Diazepam Withdrawal

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BENZODIAZEPINES ARE AMONG the most widely used pharmacologic agents in the United States,[1] and diazepam is the most commonly prescribed.[2] True addiction to diazepam is believed to be unusual.[3-5] Withdrawal reactions to diazepam are uncommon but have been described.[6-33] We report the case of a patient who had withdrawal reactions on two separate occasions and we review the English language literature on this subject.

Report of a Case

A 40-year-old nonalcoholic woman with a history of bilateral nephrectomies and being maintained on hemodialysis was admitted to hospital for abdominal pain in 1978. A surgical procedure was carried out on the second day for a ruptured abdominal aortic aneurysm. Four days after the operation she became agitated, confused and combative, screaming and waving her arms periodically. She refused to talk to anybody, but when she was communicative, she expressed fears of being hurt. She was observed talking to imagined companions. There was no improvement after routine hemodialysis. Initial treatment with haloperidol, 10 mg given orally, resulted in some improvement within six hours, and haloperidol, 2 mg taken orally every eight hours, was prescribed. The next day she became visibly tremulous. The tremor was involuntary, symmetric, mostly distal and more severe in the upper extremities. She was also noted to grimace. The tremor was intermittent, with seconds to minutes between contractions. Diphenhydramine hydrochloride, 25 mg, was given intramuscularly every four hours, which resulted in only slight relief of symptoms. By the ninth postoperative day her tremors had significantly worsened. Treatment with diphenhydramine and benztropine mesylate administered intravenously was ineffective. Intravenous administration of 5 mg of diazepam resulted in a dramatic abatement of her tremors within 30 seconds. Treatment with diazepam, 5 mg taken orally every six hours, was continued and she showed progressive improvement. Subsequently the patient related a history of having taken diazepam, 5 to 15 mg a day, for the past seven years for anxiety.

In 1980 the patient was admitted to hospital for abdominal pain and partial small bowel obstruction. She was treated with nasal gastric suction, which relieved her symptoms. Diazepam therapy was discontinued. On the third hospital day severe tremors developed, with intermittent, involuntary jerking and twitching of the muscles of her face and extremities. The contractions were mostly distal, affecting mainly the upper extremities. There was no confusion, delirium or hallucinations. Her reflexes, plantar responses and sensory examination findings were normal, as well as her vital signs. The blood urea nitrogen level was 79 mg per dl and creatinine concentration was 18.5 mg per dl, unchanged compared with her usual predialysis baseline. Serum calcium, magnesium and electrolyte levels were within normal limits. Administration of diazepam, 5 mg orally every six hours, was reinstituted. Within 24 hours her symptoms of tremors and myoclonic jerks completely resolved.

Discussion

Diazepam withdrawal reaction was first described by Hollister and co-workers in 1963[28] in studies of diazepam treatment in newly admitted schizophrenic patients. We have identified 33 cases of diazepam withdrawal detailed in the English medical literature (Table 1).[6-27] The single most convincing case was reported by Winokur and associates,[26] with verification of the diagnosis by a placebo-controlled, double-blind protocol.

The exact incidence of diazepam withdrawal reactions is not known. In addition to the 33 cases noted above, several authors have reported in a general way cases of withdrawal reactions among their patients.[28-33] One possible reason why such withdrawal reactions are uncommonly seen is that patients may abort these reactions early on. They may think that their original symptoms are returning and reinstitute taking the drug.[4]

In the 33 reported cases,[6-27] the ages of the patients ranged from 21 to 72 years; 16 were women and 17 were men. The daily diazepam intake ranged from 15 mg to 500 mg a day. The duration of diazepam use before the onset of withdrawal symptoms ranged from ten days to ten years. In all of the patients withdrawal symptoms developed within 1 to 11 days after use of the drug was discontinued. Most of the patients were taking the diazepam for anxiety or neurosis.

