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CASE REPORT

A Phantom of the Past: Withdrawal from Meprobamate Presenting with Focal Seizures

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Introduction: Meprobamate (Miltown, Equinil) is a sedative-hypnotic medication that first gained popularity as an anxiolytic and later as a muscle relaxant. It is a major metabolite of the more commonly used muscle relaxant carisoprodol (Soma). *In vitro* and electroencephalogram studies demonstrated that meprobamate modulates gama-aminobutyric acid (GABA) receptors, similar to barbiturates. Withdrawal from meprobamate manifests in symptoms ranging from mild anxiety to severe autonomic instability and death. Meprobamate is rarely prescribed, but is still given to a small subset of elderly patients.

Clinical findings: In this case of meprobamate withdrawal, the patient initially displayed altered mental status and recurrent seizures resistant to benzodiazepine therapy. Before presentation, the patient complained of several days of malaise, nausea, and tremulousness.

Diagnoses, Interventions, and Outcomes: The patient underwent a full work-up, including imaging, a lumbar puncture, a metabolic panel, and collection of additional medication history. These data revealed that the patient's symptoms were secondary to meprobamate withdrawal. The patient's seizures failed to resolve with benzodiazepines, but they responded when the patient resumed their usual dose of meprobamate.

Conclusions: Given the potential severity of withdrawal symptoms, diagnosis and proper pharmacologic management is critical for patients suffering from meprobamate withdrawal. A thorough medication history and recognizing withdrawal symptoms are key to diagnosing withdrawal syndromes. Benzodiazepine therapy alone may not sufficiently treat withdrawal seizures, so resumption of meprobamate or treatment with phenobarbital may be required. The same considerations should be made for diagnosis and treatment with carisoprodol, which is metabolized to meprobamate.

Keywords: meprobamate, withdrawal, focal seizures

CASE PRESENTATION

This case describes an elderly patient suffering from meprobamate withdrawal and is based on author experience with the case and chart review. The institutional review board at Maine Medical Center deemed this case exempt.

The patient was an 81-year-old female with a history of anxiety and back pain, and a recent knee replacement. She presented to the emergency department with witnessed tonic-clonic seizures and altered mental status. Her medications included temazepam (30 mg nightly) for sleep, gabapentin (300 mg three times daily), meprobamate (200 mg six times daily), and vaginal estrogen. Her seizures were preceded by several days of nausea, chills, tremors, and malaise. Her physical examination revealed low-grade fever, disorientation, pain with passive neck flexion, well-healing surgical scar, clear lungs, and a non-focal neurologic exam. Pertinent data from the emergency department included a mild lactic acidosis, peripheral leukocytosis, unremarkable brain imaging, cerebrospinal fluid with normal glucose and protein with 1 leukocyte/hpf, and a gram stain negative for a bacterial infection. Because of fever, leukocytosis, and confusion, meningoencephalitis was a concern. Thus, the patient was given vancomycin, ceftriaxone, and acyclovir, and she received her usual temazepam dose at bedtime.

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The next morning, the patient was afebrile, oriented, and her leukocytosis had resolved, so antibiotics were discontinued. She gave a more complete history and noted that she had been taking meprobamate for over 20 years after it was prescribed by a neurosurgeon for back pain secondary to muscle spasms. She had been taking meprobamate regularly along with tenazepam for sleep. She ran out of meprobamate several days before presentation and believed that she may have taken more than normal while recovering from her knee surgery. She also reported a history of severe anxiety and depression, requiring hospitalization as a young adult, but had been stable recently.

During an exam, she abruptly developed coarse, bilateral, upper extremity tremors, apraxia, and non-fluent speech with echolalia/palilalia with an otherwise non-focal exam. The neurology team confirmed the patient's confusion without focal neurologic deficits and determined that the findings were most consistent with a post-ictal state following a focal seizure. Clonazepam therapy was initiated with a starting dose of 0.1 mg. The patient returned to her neurologic baseline, but her neurologic abnormalities recurred approximately 2 hours later. There was a high suspicion of seizures, but no history of seizure disorder, electrolyte abnormalities, intracranial abnormalities on imaging, or evidence of infectious meningoencephalitis. Thus, the possibility of meprobamate withdrawal and the treatment strategy were reevaluated. Consultation with psychiatry and pharmacy revealed that clonazepam may not provide adequate receptor coverage for meprobamate withdrawal, so the patient was restarted on her home dose of meprobamate. An electroencephalogram (EEG) was obtained later in the day, while the patient was near baseline, which was normal. The patient was discharged after 2 days of observation without recurrence of symptoms.

Two days after discharge, she was doing well on a total dose of 1000 mg meprobamate daily (400 mg in the morning and at night, and 200 mg in the afternoon). Plans for taper and discontinuation were deferred to her primary care physician.

