Withdrawal from long-term benzodiazepine treatment

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Abstract

Long-term, normal-dose benzodiazepine treatment was discontinued in 16 patients who were suspected of being dependent on their medication. The withdrawal was gradual, placebo-controlled, and double-blind. All the patients experienced some form of withdrawal reaction, which ranged from anxiety and dysphoria to moderate affective and perceptual changes. Symptom ratings rose as the drugs were discontinued, but usually subsided to prewithdrawal levels over the next two to four weeks. Other features of the withdrawal included disturbance of sleep and appetite and noticeable weight loss. Electroencephalography showed appreciable reduction in fast-wave activity as the drugs were withdrawn, and an improvement in psychological performance was recorded by the Digit Symbol Substitution Test.

Because of the risk of dependence on benzodiazepines these agents should probably not be given as regular daily treatment for chronic anxiety.

Introduction

Benzodiazepines are widely used in medical and psychiatric practice. They are clinically effective, relatively free of serious side effects, and carry a low suicidal potential. Several surveys have suggested that about one in 10 men and one in five women take tranquillisers or hypnotics, mainly benzodiazepines, at some time during each year. Of these, between a half and two-thirds take tranquillisers for at least a month at a time. On any day or night of the year some 2% of adults take tranquillisers.[1 2] Until recently over 4% of all prescriptions were for diazepam alone.[3] The commonest drugs on repeat prescriptions are the benzodiazepines. Such widespread and chronic use is to be expected with common, recurrent, or continuing conditions such as anxiety states, tension, insomnia, and vague psychosomatic complaints.[4 5]

Recently the dependence potential of benzodiazepines has become an issue of considerable interest. It is well known that excessive doses of benzodiazepines over prolonged periods can lead to physical dependence and a characteristic withdrawal syndrome.[6-8] In some cases the changes on withdrawal of normal therapeutic doses are, however, indistinguishable from those on withdrawal of high doses, both in quality and in quantity.[9] We report a placebo-controlled, double-blind study of withdrawal from prolonged, normal-dose benzodiazepine treatment.

Patients and methods

We included in the study all patients presenting with a presumptive history of benzodiazepine withdrawal problems. Sixteen patients (nine men, seven women) were withdrawn from therapeutic-dose, long-term benzodiazepine treatment. Ten were studied as outpatients and six as inpatients. Their psychiatric diagnoses were anxiety neurosis, depression, or personality disorder with anxiety, and none were alcoholic or took other drugs. All had received benzodiazepines in therapeutic doses for at least one year (range 1-16 years). Ten were taking diazepam (mean daily dose 16·6 mg, range 10-30 mg), four had received lorazepam (mean daily dose 5·25 mg, range 1·0-7·5 mg), and two were taking clobazam 30 mg daily.

Withdrawal symptoms and numbers of patients experiencing them

	No of cases		No of cases
Anxiety, tension	16	Loss of appetite	9
Agitation, restlessness	16	Nausea, dry retching	9
Bodily symptoms of anxiety	16	Depression	8
Irritability	9	Perspiration	7
Lack of energy	6	Metallic taste, hyperosmia	12
Impaired memory and concentration	4	Blurred vision, sore eyes, photophobia	9
Depersonalisation, derealisation	4	Incoordination, vertigo	9
Sleep disturbance	16	Hyperacusis	6
Tremor, shakiness	13	Paraesthesia	5
Headache	12	Hypersensitivity to touch, pain	4
Muscle pains, aches, twitchings	10	Paranoid reaction	2

Patients were informed that at some stage during the study their medication would be replaced by identical-looking placebos. The withdrawal was gradual, double-blind, and placebo-controlled. The patients were recruited over one year and allocated at random to two groups, A and B. Both groups continued with their drugs, at full dosage, for the first two weeks; group A was then reduced to half the dose for a further two weeks before the medication was discontinued. Group B received the full dose of their medication for the first four weeks, but were then withdrawn in the same manner as group A—that is, two weeks later. During these phases placebo was substituted for the active drugs, and after withdrawal of the drugs both groups continued on placebo only for four and two weeks respectively, followed by two weeks without any tablets or capsules. During the study, which lasted 10 weeks, patients were assessed at regular intervals of three, four, or seven days using a battery of clinical, physiological, and psychological tests. Plasma concentrations of the benzodiazepines and any pharmacologically active metabolites were measured by a modified radioreceptor-binding technique[10] (expressed as ng/ml, diazepam equivalents).

