

Carisoprodol withdrawal induced delirium: A case study

Karen Ni¹
Margaret Cary²
Paul Zarkowski²

¹School of Medicine, University of California, San Diego, La Jolla, CA, USA; ²Department of Psychiatry and Behavioral Science, University of Washington, Seattle, WA, USA

Abstract: A 43-year-old woman with chronic back pain found relief by taking carisoprodol, a centrally acting skeletal muscle relaxant. She had acquired large amounts of the prescription medication through the Internet and was taking approximately three hundred 350 mg tablets each week, at times up to fifty tablets per day. She then abruptly stopped the medication and presented to the emergency room one week later with waxing and waning attention, confusion, disorientation and visual hallucinations. Oral lorazepam was dosed according to a protocol employing the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA). Her symptoms of delirium resolved rapidly and she was discharged home on day three. A review of the literature did not show any other reports of carisoprodol withdrawal induced delirium. Such withdrawal symptoms could be expected as the mechanism of action of carisoprodol is similar to that of hypnotic sedatives. Its availability and ease with which it can be acquired through the Internet puts it at great risk for a drug of abuse.

Keywords: Carisoprodol, withdrawal, Soma, internet, benzodiazepines, barbiturates

Introduction

Carisoprodol is a skeletal muscle relaxant that exerts its effect via sedation of the central nervous system rather than through direct muscle relaxation (Littrell et al 1993). Animal studies have demonstrated that carisoprodol blocks interneurons and depresses transmission of polysynaptic neurons in the spinal cord and descending reticular system of the brain. While its exact mechanism of action is unknown, it is pharmacologically similar to barbiturates and thought to have an indirect agonist effect on the same GABA-A receptor site to which barbiturates bind (Littrell et al 1993; Rohatgi et al 2005). A case study (Heacock and Bauer 2004) found that an individual taking high doses of carisoprodol had the highest stage of barbiturate tolerance during a pentobarbital challenge test. Furthermore, Flumazenil, a competitive antagonist of the GABA-A receptor site for benzodiazepines and other drugs including pentobarbital, has been shown to be an effective antidote for carisoprodol intoxication (Del Castillo and Nelson 1960; Hu and Ticku 1994; Roberge et al 2000).

With carisoprodol's cross tolerance to barbiturates, one would expect to see similar withdrawal symptoms. Indeed, there have been many reports of anxiety, insomnia, tremors and hallucinations upon abrupt discontinuation of carisoprodol (Littrell et al 1993; Reeves et al 2004). In other cases, patients withdrawing from carisoprodol reported palpitations, diaphoresis, chills, stomach cramps, headache, backpain, myalgias, arthralgias, diarrhea, severe psychomotor agitation, feelings of depersonalization, anxiety with suicidal ideation, and disorientation (Luehr et al 1990; Reeves and Parker 2003; Rohatgi et al 2005). Many of the above symptoms are considered to be characteristic of withdrawal from sedative-, hypnotic-, or anxiolytic- substances according to the DSM IV-TR. This class of substances include benzodiazepines, benzodiazepine-like drugs (eg, zolpidem), carbamates, barbiturates, barbiturate-like

Correspondence: Karen Ni
University of Washington, Box 356560,
Seattle, WA, 98195, USA
Tel +1 858 692 2668
Email kni@u.washington.edu

hypnotics (eg, methaqualone), and some prescription sleeping medications (eg, chloral hydrate and paraldehyde).

The DSM IV-TR identifies delirium as a possible symptom of withdrawal from sedative-, hypnotic- or anxiolytic- substances. Despite the similarities between this class of drugs and carisoprodol, there has yet to be a case report of delirium during carisoprodol withdrawal. Our case study is the first to describe such a case.

Case report

A 43-year-old woman with no previous psychiatric history or history of substance abuse was brought to the emergency room by her family after seven days of worsening insomnia, confusion, and hallucinations.

One and a half years prior to presentation, the patient fell into a ditch. She experienced acute low back pain which developed into chronic back pain. During the six months following her accident, the patient tried several medications and therapies to alleviate her persistent back pain but found that only carisoprodol gave her relief. When her medical insurance was terminated six months after her accident, she began ordering carisoprodol from Internet sites. Over the following year, she ordered increasing quantities from the Internet due to her tolerance. By the time the patient self-discontinued the medication at seven days prior to presentation, she had been taking approximately three hundred 350 mg tablets each week, at times up to fifty tablets per day. Thus, she was consuming over ten times the indicated dosage of carisoprodol for acute musculoskeletal pain, which is one 350 mg tablet three to four times a day (DiGregorio and Barbieri 1996).

