

# Prolonged Delirium Tremens Requiring Massive Doses Of Medication

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Delirium tremens, the most severe manifestation of alcohol withdrawal, occurs in at least 5 percent of hospitalized alcoholic patients and is associated with a mortality rate of 1 to 15 percent.<sup>1</sup> Delirium tremens usually develops on the 3rd to 5th day of alcohol abstinence and persists for 1 to 6 days; on rare occasions, the condition can last for weeks. Patients with delirium tremens respond to numerous pharmacologic agents and supportive therapies. Mildly affected patients need only general nursing care, cardiovascular stabilization, reassurance, and low doses of sedative medications. Dramatically ill patients often require higher than expected doses of drugs to quell the symptoms of neurologic and cardiovascular instability. Agents used include paraldehyde, barbiturates, magnesium,  $\beta$ -blockers, clonidine, haloperidol, alcohol itself, such narcotics as fentanyl, and various benzodiazepines, including diazepam, chlorthalidone, oxazepam, lorazepam, and midazolam.<sup>1,2</sup> Benzodiazepines are favored because of their effectiveness and large therapeutic index. We report a patient who required massive doses of medication, primarily benzodiazepines, during an 8-week period to survive prolonged delirium tremens.

## Case Report

A 67-year-old man was brought to the emergency department with a 3-day history of tremors and gait instability. According to family members, he had a long history of alcohol and tobacco abuse. His last drink followed a period of continuous intake and occurred about 3 days before admission. Physical examination showed him to be an unkempt, disoriented man with mild diaphoresis, tachycardia, tachypnea, tremulousness, brisk reflexes, and ocular dysmetria. Except for the pres-

ence of psoriatic lesions, muscle wasting, and spider hemangiomas, findings of the rest of the physical examination were unremarkable. He had no signs of hepatitis or pancreatitis and showed no other signs of delirium tremens on admission. Laboratory studies, including liver function tests, were normal except for an elevated hemoglobin (16.7 mg/dL) and hematocrit (49.3 percent) and a decreased urea nitrogen (4 mg/dL).

The patient was admitted to an unmonitored bed with the diagnoses of Wernicke encephalopathy and chronic alcoholism for observation of alcohol withdrawal. Treatment consisted of thiamine, folate, and fluid repletion, and oral chlorthalidone was given as needed for agitation. During the next several days, he became progressively confused and disoriented. Five days after admission the patient was transferred to a monitored bed after he developed marked autonomic instability, hallucinations, and extreme agitation despite receiving up to 275 mg/d of oral chlorthalidone. This dosage was further increased during the next 4 days to a total of 810 mg daily, and supplemental doses of intravenous diazepam also were given as necessary.

On day 10 the patient was intubated to decrease the risk of aspiration of copious secretions. Intravenous lorazepam was begun and titrated up to 24 mg daily, with supplemental doses given to control tremor, sweating, fever, agitation, and confusion. On day 12 intravenous haloperidol was substituted, with dosages of up to 40 mg/d failing to control agitation. On day 14 the haloperidol was discontinued, and intravenous fentanyl, in dosages of up to 130  $\mu$ g/h, was still ineffective in controlling behavior and autonomic hyperactivity.

On day 16 fentanyl was stopped, and a continuous intravenous infusion of midazolam was begun. Starting with an initial dose of 50 mg/h, the dosage was doubled every hour until symptoms were controlled, reaching a maximum rate of 520 mg/h. During a 25-hour period the patient received a total of 2025 mg of midazolam. The development of metabolic acidosis and acute renal

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failure corresponding with the midazolam infusion, however, necessitated its discontinuation. These complications resolved following cessation of this infusion.

On day 17 intravenous diazepam, 500 mg every 8 hours, was restarted and titrated to 500 mg every 6 hours with resolution of agitation and autonomic instability. Diazepam dosages were decreased during the next 12 days to 30 mg/d. At this time periodic attempts at more rapid taper met with recurrent hallucinations, agitation, tremors, and vascular instability, so a slowly progressive decrease in dosage was prescribed.

On day 52 of his hospitalization the patient received the last dose of diazepam. Ten days later he was discharged to a nursing home with tracheostomy and gastrostomy tubes. At this time the patient was awake, following commands, and performing most daily activities with minimal assistance.