Discontinuation of diazepam use was the result of a physician's attempt to detoxify a patient[16,21,25] or change the medication.[13] The history of diazepam use was known in some cases[7,9,19,24] but not in others.[8,22,23] Situations that required that nothing be taken by mouth, such as bowel or other surgical interventions, were frequently associated events.[16,26] Less common circumstances included treatment for tetanus[14] or overdose with benzodiazepines.[20] Additionally, use of the drug was discontinued or the dosage reduced by patients voluntarily[20,26,27] or involuntarily,[12,17] or there was a change in the work environment.[18]

A spectrum of signs and symptoms was seen in the reported cases.[6-27] They ranged from affective disorders with psychosis, confusion, agitation, hallucinations and delirium to motor dysfunctions with restlessness, trem-

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TABLE 1.—*Summary of 33 Cases of Diazepam Withdrawal Described in the English Literature*

Author	Age	No. of Patients	Diazepam Therapy: Sex	Diazepam Therapy: Dosage mg/d	Diazepam Therapy: Duration	Associated Conditions	Onset of Withdrawal	Signs and Symptoms of Withdrawal
Aivazian, 1964[6]	..	1	♀	30	Months	.....	Hours	Grand mal seizures
Barten, 1965[7]	52	1	♀	20	3 mo	Depression	3 d	Paranoid delusions, disorientation, tremulousness, agitation, hostility, restlessness, grand mal seizure
Relkin, 1966[8]	21	1	♂	40-60	10 d	Dystonia, musculorum deformans	1 d	Tremor, diaphoresis, tachycardia, fever, death
Gordon, 1967[9]	23	1	♀	60	1 yr	Anxiety	Days	Agitation, tremulousness, hyperhydrosis, dry mouth
Clare, 1971[10]	39	1	♀	90-500	6 yr	Disturbed sleep	Daily symptoms	Morning shakes, slurred speech, gross ataxia, withdrawal fits
Kendall and Clarke, 1972[11]	72	1	♀	70	1 mo	Tetanus	12 d of coma	Coma for 12 days
Woody et al, 1975[12]	25-26	2	♂	100-150	2-3 wk	Heroin addict taking methadone hydrochloride	2-8 d	Anxiety, insomnia, tremor, grand mal seizures, tenseness, dizziness
Bant, 1975[13]	..	2	♀	30	2 yr	Anxiety, obsessive compulsive neurosis	2 d	Shaking, inability to stand
Malatinsky et al, 1975[14]	60-66	2	♂	80-120	11-34 d	Tetanus	11 d	Visual hallucinations, confusion, disorientation, memory deficits, emotional instability, irritability, motor restlessness, negativism, mutism
Vyas and Carney, 1975[15]	..	1	♀	30	3 yr	Anxiety	2 d	Grand mal seizures, confusion
Floyd and Murphy, 1976[16]	47-64	1 4	♀ ♂	20-40	5 mo-years	Depression	3-6 d	Disorientation, visual hallucinations, stubbornness, confusion, forgetfulness, irrational behavior, jitters
Fruensgaard, 1976[17]	46-74	3	♀	5-30	2 mo-years	Tenseness, headache, depression, hysterical neurosis	2-5 d	Confusion, agitation, delirium, perspiring, frequently laughing, widely gesticulating, jabbering, paranoid tendencies, hallucinations, incoherent speech
Rifkin et al, 1976[18]	23	1	♂	30	3 mo	Anxiety	5 d	Grand mal seizures
Dysken and Chan, 1977[19]	49	1	♂	15-30	7 yr	Anxiety, hyperventilation	7 d	Suspicion, confusion, disorientation, incoherence, loose association
Preskorn and Denner, 1977[20]	34-56	1 2	♀ ♂	40-100	6 mo-2 yr	Anxiety, insomnia, cardiac neurosis, nervousness, anorexia	3-5 d	Insomnia, anxiety, restlessness, grandiose delusions, confusion, disorientation, auditory and visual hallucinations, seizures, agitation, hostility, paranoid delusions
Agrawal, 1978[21]	30	1	♀	20-140	5 mo	Backache	5 d	Tremulousness, irritability, increased psychomotor activity, muscle cramps, photophobia, retroorbital pain, insomnia, visual hallucinations, paranoia, ataxia
Minter and Murray, 1978[22]	30	1	♂	20	Years	.....	2-3 d	Auditory and visual hallucinations, confusion, agitation, disorientation, delusions
Pevnick et al, 1978[23]	37	1	♂	30-45	1½ yr	Anxiety	9 d	Tremor, muscle twitches, cramps, facial numbness, dysphonia
deBard, 1979[24]	56	1	♂	40-80	10 yr	.....	10 d	Visual hallucinations, coma, grand mal seizures, disorientation
Miller and Nulsen, 1979[25]	37	1	♀	60-80	8 yr	Hyperventilation	12 d	Diarrhea, restlessness, anxiety, emotional lability
Winokur et al, 1980[26]	32	1	♂	15	6 yr	Anxiety	Few days	Anxiety, vertigo, tinnitus, blurred vision, generalized shakiness
Abernethy et al, 1981[27]	31	1	♀	100-120	2 yr	.....	2 d	Agitation, tremulousness, weakness