Seven days prior to presentation, the patient stopped taking all carisoprodol because she was “sick of taking medication that [she] knew was bad for [her.]” Shortly thereafter, her family reports that she began to behave bizarrely and appeared increasingly confused. She slept two to three hours each night and her appetite decreased markedly. The patient was anxious and had pressured speech, psychomotor agitation and a fine bilateral hand tremor. She also experienced auditory and visual hallucinations such as seeing shadows and her fiancé talking to her through the television. One night, the patient wandered over three miles from home and was returned by the police. During the middle of the night just prior to presentation, her fiancé found her standing on the front porch, wet from rain, staring up into sky with outstretched arms.

In the emergency room, she was disoriented to date, place and purpose with waxing and waning attention. She talked nonsensically of people walking by her room and surrounding

her. She appeared to have no insight into these reported visual hallucinations. She was tachycardic at 109 beats per minute. Otherwise her vital signs were all within normal range. A neurological exam revealed postural and action tremors, but was otherwise normal. The only abnormal laboratory data were a leukocytosis of $13.1 \times 10^3/\text{ul}$ white blood cells with $9.89 \times 10^3/\text{mm}^3$ neutrophils, mildly low carbon dioxide of 19 mEq/L and slightly elevated alanine aminotransferase of 68 U/L. Her urine toxicology screen and blood alcohol level were negative.

The patient was given oral lorazepam 2 mg and admitted to the psychiatric unit. She was placed on a Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA) protocol. Oral lorazepam 2 mg was given for scores over ten. The first CIWA score was fourteen triggering a second dose of oral lorazepam 2 mg. Subsequent CIWA scores were all below ten. A computed tomography head scan did not show evidence of acute hemorrhage, swelling, white matter changes, or mass lesion. The CIWA assessments were discontinued after the patient fell asleep.

By the morning after admission, the patient's sensorium largely cleared and she remembered some of her thoughts while she had been delirious. She was oriented, attentive, with logical, reality-based thoughts. She denied hallucinations, and only endorsed some anxiety. Her vital signs were within normal limits and repeated CIWA scores were consistently less than three. She reported her back pain as better than it had been in a long while. She took two doses of 1 mg lorazepam in the afternoon and at bedtime for anxiety. On day three, the patient was discharged home, appearing to have fully recovered from her symptoms.

Discussion

The onset of delirium seen after abruptly stopping large daily doses of carisoprodol suggests that her symptoms were due to withdrawal from carisoprodol. Previous case studies have highlighted the role of meprobamate, a metabolite of carisoprodol, in the production of withdrawal symptoms (Reeves and Parker 2003). Meprobamate is a carbamate derivative and belongs to the class of sedative-, hypnotic-, or anxiolytic- medication. The use of meprobamate has declined with increasing use of benzodiazepines. While carisoprodol has a half life of only 2.5 hours, meprobamate has a half life of 11.3 hours or up to 48 hours with chronic use (Meyer and Straughn 1977). According to meprobamate's product circular, the onset of withdrawal occurs usually within 12–48 hours after discontinuation of meprobamate; symptoms usually cease within the next 12–48 hours. The patient of this case

experienced the onset of symptoms within the time frame suggested by the product circular, but symptoms persisted much longer than the indicated 48 hours, lasting 7 days and into the second day of admission. Although withdrawal delirium is a known consequence of the abrupt discontinuation of sedative-, hypnotic-, or anxiolytic- substances, this case is the first to report symptoms of delirium as component of withdrawal from carisoprodol.

The case highlights carisoprodol's potential for dependence. While the DEA is still debating whether to classify carisoprodol as a schedule IV drug, at least fourteen states have made it a schedule IV drug, including Alabama (1998), Nevada (2005), Arizona (2003), Georgia, Hawaii, Kentucky, Massachusetts, New Mexico and Oklahoma. Carisoprodol's status as a non-scheduled drug belies its potential for abuse. Carisoprodol's metabolite, meprobamate is considered to have greater abuse potential than the benzodiazepines. In addition, meprobamate is classified as a schedule IV drug.

This case also illustrates the ease with which carisoprodol can be obtained on the Internet. Since 1999, Internet companies have provided a stable supply of prescription medications to US customers – many of which do not require a visit to a physician in order to obtain a prescription but rather an online consultation which consists of an anonymous questionnaire (Forman, Woody, et al 2006). Most foreign web sites do not require prescriptions or an online consultation (Bloom and Iannacone 1999). These no-prescription websites (NPWs) generally focus on selling opioids (Forman, Marlowe et al 2006) although many drugs of abuse are available including sedatives and stimulants. Prior to 1990, a person may have had to travel to a foreign country to obtain medications illegally or “doctor shop” to obtain high quantities of medications. Today, a patient would only need access to the Internet and monetary resources to pay for the medication. With the search engines Google or Yahoo, several web sites that sell carisoprodol without a prescription can easily be found. For example, searching with the keywords “carisoprodol no prescription” in the Yahoo search engine reveals nine links to suppliers claiming they will sell carisoprodol without a prescription.

