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A Case of Combined Baclofen and Carisoprodol Withdrawal: The Hidden Dangers of Muscle Relaxants

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Abstract:

Muscle relaxant prescriptions are on the rise as treatment for chronic pain, although physician education about the effects of overdose, medication interactions, and withdrawal is limited. Possibly because of their synergistic effect, simultaneous use of the muscle relaxants baclofen and carisoprodol can result in withdrawal at relatively low doses. Prior case reports have described withdrawal from either muscle relaxant; however, this case report describes the course of a patient who was found to have combined baclofen and carisoprodol withdrawal. It is important for prescribers to be aware of these medications' withdrawal syndromes to address them appropriately.

Background:

Prescriptions for muscle relaxants (MRs) have risen sharply, doubling in the last 12 years (1). In light of the recent opioid crisis, MRs have been viewed by some providers as a safer alternative or adjunct for the management of chronic musculoskeletal pain; however, several MRs have been recognized for their abuse potential (2, 3). Due to these medications' sedative and deliriogenic properties, the 2019 Beers Criteria state a "strong" recommendation to avoid these prescriptions to the elderly altogether (4). Carisoprodol (Soma) and baclofen are two commonly prescribed MRs that act on gamma-aminobutyric acid (GABA) receptors (5, 6). In 2017, both were among the top-300 medications dispensed to patients (7). In recent years, cases of carisoprodol and baclofen withdrawal syndromes have been described individually, often with initial misdiagnoses such as postoperative delirium, neuroleptic malignant syndrome (NMS), or serotonin syndrome (8-13). However, none has described a withdrawal from concomitant carisoprodol and baclofen use.

Objective:

We present a case of combined carisoprodol-baclofen overdose and withdrawal in an elderly patient who chronically used baclofen and carisoprodol. Our objective is to increase awareness of the dangers of concomitant muscle relaxant usage, especially given the recent rise in MR prescriptions.

Case Report:

An elderly woman was brought into the hospital after being found down and unresponsive at home. The emergency response team relayed that the patient took “baclofen, Soma, and naproxen”, and had a remote history of alcohol use disorder, but the patient arrived without identifying information or contacts. On arrival, her Glasgow Coma Scale was 2-2-5; she was afebrile, with a pulse of 106, blood pressure of 136/101, and oxygen saturation of 99% on 10 liters of oxygen. Urine toxicology (including phencyclidine, ethyl glucuronide, ethyl sulfate, amphetamines, benzodiazepines, cannabinoids, cocaine, methadone, opiates, oxycodone, barbiturates) and blood ethanol levels were negative; naloxone was given without response. Other laboratory tests showed a nonspecific leukocytosis, bland metabolic panel, and negative blood and urine cultures, after which empiric antibiotics were discontinued. Pan-CT scan noted right foot and nasal fractures. Electroencephalogram showed moderate diffuse slowing consistent with nonspecific global encephalopathy and lumbar puncture was unremarkable. After a few hours, the patient became alert in the ED and was able to come off oxygen, but expressed incomprehensible sounds and was not following commands. By the morning, she became tremulous, tearful, and increasingly tachycardic. After her fractures were managed, she was admitted to Medicine on Clinical Institute Withdrawal Assessment for Alcohol (CIWA) protocol due to concern for alcohol withdrawal.

Despite frequent doses of intravenous lorazepam for several days, her delirium, tachycardia and tremulousness only worsened. The patient's family connected with the team and shared that she was 65-years-old with a history of bipolar disorder that was well-controlled on lithium, risperidone, and duloxetine, with no recent manic or depressive episodes or regimen changes. She had a 2 year history of daily carisoprodol and baclofen use, prescribed for back pain by her primary care provider (PCP) to avoid opioids. Per her family, she had frequently taken more than the prescribed dosage, leading to several recent falls.