ors, myoclonic jerks and grand mal seizures. Some patients manifested the entire spectrum,* whereas in others only the psychosis developed[16,17,19,22] or the motor dysfunctions.[6,10,13,18,23] There were rare cases of coma[11,24] or death.[8]

Our patient had been taking 5 to 15 mg of diazepam a day for at least seven years when the withdrawal reactions developed. Within three to four days after diazepam intake was discontinued her symptoms became evident. The diazepam was initially prescribed for anxiety. Her clinical course clearly showed that there are two distinct components to diazepam withdrawal, and the treatment of each may differ. During the first episode, her initial presentation was an affective disorder with psychosis, confusion, paranoid feelings and delirium. Haloperidol administration was effective in controlling these symptoms, but then the motor dysfunctions became evident. During the second episode, there was no affective disorder and her only symptom was the myoclonic jerks. Resumption of diazepam therapy resulted in dramatic resolution of the motor dysfunctions on both occasions. We therefore diagnosed diazepam withdrawal in our patient based on the criteria proposed by Eddy and colleagues.[34] They state that

> the withdrawal or abstinence syndromes are made up of specific arrays of symptoms and signs of psychic and physical nature that are characteristic for each drug type. These conditions are relieved by readministration of the same drug or another drug of similar pharmacological action within the same generic type.[34]

The physiologic mechanism responsible for the affective and the motor dysfunctions of diazepam withdrawal has yet to be determined. The long duration of action and the presence of pharmacologically active metabolites probably explain why symptoms of diazepam withdrawal generally do not appear until several days after discontinuing use of the drug.[3] The interaction of benzodiazepine receptors in the brain with γ-aminobutyric acid (GABA) receptors may be important in the pathogenesis of the withdrawal reactions.[35-38]

The most effective treatment of diazepam withdrawal reactions is to resume taking diazepam. Intramuscular or intravenous administration of diazepam in a dosage of 5 mg results in rapid improvement.[13,17,19,24] Orally given diazepam in a dosage of 10 to 60 mg a day requires a longer duration for relief of symptoms, sometimes up to several days to take effect.[13,14,16,20,23,26] Additionally, in some patients the psychosis responds to the administration of chlorpromazine hydrochloride,[7,9] phenobarbital,[17] haloperidol given intramuscularly[22] or pentobarbital given orally.[20] In others, administration of phenytoin (Dilantin)[7] or barbiturates[12] is required for control of seizures. Recently propranolol, 60 to 160 mg per day, given orally in three to four divided doses, has been shown to be effective in controlling all of the symptoms of diazepam withdrawal.[27,29]

Because diazepam is such a widely prescribed drug, physicians should be aware of the potential of withdrawal reactions associated with this agent. The condition can be prevented by ensuring that use of the drug is not abruptly discontinued. Unexplained anxiety, agitation, confusion, disorientation or frank hallucination, as well as tremors or myoclonic jerks, occurring together or independently, should alert clinicians to consider diazepam drug withdrawal. If diazepam withdrawal is implicated, intravenous or intramuscular administration of 5 mg of diazepam may abort the acute reaction. Then diazepam or propranolol should be administered orally until symptoms completely resolve. The use of both drugs is discontinued by progressively decreasing the dosages.

*References 7, 9, 12, 14, 15, 20, 21, 24-27.