During his nearly 8-week hospitalization the patient received a total of 17,658.5 mg of benzodiazepine, including daily doses of 1000 mg or more of diazepam for a 6-day period. Three electroencephalograms, three computerized tomographic scanings of the brain, and a spinal tap all failed to reveal any specific abnormality. Three neurologic consultants and a drug rehabilitation specialist supported the diagnosis of Wernicke encephalopathy and delirium tremens.

At the nursing home the patient's cognitive function dramatically improved, and he was discharged to his home after removal of the tracheostomy and gastrostomy tubes. At a follow-up visit 6 months after the date of admission, the patient scored 21/24 on a mini-mental state examination, which was limited by his inability to read or write. The patient had no memory of the events that occurred during his hospitalization.

## Discussion

This report describes a patient who required massive doses of benzodiazepine to control delirium tremens; during 8 weeks, the patient received 12,462.5 mg of diazepam (up to 2 g/d), 121 mg of lorazepam, 3050 mg of chlordiazepoxide, and 2025 mg of midazolam. Despite these large doses, clinical symptoms of agitation and autonomic hyperactivity were barely controlled, though seizures were prevented. The patient experienced no episodes of respiratory depression requiring medical intervention but was intubated to prevent aspiration.

Several authors have reported that massive benzodiazepine doses were required during treatment of acute alcohol withdrawal and delirium tremens.<sup>3-5</sup> The only previous report of high-dose midazolam involved a total of 2850 mg of midazolam administered during a 50-day period to a 25-year-old patient.<sup>3</sup> As in the patient we describe, respiratory depression did not occur despite extremely high doses.

The mechanisms explaining the need for such high doses of benzodiazepine are complex. The resistance to high-dose benzodiazepine is probably a central effect, because the pharmacokinetics of diazepam are not altered in alcohol withdrawal.<sup>5</sup> Benzodiazepines exert their actions in alcohol withdrawal by augmenting the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, at the GABA<sub>A</sub> receptor in the central nervous system. Alcohol might also exert its effect through an effect on GABA.<sup>6,7</sup>

Chronic alcohol use, as occurred in this case, could influence the activity of benzodiazepines, either by decreasing the number of benzodiazepine binding sites<sup>8</sup> or by desensitizing the GABA-benzodiazepine receptor to the effects of benzodiazepine.<sup>9,10</sup> In addition, chronic benzodiazepine use might cause down-regulation of receptor function.<sup>11-13</sup> Thus, the apparent insensitivity of this patient to normal doses of benzodiazepine might at first have been due to alcohol-induced receptor insensitivity and later to the massive doses of benzodiazepine itself.

High-dose midazolam might not be a suitable treatment for alcohol withdrawal. Metabolic acidosis occurred in this patient, probably as a result of the high acid load associated with the extremely high dose of midazolam. To maintain stability of the product, the pH of midazolam solution is adjusted to approximately 3.0. Although the exact volume of fluid administered to this patient is not known (midazolam concentrations of both 1 mg/mL and 5 mg/mL were used), a conservative estimate would be 2025 mL of this acid solution during 25 hours.

Another factor to be considered is the cost of midazolam. At a cost of \$3/mg, control of this patient's symptoms for only 25 hours cost \$50,335 and depleted citywide supplies of the drug. In contrast, considering the relatively low cost of intravenous diazepam, a dosage of 2000 mg/d amounts to only \$440.

## Summary

Delirium tremens might last for weeks and treatment requires massive benzodiazepine doses, yet it is possible to manage patients with this condition successfully. In this case of delirium tremens, standard agents at the usual recommended doses were not sufficient to achieve control of confusion and agitation or to stabilize neurologic and cardiovascular parameters. The patient required extraordinarily high doses of central nervous system depressants for an extended period. Midazolam, a short-acting benzodiazepine, was used but was associated with metabolic acidosis and was extremely expensive. Although high-dose midazolam should probably be avoided, extremely high dose benzodiazepine use for an extended period might be necessary in some cases. In this circumstance we advise diazepam because of its low cost and relative safety. The tendencies to withhold large doses for fear of side effects or to give up in cases requiring prolonged intensive support must be resisted to minimize the mortality from this severe illness.

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