Original Articles

Diazepam withdrawal syndrome: its prolonged and changing nature

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The diazepam withdrawal syndrome was studied in 10 patients who had abused the drug for 3 to 14 years. In the previous 6 months their consumption of diazepam had ranged from 60 to 120 mg daily; none had used other drugs during this period. The withdrawal period lasted about 6 weeks. The intensity of the symptoms and signs was high initially, fell during the first 2 weeks, then rose again in the third week, before finally declining. Three groups of symptoms and signs were identified. Group A symptoms occurred throughout withdrawal and included tremor, anorexia, insomnia and myoclonus. Group B symptoms and signs were largely confined to the first 10 days and were those of a toxic psychosis. Group C symptoms reached a peak in the third and fourth weeks of withdrawal and were characterized by sense perceptions that were either heightened or lowered. The symptom groups, the presence of tremor and myoclonus, and the relief of symptoms by a test dose permit diazepam withdrawal to be distinguished from anxiety. The biphasic course of the symptoms is probably related to the pharmacokinetics of diazepam.

Le syndrome de manque après retrait du diazépam a été étudié chez 10 patients qui en avaient fait abus pour une période de 3 à 14 ans. Au cours des 6 mois précédents, leur consommation quotidienne de diazépam avait varié entre 60 et 120 mg; aucun des patients n'avait fait usage d'une autre drogue durant cette période. La période de manque a duré environ 6 semaines. L'intensité des symptômes et signes était élevée au début; elle s'est atténuée au cours des 2 premières semaines, pour s'élever de nouveau durant la troisième semaine, avant de décliner finalement. Trois groupes de symptômes et signes ont été identifiés. Les symptômes du groupe A étaient présents durant toute la période de manque et comprenaient des tremblements, de l'anorexie, de l'insomnie et de la myoclonie. Les symptômes et signes du groupe B étaient largement limités aux 10 premiers jours et ressemblaient à ceux d'une psychose toxique. Les symptômes du groupe C atteignaient un maximum durant les troisième et quatrième semaines de manque et étaient caractérisés par une élévation ou un abaissement des perceptions sensorielles. Les groupes de symptômes, la présence de tremblements et de myoclonie, et le soulagement des symptômes par une dose-test ont permis de distinguer le syndrome de manque au diazépam de l'anxiété. L'évolution biphasique des symptômes est reliée à la pharmacocinétique du diazépam.

Diazepam abusers who have stopped taking the drug have given dramatic and well-publicized accounts of severe and long-lasting symptoms, but the resulting concern about diazepam dependence has been attributed to irresponsible journalism rather than to medical evidence.[1]

An early study of diazepam, however, did demonstrate that the drug was potentially addictive and that the withdrawal syndrome was similar to that produced by alcohol or barbiturates.[2] Subsequently this observation was supported by separate case reports of seizures[3-5] and acute organic psychoses resembling delirium tremens.[5-8] A further three patients all had delusions, hallucinations, clouding of consciousness, anxiety, tremors and insomnia.[9] In a blind study a placebo was substituted for diazepam once the subjects had been stabilized on a daily dose of 45 mg of the drug. Tremor was the most persistent symptom; others were weakness, anorexia, abdominal cramps, insomnia and muscle twitching.[10]

The duration of the withdrawal symptoms in this last investigation was relatively short, about 10 days. The conditions may be prolonged, though, in patients who are taking larger doses of the drug.[11] In newborn infants who have had prolonged exposure to diazepam in utero the symptoms last about 6 weeks.[12] The duration of the syndrome presumably depends also upon individual differences in diazepam metabolism.

Our aim was to define the symptoms and signs that characterize the diazepam withdrawal syndrome and to investigate their course.

Methods

The subjects were 10 patients who were consecutively

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admitted to the psychiatric unit of a general hospital with a primary diagnosis of diazepam dependence. None of them had used any other drugs during the previous 6 months, nor did they have evidence of any other major psychiatric or physical disorder during their hospital stay. Seven of the 10 were men. The subjects' ages ranged from 31 to 54 years. They had used diazepam for a mean of 5 to 6 (standard deviation 3.5) years, and the daily dose of diazepam ranged from 60 to 120 mg, with a mean of 79.0 (standard deviation 20.3) mg. The reliability of the patients' information on diazepam use was ascertained by checking with them again before they were discharged from hospital and by interviewing relatives.