Data analysis—All the patients completed the full study period, though a few recording occasions were missed by five patients. In these cases fitted means were used in the statistical analysis. Results on the first and second occasions varied considerably because of patients being unaccustomed to laboratory procedures. These were therefore combined in the analysis and on graphs. Analyses of variance with repeated measures were computed and trend analyses used where appropriate. As patients differed in types of drugs and dosage, results of drug activity in plasma are expressed as percentage change from baseline measurements. All other graphs indicate change scores from baseline values. Critical differences in mean values within groups were assessed from the error variance in the analysis of variance.

Results

Plasma drug activity—Figure 1 shows the mean percentage changes in plasma drug activity during the withdrawal. The two lines are roughly parallel and correspond with the design of the study—that is, members of group A having their medication discontinued two weeks ahead of group B. Diazepam and clobazam and their active metabolites were still detectable in plasma two to three weeks after the drugs had been stopped, reflecting the long half lives of desmethyldiazepam and desmethylclobazam. In one case of lorazepam withdrawal, active drug was detected in the plasma after two weeks, despite the shorter half life of this drug.

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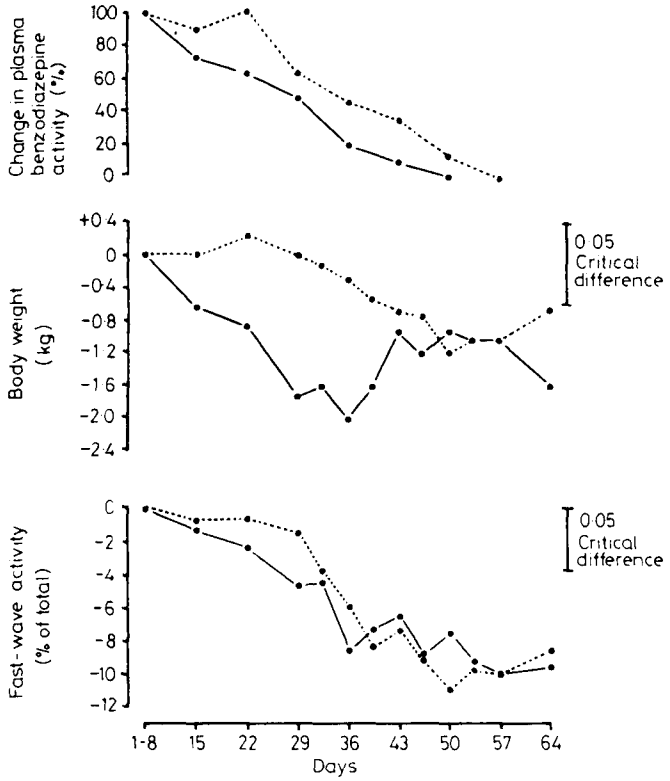

FIG 1—Mean changes in plasma drug activity, body weight, and electroencephalographic fast-wave activity (13·5-26·0 Hz) in groups A (●———●) and B (●— — —●) during withdrawal of benzodiazepine (group A full dosage first two weeks, half-dosage next two weeks, drug withdrawn; group B full dosage first four weeks, half-dosage next two weeks, drug withdrawn). Within each group critical differences further apart than shown are significant at 5% level or more.

Weight—Initially the mean body weight in group A was 63·7± SD 6·0 kg and in group B 64·9±5·8 kg. Weight changes were most pronounced during the phase of drug withdrawal and were maximal seven to 11 days after the drugs had been discontinued. At that time there was a mean reduction of body weight of 2·1 kg (3·3%) in group A and 1·2 kg (1·8%) in group B. On the 64th day the patients had on average regained roughly half their weight loss.

Electroencephalographic fast-wave activity—Both groups showed decreases with time in the percentage of the electroencephalographic voltage occurring in the fast-wave band (13·5-26·0 Hz) ($p < 0·0001$). The mean percentage for this variable was 36·9% (SEM 3·1%) for group A, and 40·6% (SEM 2·4%) for group B at the baseline measure. This declined by about a quarter on withdrawal.

Hamilton Anxiety Rating—Figure 2 shows the mean change scores of the Hamilton Anxiety Ratings in each group plotted against time. Anxiety symptoms were mild before reduction of the drugs but rose to a peak three to seven days after the medication had been stopped ($p < 0·03$). The pattern of the curves was roughly similar in both groups, with group A peaking 10 days ahead of group B, and the high anxiety values gradually resolving over the next two to four weeks.

