Diazepam withdrawal seizures

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Although it is considered uncommon, a withdrawal syndrome can occur in patients who abruptly stop taking a benzodiazepine after they have become habituated to one of these compounds.[1] Hollister and associates,[2] study 20 years ago was the first to document the apparent development of physical dependence in a patient taking a high dosage of chlordiazepoxide and the occurrence of withdrawal seizures when the patient switched to a placebo. Since then only 10 cases of seizures following the withdrawal of diazepam or chlordiazepoxide have been reported.[2-9] The duration of drug ingestion in these cases ranged from 1.5 to 72 (median 5.5) months. Very high dosages of the drug do not appear to be essential to the development of dependency, as there are three reports of withdrawal seizures in patients who took 30 mg of diazepam daily. Some patients had more than one seizure, and the first was reported to have occurred from within hours to up to 12 days after the last benzodiazepine dose (mean 6 days). Delirium and hallucinosis were associated with the seizures in three cases, but electroencephalographic evidence of changes in brain patterns was not consistently found.

Of 1355 patients admitted to the medical unit of the Clinical Institute, Addiction Research Foundation of Ontario in a 34-month period, 19 were admitted to be withdrawn from benzodiazepines (diazepam in 17 cases and oxazepam and flurazepam in 1 case each). Of the 19 benzodiazepine abusers 3 had major generalized seizures during withdrawal from diazepam. This cluster of cases is unusual because diazepam is eliminated from the body slowly, a feature that should protect patients from seizures.[10]

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Case reports

Case 1

A 28-year-old woman came to the unit requesting admission while she withdrew from diazepam, which she had been taking in a daily dose of 50 to 100 mg for 6 years, including the day of admission. She did not abuse alcohol or other drugs. She reported she had had seven separate major seizures in the past 4 years — usually about 48 hours after discontinuing diazepam — and had been admitted to other hospitals on four occasions. These admissions were confirmed. On each of these admissions she concealed her diazepam use from attending physicians, who had prescribed various anticonvulsants. Rather than taking the anticonvulsants she resumed her diazepam abuse. She had not experienced seizures at any time other than after abruptly discontinuing diazepam. There was no history of serious head injury, febrile convulsions or epilepsy. Several electroencephalograms, a brain scan and skull roentgenograms had been normal.

Other than her apparent anxiety, a physical examination revealed no abnormal findings. When samples of her blood and urine were screened for drugs, by a procedure that detects all classes of sedatives, hypnotics, opiates, alcohol and other drugs of abuse, the results were positive for benzodiazepines only. No anticonvulsant or psychoactive medication was prescribed. The patient remained anxious and anorexic, and 54 hours after admission she had a major seizure. She was given phenytoin in a loading dose of 10 mg/kg and then in a maintenance dose for 14 days until she was discharged. No serum or urine levels of drugs were determined since the patient was responding well: her anxiety resolved and there were no further seizures. An electroencephalogram recorded after her seizure showed no epileptiform activity. The levels of glucose and calcium in blood taken while she fasted were normal. The apparent half-life of diazepam in the patient was 21.5 hours, and that of N-desmethyldiazepam (the active metabolite) was 62.5 hours.

Case 2

A 22-year-old student was admitted to the unit to withdraw from diazepam, which she had been taking daily for 20 months in doses of 120 to 200 mg. Her history included alcohol, stimulant and hallucinogen abuse for 5 years, followed by 3 years of no drug abuse (so she claimed) until the diazepam abuse began, a personality disorder that had required numerous admissions to psychiatric hospitals, and frequent drug overdoses. She had no history of difficulties at her birth or of head injury, febrile convulsions or epilepsy. During the diazepam abuse she had two seizures on a day when she also took a 200-mg overdose of amitriptyline. At that time skull roentgenograms, a brain scan and an electroencephalogram were normal. Nearly a year later, during anesthetic induction with fentanyl and alphaxalone–alphadolone she began to have generalized clonic–tonic movements. These ended when she was given 5 mg of diazepam intravenously but recurred in the recovery room. A subsequent electroencephalogram showed paroxysmal spike and wave activity following hyperventilation and then spontaneously in short paroxysms during the remainder of the recording session.

In the month before admission to the unit she had smoked six marihuana cigarettes a week and drunk six bottles of beer a day as well as abusing diazepam daily. Benzodiazepines were the only drugs detected in her blood and urine at the time of admission. She was anxious and agitated when admitted and had horizontal nystagmus, presumably from diazepam intoxication. There were no other abnormal neurologic findings. Her blood pressure was 100/70 mm Hg and did not drop when she stood.

After admission she was treated with relaxation techniques but not given psychoactive medications. For the first week she remained anxious, nauseated and anorexic. On the 11th hospital day she had a major seizure. She was offered phenytoin but declined it, as she

wanted to become completely drug-free.