This series of subjects represented only 2.5% of admissions to the service of one of us (C.S.M.) over nearly 3 years. In some other patients who were admitted during this period diazepam abuse was a significant but not the primary cause of mental disorders. Originally a chronic anxiety state had been diagnosed in six of the subjects. Two of the men had come to abuse diazepam by way of alcoholism but had abstained from ethanol for more than 2 years. One of them had originally been considered to have involutional depression, and another had first been given diazepam for the muscular spasm accompanying an orthopedic condition. Only one subject admitted to obtaining diazepam from nonmedical sources; the rest had maintained their high dosages by obtaining prescriptions from several physicians and having them filled at different pharmacies.

Once the diagnosis was made the subjects were informed that they had diazepam dependence and that they should stop taking the drug. They were told that they would be given medication to reduce their symptoms but not diazepam or any other benzodiazepine unless they felt unable to tolerate the symptoms. The use of drugs to which the patient may have cross-tolerance can prolong the withdrawal period because some patients become increasingly reluctant to discontinue them; such drugs were therefore avoided.

The first three subjects were given chlorpromazine, the next five hydroxyzine and the last two a lactose placebo. The active drugs were administered as required, 50 mg at a time up to 300 mg in a day. The subjects were instructed about drug dependence and were given relaxation training. The main form of management was intensive support and reassurance by the nursing staff.

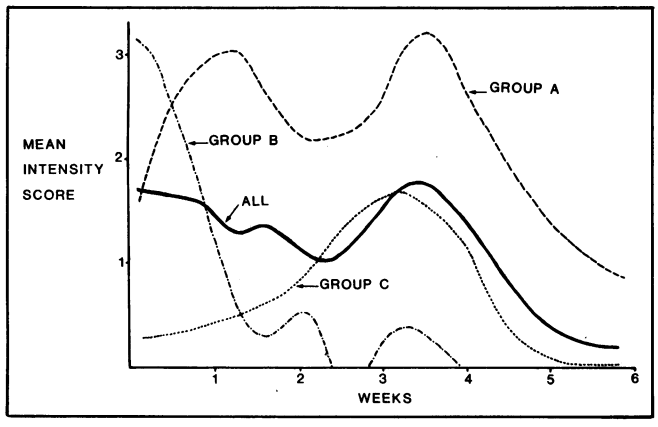

FIG. 1—Mean symptom and sign intensities in 10 diazepam-dependent patients experiencing the withdrawal syndrome. Group A, B and C symptoms and signs are listed in Tables I to III. Curves smoothed by use of moving 3-day average.

The subjects' symptoms and signs were assessed with the alcohol-withdrawal rating scales developed by Gross and colleagues.[13] The staff were familiar with these scales and had achieved a satisfactory level of reliability in scoring. The short scale was used by the nursing staff for each 8-hour period and the long scale by the medical staff every 24 hours. Our experience with the first three subjects led us to add several features to the scales: myoclonus, altered perception (vision, hearing and cutaneous sensation), ataxia, abdominal pain and pallor. Most of the symptoms and signs were rated on an eight-point scale.

The symptom intensity scores reported are the mean daily scores of all the symptoms that occurred during the withdrawal period. The data were smoothed by using a 3-day moving average.

Results

The study continued until the subjects felt that their symptoms had diminished to a level that would be tolerable outside the hospital. This corresponded to an average symptom intensity level of less than 1. We saw no differences in the effects of chlorpromazine, hydroxyzine and placebo. The subjects remained in hospital for a remarkably uniform period, from 38 to 44 days, except for one subject, who discharged herself after 28 days and resumed taking diazepam. She had been given hydroxyzine.

The subjects showed a slow but steady lessening of their symptoms during the second week of the withdrawal period, but in the third week 7 of the 10 subjects became worse again. Their symptoms reached a second peak in the fourth week and then diminished through the fifth and sixth weeks (Fig. 1).

