaxation is accentuated by activation and cold.

Neuromyotonia has several causes. It may be idiopathic, autoimmune mediated, associated with neuropathy, or a rare side effect of drugs, radiotherapy, or toxins. The underlying abnormality in neuromyotonia is hyperexcitability of the peripheral axon. Either persistent sodium channel activity or decreased potassium conductance can be a mechanism for producing axonal hyperexcitability and repetitive discharges. Non inactivating sodium channels in sensory axons are thought to produce the repetitive discharges that underlie paresthesias. Autoimmune blockade of voltage-gated potassium channels and exposure of sodium channels in para-nodal regions have been implicated in neuromyotonia. Neuromyotonia has been successfully treated with anticonvulsant drugs such as phenytoin and carbamazepine in

some patients [29]. Carbamazepine blocks repetitive firing of neurons in vitro.

Pregabalin is a novel compound that has analgesic, anticonvulsant, and anxiolytic effects. Pregabalin, akin to gabapentin shares a similar mechanism of action: binding to calcium channels and modulating calcium influx as well as influencing GABAergic neurotransmission. This mode of action translates into anti-epileptic, analgesic and anxiolytic effects. Because it is more potent than gabapentin, pregabalin achieves efficacy at lower doses. This increases its therapeutic index with respect to gabapentin and should lead to fewer dose-related side effects. Clinical studies with pregabalin have been carried out on over 10,000 patients worldwide. The FDA approved this medication for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia and as an adjunctive therapy for adults with partial onset seizures [30]. Pregabalin has very few adverse effects; most of the adverse effects are dose dependent and occur within the first two weeks of treatment. The most common adverse events are related to the central nervous system, and these are responsible for discontinuation of the drug. Somnolence and dizziness occur most frequently (up to 50 and 42% of patients, respectively). The third commonest adverse effects have included peripheral edema in neuropathic pain trials (19%), ataxia in epilepsy trials (27%), and headache in the anxiety trials (29%).

Our patient did not have any known adverse effects secondary to pregabalin. This is the first case report of successful treatment of hyperexcitability syndrome as a result of oxaliplatin, by giving usual doses of pregabalin. Future studies are needed to confirm this, as well as to study long-term adverse reactions of this drug. The role of calcium and magnesium salts may need to be explored for the management of this form of acute neurotoxicity associated with oxaliplatin [31], although we need to wait till the results of the CONCEPT study are fully mature [32].

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