An electroencephalogram made on day 11 revealed no abnormality while she was awake but very occasional discharges while she slept that were suggestive of atypical spike and wave activity, not reaching definite spike and wave potentials. A brain scan, a computer-assisted tomographic head scan and the blood glucose level while fasting were normal.

Case 3

A 27-year-old labourer was admitted to the unit to withdraw from diazepam, which he had been abusing for 12 years. The drug had initially been prescribed for reactive anxiety at the age of 15 years. At 17 years of age he had tried to stop taking it but resumed its use a few days later because of agitation and paranoid feelings. At the age of 23 years he tapered his daily dose from approximately 100 mg to zero in 1 week. Ten days after his last dose he experienced a major seizure. A brain scan and an electroencephalogram made at that time were normal. He resumed taking diazepam in a dose of 100 to 150 mg daily. For several years he had also taken up to 10 tablets containing 325 mg of acetaminophen plus 8 mg of codeine (Tylenol no. 1) several times a week for tension headaches. He did not abuse alcohol or other drugs.

When admitted to the unit he was calm and showed no evidence of sedative intoxication or withdrawal or any other abnormality. However, benzodiazepines, acetaminophen and codeine were detected in his blood and urine.

In view of his previous seizure he was given phenobarbital orally according to the protocol for treating patients withdrawing from other hypnosedatives.[11] He did not show evidence of sedative withdrawal until 96 hours after his admission, when he had a major seizure. He was treated with a loading dose of 1000 mg of phenytoin and thereafter was given 100 mg three times daily for 7 days. An electroencephalogram made 3 days after the seizure did not show epileptiform activity. On his 11th day in hospital, 2 days after discontinuing phenytoin, he had another seizure. He was treated with phenytoin for a further 9 days. The blood level of phenytoin 24 hours after his last 300-mg dose was 2 mg/l. Benzodiazepines were detected in the urine for 14 days after admission. The levels of glucose, calcium and magnesium in blood taken while he was fasting were normal.

He remained in a rehabilitation program for another 5 weeks and experienced no further problems.

Discussion

Others have reported that seizures during diazepam withdrawal may be followed by delirium, confusion and even coma,[5,6,9] although these are more often noted in patients suspected of concurrent abuse of other sedatives or alcohol.[5,6] Such a suspicion is unlikely in our patients, however, as no other drugs that might have been associated with the withdrawal seizures were found by drug screening, and the seizures were not followed by delirium, confusion or hallucinations, despite the fact that diazepam was not given after the seizures. Conversely, patients have suffered psychosis and delirium but not seizures during benzodiazepine withdrawal.[2,6,12,13]

When the patients in cases 1 and 2 were admitted we thought that seizures during diazepam withdrawal were unlikely in view of the long half-lives of diazepam and N-desmethyldiazepam — 31 and 62 hours respectively.[10] However, Miller and Nulsen[14] reported significant levels of N-desmethyldiazepam for up to 21 days in a patient withdrawing from diazepam and suggested that a longer stay in hospital may be necessary for successful withdrawal in diazepam abusers.[15] We now treat patients with a history of seizures who have been admitted to withdraw from high-dose abuse of diazepam with gradual tapering from their alleged dose to zero over approximately 20 days. Patients without a history of seizures may be withdrawn abruptly if no other risk factors, such as alcohol, barbiturate or opiate abuse, are present.

Several authorities, presuming cross-tolerance between barbiturates and benzodiazepines, have recommended phenobarbital as a suitable drug during benzodiazepine withdrawal.[16,17] However, it has now been established that benzodiazepines have their own central nervous system receptors,[10] and therefore we do not recommend phenobarbital treatment for benzodiazepine withdrawal. In case 3 an adequate phenobarbital load[11] proved unsuccessful in preventing a seizure. The efficacy of phenytoin and other anticonvulsants in the treatment of diazepam withdrawal seizures is unknown. At times we have found propranolol a useful adjunct in patients with marked autonomic signs and symptoms, but this drug is unlikely to prevent such important withdrawal problems as seizures and psychoses.

The rarity of seizures or delirium in patients withdrawing from diazepam or chlordiazepoxide has been attributed to the long half-lives of these drugs and their metabolites. Consistent with this is the generally late appearance of the seizures when they do occur. Our patients had seizures on days 2, 4 and 11 of withdrawal. One study has correlated early onset (within 48 hours) of withdrawal symptoms to moderate decreases in blood levels of diazepam and N-desmethyldiazepam. Thus, withdrawal symptoms may occur before the drug has been completely eliminated. With long-term high-dosage abuse of benzodiazepines there may be other mechanisms independent of the rate of drug elimination that are responsible for withdrawal phenomena, but this remains to be established. Furthermore, we are not aware of seizures developing during withdrawal from short-acting benzodiazepines, which would be expected if the rate of elimination were the responsible factor, as it appears to be with barbiturates and other hypnosedatives.[18-20]

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