

Barbiturate Withdrawal Following Internet Purchase of Fioricet

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Background: The Internet enables businesses to advertise their pharmaceutical products and services without medical supervision. The Internet also allows for the unsupervised purchase of medications that may have neurologic consequences.

Objective: To describe acute withdrawal delirium following the abrupt discontinuation of Fioricet.

Patient: The patient was a 37-year-old woman with a history of depression and migraine headaches but not drug abuse. She developed a florid withdrawal delirium following the discontinuation of a drug she purchased online. The medication, which contained butalbital, was self-administered in escalating doses for the treatment of chronic headaches. Daily doses of up to 750 mg to 1000 mg were reported.

Results: The patient was admitted to the hospital for the treatment of unexplained seizures that were followed by

several days of an intense withdrawal syndrome. Little improvement was noted after the administration of benzodiazepines and phenothiazine. After parenteral phenobarbital administration, her symptoms resolved.

Conclusions: The withdrawal state from barbiturates is similar to that from ethanol. Tolerance can develop with prolonged abuse, leading to escalating drug doses to achieve the desired effect. The suggested management of both types of withdrawal syndromes is similar, but the relative resistance of the behavioral and autonomic features in patients was remarkable. Physicians should be aware of the ease with which medications can be purchased without supervision from Internet pharmacies. The magnitude of the number of drugs that are made available through this means creates a proclivity to withdrawal states.

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SEVERAL AUTHORS HAVE COMMENTED on the vast “underground drug information” the Internet can provide.¹⁻³ The World Wide Web can be used to obtain data on drug dosing, adverse effects, overdose, warnings, pharmacology, and current patient information.⁴⁻⁶ It also allows completely unfettered purchases of medications that may have neurologic consequences. We treated a patient who had repeated seizures followed by several days of an intense withdrawal delirium. The patient described a massive and prolonged daily ingestion of Fioricet (a combination drug composed of acetaminophen, butalbital, and caffeine) that she had purchased without a prescription, through the Internet, for the unsupervised treatment of headaches. This observation highlights the need for physicians to understand alternative means by which patients may obtain medications with serious neurologic sequelae.

REPORT OF A CASE

A 37-year-old woman was brought to the emergency department after 3 consecutive grand mal seizures. She had a history of depression and migraine headaches but not of drug abuse. A large tongue laceration was evident, as were bruises and abrasions on her

face, arms, and trunk. The patient was calm but intermittently disoriented and easily distracted, with incoherent and pressured speech containing paraphasic errors. A urine toxicology screen detected the presence of barbiturates. She was able to relate that she had periodic migraine, recurring a few times per year since the age of 21 years. The frequency of headaches had increased during the past year, as did her reliance on Fioricet to control them. During the 3 months before her seizures, she reported consumption of 15 to 20 tablets a day. The medication had been prescribed once by a neurologist years earlier, and she subsequently obtained the medication from multiple Web sites, including http://rx-refills.net/_buy_migraine_relief_prescriptions.html. A computed tomographic scan revealed a small epidural hematoma with an overlying temporal bone fracture. She was treated with phenytoin in the neurologic intensive care unit.

The following day, 48 hours after her last ingestion of Fioricet, she became agitated, tachycardic, and had a low-grade temperature of 37.2°C. Her blood pressure was 133 mm Hg/77 mm Hg. Her electroencephalogram showed no abnormalities. Visual hallucinations, insomnia, diaphoresis, hyperreflexia, and intense psychomotor agitation followed; however, she was not tremulous. Phenobarbital sodium (100 mg by mouth

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[PO] 3 times a day), lorazepam (2 mg intravenously every 4 hours), haloperidol lactate (5 mg intravenously every 6 hours), oxazepam (30 mg PO every hour), and olanzapine (5 mg PO 2 times a day) were administered without effect. Her agitation was so intense that she became tangled in her bedsheets and repeatedly attempted to climb over the bedrails. Intravenous midazolam hydrochloride (0.05 mg/kg per hour) was required to sedate her; reducing the dose exposed a hyperkinetic-delirious state. On the fifth day, she was cognitively normal. Treatment with phenobarbital sodium (100 mg PO 3 times a day) was continued through her hospitalization and was slowly withdrawn.

