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Stress and epilepsy: the value of a benzodiazepine – lorazepam

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SUMMARY Twenty four patients with drug resistant epilepsy were given lorazepam and placebo added to their pre-existing drug regime. With lorazepam there was a significant reduction in seizures, especially in those with focal and partial complex attacks. The drug proved effective whether or not the patients regarded stress as a trigger to their seizures, but on the Middlesex Hospital Questionnaire there were differences between those with high and low scores.

Many patients with epilepsy complain that various forms of stress precipitate seizures, of which there have been anecdotal reports and occasional studies.[1] The present investigation was carried out in an attempt to clarify this issue, using the benzodiazepine, lorazepam, because of both the anticonvulsant and anxiety reducing effects of the drug. It is of proven value given intravenously in status epilepticus[2] and can control by this route EEG paroxysms in patients with seizure disorders where there are no overt clinical manifestations.[3] The aim of the study was to compare oral lorazepam in a small dose, or placebo, added to the pre-existing anticonvulsant regime of patients with drug resistant epilepsy of long standing. Their pre-trial drug dosage remained unchanged throughout the investigation. A variety of tests were used to study the psychological state, including the Middlesex Hospital Questionnaire (MHQ),[4,5] specially devised visual analogue scales, and quantitative assessment of whether stress precipitated attacks.

Method and materials

The 24 patients had been under surveillance over several years in an epilepsy clinic, always seen by one of us (DFS), and the nature of the fits and other factors were well known. The diagnosis of the disorder was as complete as possible with EEG and other investigations, such as the CT scan. The anticonvulsant blood levels were within the accepted therapeutic range before the patients were admitted to the study. The purpose of the investigation was explained and only those individuals who indicated their agreement, took part.

There were 14 males and 10 females with an average age of 36 years. Ten had partial complex seizures (temporal lobe epilepsy), eight primary generalised fits and six focal epilepsy starting from other sites (See table 1). Originally 28 patients entered the study, but four were excluded because they failed to comply with the trial design. The seizure disorders were chronic in all patients (table 2) with an overall average duration of 22·5 years. They were all receiving very complex drug regimes when first referred to the epilepsy clinic. These were simplified but even so only seven were eventually receiving single drugs, when the study started. Eleven patients were on sodium valproate, 10 were taking carbamazepine and a similar number phenytoin. Eight received the commonest combination, namely carbamazepine and sodium valproate. Other drugs were used in the combinations but only one patient was taking phenobarbitone.

At the pre-treatment assessment, patients were given questionnaires to determine on a graduated scale, whether stress precipitated their seizures, and whether or not they regarded themselves as tense. Apart from interview, visual analogue scales were given to determine such features as, for example, problems with sleep or depressive symptoms. In addition the Middlesex Hospital Questionnaire[4,5] was used to determine the presence of neurotic symptomatology; the sub-tests are free floating and phobic anxiety as well as somatic, depressive, hysterical and obsessional features. The patients were divided into high and low scorers using a cut-off point of 45, giving 13 patients in the high and 11 in the low group. An EEG was also performed. The study was a double blind, cross-over using lorazepam 1·0 mgs. or placebo, randomly assigned, each for 6 weeks. Subsequently at the end of the 3 month period, patients reporting benefit from the treatment were given oral lorazepam routinely in the same dose. There was no "wash-out" period, and no difficulties arose during the cross-over from drug to placebo or vice versa. The results of the various assessments were analysed using non-

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Table 1 *Patients studied (numbers by type of epilepsy, age range (yr) in brackets. Males 14, Females 10)*

	Partial complex	*Focal*	*Primary generalised*
Males	6 (18–62)	5 (20–51)	4 (28–56)
Females	4 (31–48)	1 (18)	4 (28–50)
	Average 36 years		

Table 2 *Average duration of epilepsy in years*

	Partial complex	*Focal*	*Primary generalised*
Males (n = 14)	13·0	15·6	22·0
Females (n = 10)	11·5	11·5	14·0
Average seizures	12·4	14·3	18·0
	Overall average 22·5 years		

parametric methods including the Mann Whitney U test and the Wilcoxon matched-pairs signed-rank test.