One on-line seller site explains that their online questionnaire provides them with the information needed to grant a prescription – the questionnaire being a tool used by a licensed US doctor who writes the prescription. One study looked at 46 sites all of which failed to reveal the associated physician's name or location (Bloom and Iannacone 1999). The conflict of interest is apparent with a doctor providing

both the prescription and reaping profits from the sale of the medication he or she prescribed.

A danger to receiving drugs via the Internet is the possibility of obtaining counterfeit or substandard medications. A customs lab analysis by the General Accountability Office and FDA showed that out of 180 drug samples seized, 67% were either never approved by the FDA or had been withdrawn from the U.S. market for safety reasons, 5% contained no active ingredients and 28% contained controlled substances prohibited from importation (Spake 2004). Counterfeit and substandard drugs are a huge industry with over \$32 billion annual sales globally. With the Internet, it is unknown where medications are obtained. The FDA estimates that up to 25% of the medicines in developing countries are poor or substandard. In an FDA “blitz” where they examined 1,153 imported drugs, 99% contained unapproved drugs – many of which could pose safety problems (FDA 2003). The WHO database showed in 1999 that 77% of substandard medicines coming into the United States were from developing countries and that 60% of these medicines were missing the active ingredient (WHO 2003).

In general, the availability of NPWs increases the risks of drug abuse and diversion. Were it not for NPWs, the patient in our case study may not have had access to such a large quantity of carisoprodol and thus could have avoided her subsequent hospitalization. These authors believe that carisoprodol, a drug with abuse potential that can be acquired relatively easily, should be considered a scheduled drug to restrict its potential for harm.

References

- Bloom BS, Iannacone RC. 1999. Internet availability of prescription pharmaceuticals to the public. *Ann Intern Med*, 131:830–3.
- Del Castillo J, Nelson T. 1960. The mode of action of carisoprodol. *Ann NY Acad Sci*, 86:108–42.
- DiGregorio G, Barbieri E 1996. Handbook of commonly prescribed drugs. West Chester, PA: Medical Surveillance Inc.
- FDA. 2003. FDA/US customs import blitz exams reveal hundreds of potentially dangerous imported drug shipments [online]. Accessed 16 April 2007. URL: <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00948.html>
- Forman RF, Marlowe DB, McLellan AT. 2006. The internet as a source of drugs of abuse. *Curr Psychiatry Rep*, 8:377–82.
- Forman RF, Woody GE, McLellan T, et al. 2006. The availability of web sites offering to sell opioid medications without prescriptions. *Am J Psychiatry*, 163:1233–8.
- Heacock C, Bauer MS. 2004. Tolerance and dependence risk with the use of carisoprodol. *Am Fam Physician*, 69:1622–3.
- Hu XJ, Ticku MK. 1994. Chronic flurazepam treatment produces decreased efficacy of the benzodiazepine ligands and pentobarbital with gamma-aminobutyric acidA receptors in cortical neurons. *J Pharmacol Exp Ther*, 270:485–90.
- Littrell RA, Hayes LR, Stillner V. 1993. Carisoprodol (Soma): a new and cautious perspective on an old agent. *South Med J*, 86:753–6.

- Luehr JG, Meyerle KA, Larson EW. 1990. Mail-order (veterinary) drug dependence. *JAMA*, 263:657.
- Meyer MC, Straughn AB. 1977. Meprobamate. *J Am Pharm Assoc*, 17:173–6.
- Reeves RR, Beddingfield JJ, Mack JE. 2004. Carisoprodol withdrawal syndrome. *Pharmacotherapy*, 24:1804–6.
- Reeves RR, Parker JD. 2003. Somatic dysfunction during carisoprodol cessation: evidence for a carisoprodol withdrawal syndrome. *J Am Osteopath Assoc*, 103:75–80.
- Roberge RJ, Lin E, Krenzelok EP. 2000. Flumazenil reversal of carisoprodol (Soma) intoxication. *J Emerg Med*, 18:61–4.
- Rohatgi G, Rissmiller DJ, Gorman JM. 2005. Treatment of carisoprodol dependence: a case report. *J Psychiatr Pract*, 11:347–52.
- Spake A. 2004. Fake drugs, real worries: high prices and the Internet are making US patients easy prey. US and News World Report.
- WHO. 2003. Substandard and counterfeit medicines [online]. Accessed 16 April 2007. URL: [http://www.who.int/mediacentre/factsheets/2003/fs275/en/](http://www.who.int/mediacentre/factsheets/fs275/en/)