We recognized three major groups of symptoms and signs that clustered in different parts of the withdrawal period:

- Group A symptoms (Table I). These were found throughout, although their severity varied over time (Fig. 1). Almost all the subjects had all of these symptoms. The tremor we observed was identical to that occurring in withdrawal from alcohol, being predominantly postural, with a frequency of 8 to 10 Hz. It could be distinguished from anxiety tremor by palpation for

Table I—Group A symptoms: those occurring throughout diazepam withdrawal period

Symptom	No. of patients
Tremor	10
Anorexia	10
Sweating	10
Anxiety	10
Agitation	10
Insomnia	10
Myoclonus	9

Quinquaud's sign.[14,15] This sign is elicited by having the patient hold his or her hand vertically, with the tips of the second and third fingers touching the palm of the examiner's horizontally outstretched hand. After a few seconds' delay the examiner feels an irregular tapping. The sensation experienced by the examiner has been likened to the crepitus of broken bone. Myoclonus was most readily seen in the facial muscles, particularly when the patient was asleep. It varied from fibrillating twitching to spasms of large muscles.

- Group B symptoms and signs (Table II). These occurred mostly during the first 10 days and were similar to those found in alcohol and barbiturate withdrawal. The clinical picture in four patients at this stage resembled delirium tremens.
- Group C symptoms (Table III). These were present throughout most of the withdrawal period but increased in intensity during the second week and reached their peak 3 weeks after the drug had been stopped. They were all perceptual disorders, with heightened perception accounting for the photophobia and hyperacusis. Abnormalities of cutaneous sensation, including burning, tingling and feelings of cold and numbness, were major sources of complaint. The subjects had great difficulty localizing these experiences, which distinguished them from both real sense perceptions and tactile and thermic hallucinations. Some subjects were in considerable distress from abdominal pain, although they typically had difficulty in describing its character and location. This pain was often associated with marked pallor, which twice suggested an "acute abdomen" to us. The "ataxia" was characterized by a subjective feeling of unsteadiness in walking and other motor activities that was out of proportion to the patient's degree of incoordination.

Discussion

Drug withdrawal symptoms do not usually last as long as 6 weeks, nor do they run a biphasic course. Although the fall in the blood level of a drug does not always parallel the development of withdrawal symptoms, the rates of elimination of diazepam and its principal active metabolite, desmethyldiazepam, provide an explanation for our findings. In ordinary clinical use diazepam appears to have a half-life of 24 to 48 hours,[16] but the half-life increases with age[17] and repeated use of the drug.[18] Desmethyldiazepam has a longer half-life (51 to 120 hours) and may accumulate for 3 weeks before reaching a steady state.[19] The ratio of plasma levels of diazepam and desmethyldiazepam varies from 0.21 to 1.7. Not surprisingly, then, a patient who had taken 60 to 80 mg of diazepam daily still had significant blood levels of desmethyldiazepam 21 days after the drug was last taken.[11]

Data on the pharmacokinetics of diazepam in subjects taking large amounts of the drug over long periods are scanty. However, among patients receiving long-term treatment with desmethyldiazepam a half-life even longer than 120 hours was calculated.[20] Equally relevant to our observations was the bi-exponential elimination curve found in that study. The first component was a half-life of 96 to 349 hours, but when the drug's plasma level had fallen to about 550 ng/ml the rate of elimination increased, resulting in a half-life of 26 to 36 hours.

The long duration of the diazepam withdrawal syndrome we observed appears to be consistent, then, with the pharmacokinetic evidence. Even the biphasic nature of the syndrome may be explained by the differences in the elimination rates of diazepam and desmethyldiazepam, particularly if the bi-exponential pattern for the latter substance is confirmed. We were not able to measure the plasma levels of diazepam and its principal metabolite in our own study.

The diversity of symptoms found in this withdrawal syndrome may be explained by the varied clinical effects of the drug. Diazepam is an anticonvulsant and has a direct effect upon the cerebral cortex, where there are many benzodiazepine receptor sites.[21] Thus, diazepam in part resembles the central depressant drugs, which may account for the similarity between group A and B symptoms and signs and those of alcohol and barbiturate withdrawal.

Diazepam also reduces excessive alertness and returns responsiveness to stimuli to normal levels. The converse of this effect occurs during withdrawal, causing especially the group C symptoms, which are mainly disorders of perception. Most group C symptoms can be attributed to a high level of arousal and a low threshold for sensory stimulation.