COMMENT

The withdrawal state from barbiturates is similar to that from ethanol.^{7,8} Tolerance can develop with prolonged abuse and lead to escalating drug doses in order to achieve the desired effect. In the withdrawal syndromes, removal of GABA (γ -aminobutyric acid)-ergic inhibitory tone in the central nervous system has been proposed to cause hypertension, tachycardia, diaphoresis, tremors, hyperthermia, and seizures. Seizures followed by a confusional state that progresses to a hyperkinetic and hypersympathetic delirium with hallucinosis are common to both barbiturate and alcohol withdrawal syndromes, including a rapid resolution. We only comment that our patient notably lacked the tremulousness that is so characteristic of alcohol withdrawal.

The suggested management of both types of withdrawal syndromes is similar, but the relative resistance of the behavioral and autonomic features in patients was remarkable. Symptoms of psychomotor agitation and tachycardia are treated with sedative-hypnotic agents. Benzodiazepines are used for ethanol withdrawal, and phenobarbital has been suggested for barbiturate withdrawal with a dose reduction of 10% per day once the patient's condition is stabilized while the medications are taken.⁸ It is possible that high doses of benzodiazepines address both withdrawal syndromes. Delirium continued in our patient despite the administration of phenobarbital; perhaps higher doses or a loading dose was required.⁹

Butalbital, a component of Fioricet, is an intermediate-acting (3-6 hours) barbiturate. It binds to the GABA receptor complex and prolongs the opening of the chloride channels in response to GABA, thereby inhibiting excitable cells of the nervous system.⁸ Butalbital is a weak acid with a volume of distribution of 0.8 L/kg of body weight and 26% protein binding in the plasma. With therapeutic doses, plasma concentrations generally peak in 40 to 60 minutes. Butalbital is metabolized by the liver and has a half-life elimination of 1.6 to 5.8 days. It is excreted in the urine.¹⁰

Ethanol also binds to the GABA receptor complex. Activation of the postsynaptic GABA_A receptor and prolonged chloride influx lead to cell hyperpolarization and a decrease in the firing rate of neurons. The result is an overall clinical effect of sedation.^{7,8} In the withdrawal state, patients can experience tremors, hallucinations, seizures, and delirium tremens. The hallucinations that result from alcohol abstinence typically have an onset of 7 to 48 hours after the last drink. This is similar to the time of onset of withdrawal seizures, although the peak seizure incidence is between 12 and 24 hours. Lastly, delirium tremens can

occur 48 to 72 hours after cessation of drinking, with a peak incidence on the fourth day of abstinence. The symptoms are characterized by autonomic instability, diaphoresis, fever, tremulousness, and profound confusion.^{7,8}

After a rudimentary investigation, we are able to report that Internet search engines can be easily used to locate numerous merchants who readily provide a steady supply of medication on demand to any customer wishing to buy Fioricet or a host of other medications. These online merchants claim "no prescription required, because the online pharmacy will provide a quick and easy online doctor's consultation, free of charge, when you order Fioricet on-line."¹¹ Our patient reported purchasing 500 pills per order without difficulty.

Physicians may wish to be aware of the ease with which certain medications can be purchased from "online pharmacies." Various Web sites we visited offered zolpidem (Ambien), zaleplon (Sonata), orlistat (Xenical), sibutramine hydrochloride monohydrate (Meridia), tramadol (Ultram), cyclobenzaprine (Flexeril), tizanidine (Zanaflex), carisoprodol (Soma), and many other medications that are subject to abuse and to withdrawal states. Furthermore, patients may suffer either somatic withdrawal effects or rebound headaches that only reinforce further self-medication.

Unrestricted access to pharmacological products such as narcotics, sedatives, or drugs with other psychotropic effects or otherwise habituating or addicting properties may cause serious adverse effects if used incorrectly.^{7-10,12,13} The magnitude of the number of drugs that are made available through this means creates a proclivity to withdrawal states.

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