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BRIEF COMMUNICATION

Computed axial brain tomography in long-term benzodiazepine users

M. H. LADER,[1] M. RON AND H. PETURSSON
From the Institute of Psychiatry, London

SYNOPSIS Twenty patients who had taken long-term benzodiazepines were submitted to brain CT scan examinations. Some scans appeared abnormal. The mean ventricular/brain area measured by planimetry was increased over mean values in an age- and sex-matched group of control subjects but was less than that in a group of alcoholics. There was no significant relationship between CT scan appearances and the duration of benzodiazepine therapy. The clinical significance of the findings is unclear.

INTRODUCTION

Several surveys in different countries have concurred that about 1 in 10 adult males and 1 in 5 adult females take tranquillizers or hypnotics, mainly benzodiazepines, at some time during the course of each year. About 1·5% of the adult population take these drugs chronically throughout the year and 0·7% have taken these drugs for over 7 years (Balter *et al.* 1974; Lader, 1978; G.D. Mellinger, personal communication).

Normal-dose benzodiazepine dependence as evidenced by a specific withdrawal syndrome has been demonstrated by us (Petursson & Lader, 1981) and by others (Tyrer *et al.* 1981; Rickels, 1981). Relatively few patients become tolerant and escalate their dosage to levels so high that the prescriber suspects dependence. However, after prolonged use (6 months or more) at normal doses, a withdrawal reaction may occur, characterized by anxiety and insomnia, bodily changes such as tremor, sweating and palpitations, and perceptual changes such as photophobia, hyperacusis, paraesthesiae, strange smells and tastes. The incidence of benzodiazepine dependence remains unknown, but may be a factor in perpetuating chronic use.

One acute unwanted effect of benzodiazepines is psychological impairment seen in normal subjects and after short courses of treatment in anxious patients (McNair, 1973). Almost nothing is known of any such deficit during long-term treatment, it being generally assumed that tolerance occurs to the acute impairment. However, our patients withdrawing from benzodiazepines improved their performance, suggesting that selective impairment may persist even after years of drug ingestion. Simple repetitive tapping (a motor test) improved on drug withdrawal and psychomotor test performance, such as digit-symbol substitution and symbol copying, was significantly depressed as compared with that in an age- and sex-matched group of normals. Other tasks, such as digit cancellation and reaction-time, were not affected (Petursson *et al.* 1984).

Structural brain abnormalities have been described in conjunction with cognitive impairment in subjects who have abused alcohol for prolonged periods (Ron *et al.* 1982). The present preliminary study was prompted by the possibility of such abnormalities being present in benzodiazepine users in some of whom cognitive impairment was detectable during withdrawal. The advent of computerized tomography (CT scan) allowed us to study a group of such subjects and to compare them with normal controls and with chronic alcoholics.

MATERIALS AND METHODS

Subjects

Twenty patients receiving or recently withdrawn from long-term benzodiazepine treatment were

[1] Address for correspondence: Professor M. H. Lader, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF.

Table 1. *Clinical characteristics of patients treated with long-term benzodiazepine therapy*

Sex	Age	Main drug involved	Usual daily dose (mg)	Years on benzodiazepines	Diagnosis
M	23	Lorazepam	2	3·5	Anxiety state
M	40	Diazepam	20	11	Personality disorder, anxiety state
F	49	Diazepam	10	7	Insomnia
M	37	Clobazam	60	16	Anxiety state
M	43	Diazepam	15	11	Personality disorder, anxiety state
F	35	Lorazepam	5	6	Anxiety state
M	42	Diazepam	15	6	Anxiety state
F	49	Lorazepam	3	12	Personality disorder, anxiety state
M	58	Lorazepam	3	20	Anxiety state
F	40	Lorazepam	7·5	2·5	Anxiety state
F	38	Lorazepam	4	10	Personality disorder, anxiety state
M	27	Diazepam	6	7	Anxiety state
F	37	Lorazepam	2	12	Anxiety state
M	76	Diazepam	15	20	Anxiety with depression
M	34	Lorazepam	7·5	13	Anxiety state
M	50	Diazepam Lorazepam	10 1	8	Personality disorder, anxiety state
M	59	Clobazam	30	16	Depression with anxiety
M	63	Lorazepam	7·5	14	Anxiety state
F	34	Lorazepam	7·5	6	Anxiety state
M	32	Diazepam	15	10	Personality disorder, anxiety state