Psychological performance—Improvement in coding performance was judged by the Digit Symbol Substitution Test (a subtest of the Wechsler Adult Intelligence Scale). Figure 2 shows the change in mean number of items completed in 90 seconds. The basal scores were 46·0 (±3·7 SEM) and 49·9 (±2·9) for groups A and B respectively, and had improved by 31·0% and 34·4% respectively on the 64th day. The improvement on this variable with time was significant for both groups ($p < 0·0001$).

Withdrawal symptoms—All the patients had some form of withdrawal reaction. The table lists the main withdrawal symptoms and numbers of patients complaining of them. Anxiety rose sharply during withdrawal, and to a point of panic in several patients. Patients commonly experienced bodily symptoms of anxiety, such as choking feeling, dry mouth, hot and cold, legs like jelly, etc. Several became irritable and a few complained of unpleasant feelings of depersonalisation and derealisation. All experienced significant sleep disturbance, sleeping only two to three hours a night during the first three or four days of drug withdrawal, and most having returned to normal sleep patterns eight to 10 days after discontinuation. Some experienced hand tremor and profuse perspiration, and others had severe headaches and generalised aches and pains. More than half of the patients lost their appetite and felt nauseous, and a few vomited in the mornings. Clinical depression was detected in eight patients but this was neither severe nor prolonged.

More important, a substantial number of subjects had mild to moderate perceptual disturbances. Some complained of intolerance to loud noises and bright lights, numbness, paraesthesia, unsteadiness, and a feeling of motion. Others complained of strange smells and a metallic taste; some chronic heavy smokers even had to give up cigarettes temporarily.

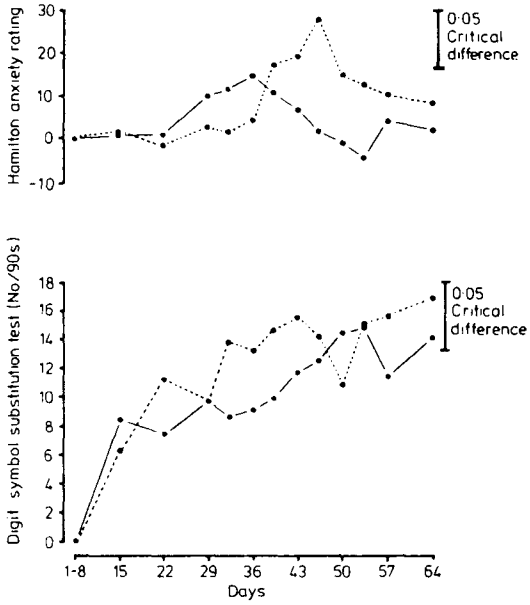

FIG 2—Mean Hamilton Anxiety Rating scales and results of Digit Symbol Substitution Test in group A (●———●) and B (●— — —●) during withdrawal of benzodiazepine (group A full dosage first two weeks, half-dosage next two weeks, drug withdrawn; group B full dosage first four weeks, half-dosage next two weeks, drug withdrawn). Within each group critical differences further apart than shown are significant at 5% level or more.

Discussion

All of these patients had some form of withdrawal reaction, which was most pronounced three to seven days after stopping the medication. More important, perhaps, the changes on withdrawal were in most cases indistinguishable from those on withdrawal of higher doses in other patients, both in quality and in quantity.[9] Patients suffered appreciable weight losses, though it is not clear whether this was due to anorexia or some other metabolic disturbance resulting from the drug withdrawal. Anxiety ratings rose as the drugs were discontinued, but usually subsided to prewithdrawal values over the next two to four weeks. This in itself suggests that the symptoms represent a true withdrawal syndrome and not a revival of the original anxiety symptoms. If the affective changes were merely a return of the original symptoms, we should have expected them to persist at their peak value, as no medication was given. Furthermore, some of the symptoms were quite untypical of anxiety. The dysphoria was an amalgam of anxiety, depression, malaise, and depersonalisation, and perceptual changes were common. Certain other symptoms such as lack of co-ordination and unsteadiness are not characteristic of anxiety. Possibly the dependence was psychological, though the placebo substitution and blind procedures makes this unlikely. Further support for dependence was that many patients had attempted to stop their medication, and on each occasion withdrawal symptoms were alleviated by reinstatement of the drugs.

Physiologically the electroencephalographic changes comprised pronounced reduction in fast-wave activity as the drugs were withdrawn. This drug-related effect is the reverse of the increase normally seen after administration of benzodiazepines.[11] We have also observed that auditory-evoked responses to clicks increase from very small prewithdrawal values to normal values over the same time. These effects may reflect psychological variables such as attention and arousal, and could be regarded as objective indicators of the hypersensitivity reported by many patients.