Her delirium was felt not to be consistent with acute mania or depression, and her lithium level was normal, with broad toxicologic and infectious evaluation, unrevealing. The team concluded that her fall and unresponsiveness were caused by MR overdose, and her subsequent delirium and autonomic instability, by MR withdrawal. CIWA was discontinued and, off lorazepam, she was able to intermittently answer questions with 'yes' or 'no' but was still confused, tremulous, and tachycardic. The team could find no guidelines on how to manage her withdrawal. On hospital day 3, she passed a swallow evaluation, and with the guidance of Addiction Medicine consultation, the team restarted her home baclofen and carisoprodol doses with a plan to slowly taper. This resulted in mental status improvement back to baseline within one day. Her rapid improvement with reinstatement of baclofen and carisoprodol confirmed a diagnosis of a withdrawal syndrome.

Thereafter, with restored lucidity and stabilized vitals, the patient stated she had been taking baclofen 20mg TID, and carisoprodol 350mg daily (confirmed by Controlled Substance Utilization Review and Evaluation System review). Shortly before her fall, she had taken 700mg of carisoprodol (double her usual dose), in addition to the 20mg of baclofen, leading to instability, sedation, and the fall causing injuries, and ultimately, withdrawal. As her mental

status improved, the patient recognized the danger of her muscle relaxant usage and expressed a desire to reduce them. She was thus weaned off her carisoprodol, began tapering her baclofen, and was discharged on hospital day 7.

Discussion:

Carisoprodol is commonly prescribed for painful musculoskeletal conditions and is often considered safe in the short term, although chronic use has been associated with abuse potential and risk for overdose and withdrawal. Only a moderate decrease in carisoprodol prescription rates was observed after it was deemed schedule IV in 2012 (14). Baclofen is prescribed for similar reasons to carisoprodol: spasticity, chronic musculoskeletal pain, and alcohol withdrawal, though it is not a controlled substance.

Several cases of baclofen withdrawal and carisoprodol withdrawal have been described. One case in 2016 reported a patient who overdosed on carisoprodol, with subsequent withdrawal (8), characterized by episodic severe agitation unresponsive to benzodiazepines. She required high doses of sedating agents, but ultimately, her symptoms resolved with carisoprodol reinstatement. Another involved carisoprodol withdrawal-induced delirium; however, in this case the patient was responsive to lorazepam (though they had a shorter duration of carisoprodol use prior to hospitalization than the aforementioned case and our patient) (9). Carisoprodol's mechanism is unclear but is thought to have a barbiturate-like molecular effect on the GABA-A binding site, which over time may cause withdrawal unresponsive to benzodiazepines (5). This is supported by in vitro studies that show carisoprodol's effects are blocked by barbiturate antagonists, but not flumazenil (a benzodiazepine antagonist) (5). A baclofen withdrawal syndrome has been identified since the 1980s. Although frequently associated with intrathecal baclofen, withdrawal from oral administration has been described, most often characterized by

delirium (11-13). Baclofen acts on a different GABA receptor, GABA-B, which mediates slow and prolonged inhibitory action on the nervous system as compared to the fast inhibitory signals of GABA-A, on which benzodiazepines act (15). It is possible that the barbiturate-like effect of carisoprodol, combined with the GABA-B agonism of baclofen, rendered our patient refractory to benzodiazepine therapy for her withdrawal.

Although both baclofen and carisoprodol withdrawals have been described, our case is unique in demonstrating a combined withdrawal from both baclofen and carisoprodol, leading to a severe syndrome at relatively low doses. Although the prevalence of concomitant prescriptions for multiple MRs is not known, in practice, these agents are not typically co-prescribed; interaction checkers advise caution given that their additive effect on GABA.

Our case shows that management of baclofen and carisoprodol withdrawals presents several challenges. Both withdrawal syndromes may mimic alcohol withdrawal or other illnesses that result in tremulousness and delirium. MR withdrawal syndromes are rarely emphasized in medical education and may not be part of physicians' differential diagnosis. The inherent difficulty of this diagnosis may lead to premature closure with misdiagnosis and prolonged hospital stays, as was the case for our patient. The delirium experienced by patients may render them unable to tolerate oral medications, but intraveous versions of MRs are either expensive or nonexistent. Carisoprodol and baclofen are rarely on hospital formularies, resulting in additional delay in management of the withdrawal even if it is identified. Finally, questions remain in MR withdrawal management, including the role of benzodiazepines and barbiturates (8). The medical field would benefit from more education surrounding muscle relaxants, including safe practices, medication interactions, overdose, and withdrawal.

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