Diazepam acts as a muscle relaxant, too, probably through its effect on the spinal cord, which is also well endowed with benzodiazepine receptor sites.[22] This could explain the muscular pain and myoclonus, especially the fibrillary form. The contribution of the spinal component to tremor is more speculative, but we have observed tremors in the paralysed limbs of a paraplegic in diazepam withdrawal.

It has been suggested that the symptoms appearing when benzodiazepines are discontinued usually reflect a

Table II—Group B symptoms and signs: those occurring during first 10 days

Symptom or sign	No. of patients
Tachycardia	9
Hypertension	8
Clouding of consciousness	7
Hallucinations	
All types	4
Visual	3
Tactile	2
Auditory	2
Gustatory	1

Table III—Group C symptoms: those with maximum intensity after 3 weeks

Symptom	No. of patients
Paraesthesia	8
Thermic	6
Touch	4
Photophobia	8
Hyperacusis	8
Abdominal pain	8
Ataxia	5
Hypoesthesia	4
Muscular pain	4
Depersonalization	3
Pallor	7

recurrence of the condition for which the drugs were first prescribed.[1] A withdrawal syndrome, demonstrating physical dependence, is easily recognized when a short-acting benzodiazepine, such as oxazepam, is withdrawn. Diazepam, because of the long duration of its action, may not present such a clear relation between the reduction or stoppage of the drug and the symptoms of withdrawal. The nature of these symptoms may therefore be misinterpreted and diazepam dependence go unrecognized.

Symptoms occurring some time after recognized diazepam withdrawal are occasionally attributed to the anxiety associated with psychologic dependence on the drug. The early stages of withdrawal resemble those of ethanol withdrawal and do not present diagnostic difficulties. However, if the patient's condition again deteriorates some 3 weeks after the drug is stopped a diagnosis of diazepam withdrawal may be cast in doubt. The combination of the symptoms in groups A and C is, of course, unusual in anxiety states, and these in conjunction with three specific observations should distinguish diazepam withdrawal from anxiety. First, the tremor in diazepam withdrawal is palpable, Quinquaud's sign being evident, whereas the tremor in anxiety states is not. Second, it is unusual in anxiety states to find myoclonus as severe as we observed, particularly when the patient is asleep. Myoclonus was recorded for almost all of our subjects throughout the period of withdrawal. Third, a test dose of benzodiazepines will relieve the symptoms of diazepam withdrawal, whereas a nonbenzodiazepine tranquillizer such as hydroxyzine has little effect. Both types of drugs modify the symptoms in anxiety states.

Physicians should also consider the possibility that patients receiving long-term diazepam treatment who complain of episodes of anxiety may be suffering from intermittent withdrawal symptoms. Characteristically such patients have reduced their dose of diazepam after being symptom-free for a period. A week or so later their condition apparently recurs, so the previous dosage is resumed and they obtain relief. Sometimes the dose of the drug has not changed, yet the symptoms reappear, causing the dose to be raised until they disappear. Awareness of the unusual pharmacokinetics of diazepam and the prolonged and changing nature of its withdrawal syndrome will help the physician recognize this condition.

We wish to acknowledge the assistance given by the nurses in the psychiatric unit at St. Clare's Hospital, who scored the subjects' symptoms and signs. We are especially grateful to Judith Marshall, who developed the methods for nursing the patients.

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On the cover of this issue of *CMAJ* is "Winter Landscape" by Marc Aurèle de Foy Suzor-Côté (1869–1937). Suzor-Côté, a Canadian painter and sculptor, studied at l'École des Beaux Arts and the Julian and Colarossi academies in France. He won the grand prize at the Paris Salon in 1898 for his "Death of Archimedes". Returning home in 1908, he introduced impressionism to French Canada by adapting this European style to a French Canadian context. He was elected an associate of the Royal Canadian Academy of Arts in 1912 and a member in 1914. An open river or stream wending its way through the snow and ice was one of his favourite themes. "Winter Landscape", painted in 1909, is a scene from the Nicolet River near Suzor-Côté's home town of Arthabaska, PQ. This painting is reproduced courtesy of the National Gallery of Canada, Ottawa. It was a gift to the gallery in 1943 from Senator Arthur C. Hardy, of Brockville, Ont.