Psychological performance improved with time, as shown by the Digit Symbol Substitution Test. This test is subject to some effect of practice but not usually beyond two or three occasions. Furthermore, the improvement was too large to be explained by this alone. More likely it implies psychological impairment during chronic benzodiazepine ingestion, which suggests that such chronic usage has its drawbacks.

Other reports have generally suggested little concern,[12] but most were on patients who had escalated their dosage. Our findings, like those of other recent reports,[9 13 14] show that patients taking benzodiazepines in therapeutic doses risk developing some form of dependence.[15] We emphasise, however, that our patients were long-term users of benzodiazepines and were self-selected, in that they were referred because of their inability to stop their medication. Hence the present cohort may not be representative of benzodiazepine users generally, an issue which will be resolved only with proper epidemiological studies. Nevertheless, detecting withdrawal symptoms in patients taking normal therapeutic doses increases the urgency of the problem and argues against regular daily medication for chronic anxiety. Many thousands of patients may be at risk, as some 2% or so of the adult population take benzodiazepines chronically.

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SHORT REPORTS

Calcification of radiolucent gall stones during treatment with ursodeoxycholic acid

Both chenodeoxycholic acid and ursodeoxycholic acid reduce the cholesterol saturation index of bile and induce the dissolution of cholesterol gall stones in man. Ursodeoxycholic acid has been described[1] as the treatment of choice because it is effective at a lower dose and is free from side effects such as diarrhoea. The solubility of conjugates of ursodeoxycholic acid in bile is inferior to that of conjugates of chenodeoxycholic acid, and Igimi *et al*[2] predicted that precipitation of glyco-ursodeoxycholic acid could occur during treatment with ursodeoxycholic acid. This phenomenon would probably be associated with the precipitation of calcium, possibly as calcium glyco-ursodeoxycholate. We report calcification of gall stones in six patients during treatment with ursodeoxycholic acid.

Patients, methods, and results

Altogether 178 patients with radiolucent stones in radiologically functioning gall bladders were treated with chenodeoxycholic acid (122 patients) or ursodeoxycholic acid (56) for six months or more. The response to treatment was assessed in all patients by repeating oral cholecystography at six-monthly intervals. Calcification of the gall stones was assessed by radiologists who were unaware of which treatment had been given.

Six of the 56 patients given ursodeoxycholic acid developed calcification: in four patients this occurred within six months and in two within 12 months. None of the patients treated with chenodeoxycholic acid showed any evidence of calcification; this difference between the treatments was significant ($p < 0.002$, Fisher's exact test).

In four of the patients receiving ursodeoxycholic acid who developed calcification bile samples were obtained before and during treatment. Before treatment ursodeoxycholic acid (measured by gas-liquid chromatography combined with enzymatic assay) constituted 0-3·8% of the total bile acids, and the proportion increased to 32·3-85·8% during treatment, 75-97% being conjugated with glycine. One gall stone that showed radiological calcification during treatment was removed surgically and subjected to chemical analysis. The different constituents of the stone expressed as the percentage of the total weight of the stone were cholesterol (94%), glyco-ursodeoxycholic acid (2·3%), other bile acids (2·3%), calcium salts (1%), and unidentified matter (0·4%). Glyco-ursodeoxycholic acid and calcium salts were found mostly in the outer surface of the stone. Further analysis by the *x*-ray powder diffraction method confirmed that most of the calcium was in the outer surface of the stone and that it was not in the form of calcium bilirubinate. It was not possible to confirm that it was in the form of calcium glyco-ursodeoxycholate.

Comment

Six out of 56 patients with radiolucent gall stones who received ursodeoxycholic acid but none out of 122 patients who received chenodeoxycholic acid developed gall-stone calcification. The possibility of calcification during treatment with ursodeoxycholic acid should therefore be borne in mind when choosing which bile acid to use for medical dissolution of cholesterol gall stones, since calcification of gall stones renders bile-acid treatment ineffective.[3]

We are grateful to our various radiological colleagues for assessing gall-stone calcification. We are also grateful to Dr June Sutor for analysing one of the gall stones by the *x*-ray powder diffraction method. We thank Weddel Pharmaceuticals for supplies of chenodeoxycholic acid (Chendol) and Giuliani Company, Tokyo Tanabe, and Lepetit Pharmaceuticals for supplies of ursodeoxycholic acid.

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