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Acute Idiosyncratic Reaction to Hydrochlorothiazide Ingestion

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ADMINISTRATION OF THIAZIDE DIURETICS has been reported to produce various idiosyncratic reactions including skin rash,[1] urticaria, photosensitivity,[2] jaundice, necrotizing vasculitis[3] and bone marrow depression.[4-7]

There have been six reported cases of idiosyncratic pulmonary edema reactions immediately following the ingestion of hydrochlorothiazide.[8-12] These previously reported cases have not been associated with bone marrow depression. We report a case of hydrochlorothiazide-induced acute pulmonary edema and associated severe leukopenia and thrombocytopenia in a patient shortly after she ingested a single 50-mg tablet of hydrochlorothiazide.

Report of a Case

A 50-year-old woman entered the Los Angeles County-University of Southern California Medical Center emergency room in April 1980 because of nausea, vomiting and light-headedness. She had been in her usual state of good health aside from a history of mild hypertension, untreated except for salt restriction. The day of admission she had seen a physician and was given hydrochlorothiazide for mild hypertension. Two and a half hours after taking the first 50-mg tablet, nausea and vomiting developed and she became light-headed. She took no other medication.

She stated that a similar problem had occurred two years previously after taking hydrochlorothiazide and she had not taken the drug again. She said she had had no previous cardiac or pulmonary disease. She did not smoke.

On physical examination she was noted to be slightly obese and appeared mildly distressed. Her skin was diaphoretic and cool. Blood pressure was 90/60 mm of mercury without postural changes, pulse rate was 110 beats per minute and regular, respirations were 18 per minute and the temperature (taken orally) was 35.8°C. There was no neck vein distension. Auscultation of the chest showed decreased breath sounds at both lung bases. On examination of the heart she had neither murmurs nor gallops. There was no calf tenderness, clubbing or edema. The remainder of the examination showed no abnormalities.

Admission laboratory data within normal limits included serum enzymes, bilirubin, calcium, phosphorous, blood urea nitrogen, creatinine, serum albumin, total protein and serum electrolytes. Analysis of urine gave normal findings. The initial leukocyte count was 1,200 per cu mm, with 40 percent segmented neutrophils, 58 percent lymphocytes and 2 percent monocytes. No eosinophils or band forms were seen. The antinuclear antibody titer was positive at 1:20. The hemoglobin level was 15.4 grams per dl, hematocrit 45.2 percent and the platelet level appeared to be decreased. The electrocardiogram appeared unremarkable, but the chest x-ray study showed pulmonary edema (Figure 1) when compared with a normal film taken two months earlier (Figure 2).

The arterial blood gas determinations made 24 hours after admission while the patient was breathing room air showed an oxygen partial pressure of 74 mm of mercury, a carbon dioxide partial pressure of 30 mm of mercury and a pH of 7.47. The platelet count was 86,000 per cu mm. Various viral titers were negative, including cold agglutinins and complement fixation for histoplasmosis and coccidioidomycosis.

On admission to hospital, initial treatment included administration of oxygen and intravenous replacement of fluids. The patient responded well and had no further respiratory distress; no systemic corticosteroids or other medicines were given. The leukocyte count rose to 6,700 per cu mm after four days, with a normal differential count, and the platelet count returned to within normal limits. She was discharged after four days in hospital; no abnormalities were noted on an x-ray film of the chest.

Discussion

In view of the present widespread use of thiazide diuretics, the life-threatening adverse effects of these compounds are of great practical import. The spectrum of other significant drug-induced pulmonary disease has been reviewed in the past.[13] The previous reports of thiazide-induced pulmonary edema were not associated with severe bone marrow depression, though bone marrow depression due to the ingestion of hydrochlorothiazide has been reported,[4,7] and at least one case of hydrochlorothiazide-induced pulmonary edema was associated with moderate leukopenia.[12] Thiazide diuretics are frequently prescribed for edematous states and often for congestive heart failure. In our patient there had been no previous history of organic heart or pulmonary disease; as a matter of fact, the patient had had normal findings, except for transient hypertension, at a clinical examination two months earlier.

Apparently a similar reaction had occurred earlier in this patient after ingestion of a single thiazide tablet. The sequence of events following the last oral ingestion of a single thiazide tablet suggests an idiosyncratic re-

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