studied with detailed clinical assessments (Table 1). Doses were within the therapeutic range, i.e. up to 30 mg/day of diazepam or equivalent. Nine patients were scanned at an average of 3 months following withdrawal of the drugs, as previously described by Petursson & Lader (1981). Eleven patients were investigated while still receiving their treatment. The total group comprised 7 women and 13 men, mean age 43·3 years. Diagnoses included anxiety, personality disorder with anxiety, insomnia and depression, and none abused alcohol or took other drugs. The mean (±S.D.) duration of their benzodiazepine treatment was 10·6 years (±4·8). Two groups of 19 were used for comparison, normal controls and alcoholics. Their records were available from a series of subjects already reported (Ron *et al.* 1983). Subjects were selected by age and sex to match the benzodiazepine users. Where choices of controls or alcoholics were available, the selection was random.

Method

Patients and controls were scanned, using an EMI CT1010 head scanner. Five or 6 contiguous pairs of slices were taken parallel to the orbito-meatal line. The scans were first reported on routinely by the neuroradiologists. Later, all the scans, including those of the comparison groups, were analysed 'blind' by a senior radiologist. CT scan measurements were made using the photographic negatives and CT scan indices were made using the procedure described by Ron *et al.* (1983) and provided the following estimates:

Sulcal widening was rated on a 4-point scale (0–3), 0 representing normality and 3 gross widening.

Sylvian fissure widening was rated on a 3-point scale (0–2).

Interhemispheric fissure widening was rated as absent or present.

A composite 'cortical score' was obtained by adding these 3 scores.

Ventricular area was expressed as a percentage of the total area within the inner table of the skull. The measurements were made with a Stanley Allbrit planimeter in two contiguous slices showing the maximum ventricular area. The ventricle/brain ratio (V/B) was the mean of these two ratios.

The interrater reliability of all these measures was very high and similar to that reported by Ron *et al.* (1983). In the statistical analysis only the measurements taken by M.R. were used. Student's *t*-test and linear regression analysis were applied to the data as appropriate, with two-tailed tests of significance throughout.

Clinical data were available from detailed histories of the patients, including an account of

Table 2. *Mean ratio of ventricle/brain area expressed as percentage, number of individuals with abnormal scans, and 'cortical score' in normal controls, long-term benzodiazepine users and alcoholics*

Group	Age (mean ±S.D.)	No. with definitely abnormal scan (sex, age)	Ventricle brain area (%) (mean ±S.E.M.)	'Cortical score' (mean ±S.E.M.)
Normals ($N = 19$)	41·5±10·5	1 (M52)	5·77±0·41	1·4±0·1
BZ users ($N = 19$)+1M 76	41·6±10·5	3 (M34; M32; F39)	7·09±0·46*	1·8±0·2†
Alcoholics ($N = 19$)	41·4±10·6	3 (M58; M40; F40)	9·22±0·63**	2·8±0·3**

Difference from normals: $*P < 0·05$; $**P < 0·001$.
Difference of BZ users from alcoholics: †$P < 0·05$.

drug and alcohol use, previous illnesses including head injuries etc.

RESULTS

Definite abnormalities were reported by the radiologist in 3 benzodiazepine users, as compared with 1 control and 3 alcoholics (Table 2). The abnormalities comprised ventricular enlargement, widening of sulci, Sylvian and interhemispheric fissures.

Table 2 shows that the V/B ratio of the alcoholics was significantly different from those of the normals ($P < 0·001$). The results for the benzodiazepine group were, on average, intermediate between but significantly different from those of control subjects ($P < 0·05$), and those of the alcoholics ($P < 0·02$). Table 2 shows that the mean±S.E.M. of the ventricle/brain ratio of the normal controls was 5·77±0·41. One normal subject, 10 alcoholics and 2 benzodiazepine users had values above the normal mean +2 S.D.s (9·4, see Fig. 1).