DISCUSSION

Here we describe an unusual case of meprobamate withdrawal presenting with altered mental status and seizure-like activity. The patient's symptoms and neurologic findings agreed with previous reports of meprobamate withdrawal. The symptoms of tremulousness, anxiety, and anorexia have been described in other case reports[1-6] and clinical studies.[7,8] In a placebo-controlled trial, 44 of 47 patients who received meprobamate showed withdrawal symptoms, with 3 patients displaying grand-mal seizures 36-48 hours after drug cessation.[7] Withdrawal seizures were also reported in a small EEG study one year later.[8] While not confirmed with EEG, our patient's intermittent spells of confusion, echolalia, palilalia, tremor, and agitation were consistent with focal seizure activity. This presentation is similar to a case in which an 80-year-old female presented with episodic generalized seizures that resolved with high doses of diazepam. Later, this patient showed transient bouts of "agitation, startle myoclonus, and generalized hypertonia" with EEG, showing evidence of both generalized and focal seizure activity.[6] Our patient's daughter confirmed that the patient had been taking 2400 mg of meprobamate daily and had run out of medication 24 hours before presentation. The patient ultimately required treatment with phenytoin, carbamazepine, and clonazepam. As seen in this and other cases, there is a clear temporal pattern of symptoms in meprobamate withdrawal that start with symptoms of malaise, gastrointestinal upset, and tremulousness that are followed by seizures 1-2 days later. This agrees with meprobamate's half-life of approximately 10 hours, as the onset of seizures correlates with significant clearance of the drug (at 3-5 half-lives).

There is no established dose of meprobamate at which withdrawal symptoms are more likely. However, our patient showed symptoms after withdrawal from a low dose of 1200 mg per day (the drug is typically prescribed at 1200-1600 mg per day). We do not know why only some patients develop seizures, but risk factors may include underlying seizure disorders, a history of brain injury, or medications. While case reports generally feature patients who have been taking meprobamate for many years, one study described patients exhibiting withdrawal symptoms after taking meprobamate for only 40 days.[7] Thus, withdrawal should be considered in patients with any recent history of meprobamate use.

There is no current recommendation or protocol for treating meprobamate withdrawal. In our case, the patient continued to experience seizure-like activity despite treatment with clonazepam.

Her symptoms resolved only after restarting meprobamate. This approach was suggested in previous reports.[2,4] In contrast, one study described a patient who was successfully withdrawn from a home dose of 6 g meprobamate using a diazepam taper starting with a dose of 10 mg given 4 times daily.[5] However, the treatment was elective. Also, the patient did not present in withdrawal, but was started on benzodiazepines immediately after stopping meprobamate. Of note, the patient already attempted cross-taper as an outpatient using a relative's diazepam, but they stopped due to symptoms of fatigue and lethargy. The differences in response to clonazepam during withdrawal may be due to differences in patient tolerance, metabolism, and meprobamate clearance. Another factor may be the timing of benzodiazepine administration in relation to meprobamate cessation.

While there is some debate on the exact mechanism of action of meprobamate, an *in vitro* study demonstrated that meprobamate acts as a direct gama-aminobutyric acid (GABA) receptor agonist.[8] Other studies showed that, similar to barbiturates, meprobamate has activity at GABA receptors, and its effects may be reversed with the barbiturate-reversal agent bemegride.[9] Notably, meprobamate's action *in vivo* appears much more similar to phenobarbital than benzodiazepines, with EEG studies showing similar effects.[10,11] Further, meprobamate may potentiate the action of adenosine in the central nervous system, adding to its sedative effects with GABA agonism.[12,13] Because meprobamate's interaction with GABA receptors and adenosine differ from benzodiazepines, benzodiazepines alone may not sufficiently treat cases of severe withdrawal.

Meprobamate is rarely used and only available as a generic medication at limited pharmacies in the United States. However, the muscle relaxant carisoprodol (Soma), which is metabolized to meprobamate, is more widely prescribed. Carisoprodol has caused a similar abstinence syndrome that includes vomiting, tremor, myoclonic twitches, anxiety, and occasionally seizures. The proposed mechanism of these symptoms is withdrawal from the major metabolite, meprobamate.[14] As both drugs are prescribed less frequently, the risk of withdrawal in patients triggered by lack of availability to these medications becomes a concern. In our case, meprobamate was non-formulary at our hospital and had to be sourced from an outside pharmacy.

In summary, we have described a case of meprobamate withdrawal presenting with seizure-like activity resistant to initial treatment with benzodiazepines, and we discussed the pharmacology and abstinence syndromes related to meprobamate and carisoprodol. Clinicians should be aware of the possibility of withdrawal from these medications. They should also gather a detailed medication history, which is critical in quickly identifying and treating abstinence syndromes caused by these drugs. They should also be aware that benzodiazepines may not sufficiently manage withdrawal seizures, and thus should consider restarting the medications or using more closely related alternatives, such as phenobarbital.

Conflicts of Interest: None

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