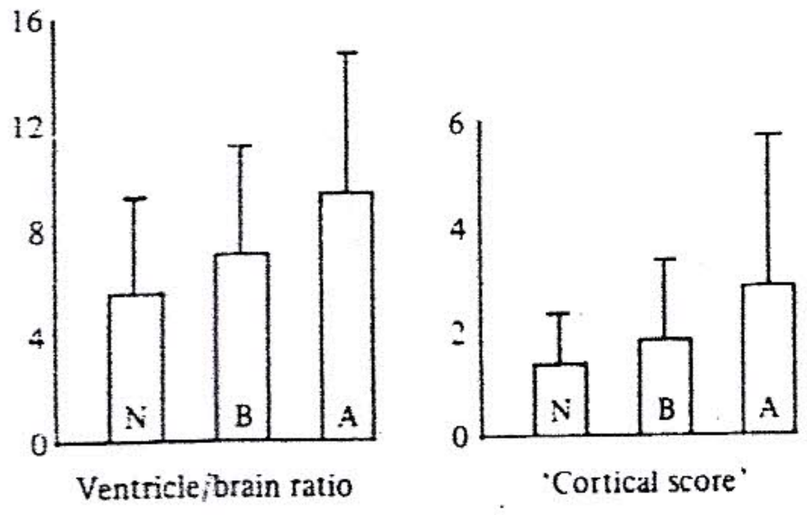

FIG. 1 Ventricle/brain ratio (%; ±2 S.D.s) and 'cortical score' (±2 S.D.s) in normals (N), benzodiazepine users (B) and alcoholics (A).

Among the benzodiazepine users the ventricle/brain ratios were significantly larger in males than in females ($P < 0·05$), but there was no correlation with age ($r = 0·05$, NS), or with duration of previous benzodiazepine usage ($r = 0·03$, NS). Furthermore, there was no significant difference between those patients on or off their medication.

Table 2 presents the mean 'cortical scores' for the groups. The mean score for the alcoholics was significantly higher than those for the controls and for the benzodiazepine users. One-quarter of the controls, 45% of the drug users and just over half the alcoholics had positive 'cortical scores'.

The mean age of those benzodiazepine users who had positive 'cortical scores' was 51·6 years (±13·2), compared with 36·5 (±6·7) for those with no demonstrable abnormalities ($P < 0·01$). The 'cortical score' was positively correlated with age ($r = +0·47$, $P < 0·05$). However, as in the case of the planimetric data, no correlation was found between the duration of previous benzodiazepine usage and the 'cortical score' ($r = 0·23$, NS). Again, for the benzodiazepine group, scores were primarily evident among the men, 8 out of 13 (61·5%), compared with only 1 case among the 7 women.

DISCUSSION

The benzodiazepine users, as a group, had larger ventricle/brain ratios than the controls but less than that of the alcoholics. About half of the patients' scans had positive 'cortical scores' as compared with only a quarter of controls. This is surprising, in view of the relatively young ages of most of our patients.

Scan appearances for the benzodiazepine patients were intermediate between those of the control subjects and those of the alcoholics. One possibility is that benzodiazepines taken on a long-term basis result in radiological changes. Another is that individuals with radiological changes due to other causes are prone to develop anxiety states which only respond to sedatives, and consequently drug therapy becomes prolonged. The abnormalities seen in alcoholics tend to improve during abstention. The benzodiazepine withdrawal syndrome is usually associated with a loss of body weight (Petursson & Lader, 1981), perhaps due to loss of fluid. However, the present study did not reveal any significant differences between those patients still receiving benzodiazepine treatment, and those who had been withdrawn.

Although age correlated significantly with the 'cortical score', there was no correlation between the planimetric data and age. This is consistent with results of some other studies (Jacoby *et al.* 1980). Although our detailed evaluation of the benzodiazepine users excluded long-term alcohol abuse, it is possible that some patients resorted to alcohol sporadically. The reverse might apply to our alcoholic group, although persistent drug use was an exclusion criterion in the original study. In view of the known potentiation of alcohol and benzodiazepines in other areas, this possibility needs further investigation.

The finding of no association between radiological changes and the duration of previous benzodiazepine therapy leaves the clinical significance of these findings unclear. In view of the very extensive and often prolonged use of the benzodiazepines in normal dosage in therapeutic practice, with or without alcohol, it is important to establish the nature, extent and reversibility of functional and structural brain changes by relating them to clinical factors and to detailed neuropsychological testing. Such a study is in progress.

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