Results

There was a highly statistically significant reduction in fits during the treatment with lorazepam ($p < 0.001$) compared with placebo, and with the pre-treatment seizure frequency. A definite decline was also noted when the pretreatment and placebo periods were compared ($p < 0.05$).

Considering the decrease in seizure frequency for the different forms of epilepsy (table 3), patients with focal epilepsy and partial complex seizures showed the greatest reduction. Significantly less fits were recorded in the lorazepam period compared with the pre-trial period ($p < 0.001$) and compared with placebo ($p < 0.01$). There was no significant difference between placebo and the pre-trial fit frequency. In the primary generalised group a significant reduction from the pre-trial values occurred while on lorazepam ($p < 0.01$), and on placebo ($p < 0.05$), but no significant difference between lorazepam and placebo was noted. This is probably due to the fact that some patients in this seizure group were fit free throughout the whole 3 months of the study.

The patients who were fit free during the study, had each had seizures in the 6 week period prior to the commencement of the investigation, on average 3·4 (see table 3). Following the first 6 weeks of "treatment", six were fit free after lorazepam, and five after placebo. This contrasts with the result after the 2nd period of "treatment" when eight had no seizures, and only two following placebo. No difficulties were encountered in the cross-over period.

The patients were divided into two categories on the basis of whether or not the majority of their fits were triggered by stress. There was for both categories a significant reduction in seizures ($p < 0.05$), when the active drug was given. With placebo little difference was noted in this period compared with the pre-trial values. Those patients who said they were not tense still had a significant reduction in attacks with lorazepam ($p < 0.001$) compared with placebo, and the pre-treatment period. There was also a decrease in the same direction for tense patients, but the effect of lorazepam was less marked.

Table 3 *Average fit frequency before the trial (B), with lorazepam (L) and placebo (P). (Note this was not the order of administration)*

	Partial complex			*Focal*			*Primary generalised*		
	B	*L*	*P*	*B*	*L*	*P*	*B*	*L*	*P*
Males (n = 14)	6·7	2·0	6·3	49·0	12·5	43·5	3·8	0·0	2·0
Females (n = 10)	9·0	2·0	5·0	7·5	2·7	9·3	7·2	0·0	1·8
	Overall average 3·4 fits per 6 weeks								

The Middlesex Hospital Questionnaire scores were compared in relation to improvement with treatment. The patients, irrespective of whether high or low scorers showed a significant reduction during lorazepam compared with the pre-treatment period ($p < 0.001$). However, when comparing the two groups taking placebo only the high scorers showed a reduction in fit frequency ($p < 0.05$). Both groups had fewer attacks on lorazepam compared with placebo. The significance value for the high scorers was ($p < 0.01$) and the low scorers, ($p < 0.05$).

There was no systematic change in the EEG paroxysmal features when drug and placebo were compared.

Discussion

This investigation showed that the addition of a small dose of lorazepam to the current regime of patients with long standing epilepsy had beneficial effects. Perhaps surprisingly this was most marked in those with seizures of focal origin. The other anticonvulsants remained unchanged throughout the period of the study. The initial aim was to determine whether, on the basis of psychological scores, it was possible to predict which patients would find an anxiety reducing drug helpful and of value, and conversely those in whom it would prove largely fruitless. We were unable to predict those who would benefit on the basis of the tests used.

One interesting point that emerged was the much

greater response to lorazepam when this was given following placebo, bearing in mind that the design of the study was balanced. This implies that even in patients with epilepsy of very long standing, placebo effects are important; reinforced by the Middlesex Hospital Questionnaire results which showed response to placebo especially in the high scorers. Apart from reduction in fit frequency there was improvement of sleep and in general well being for many patients. Adverse effects of lorazepam, namely complaints of sedation, occurred in two patients who were withdrawn from the study. Otherwise no untoward features were noted. In particular change over from drug to placebo or *vice versa* was not marked by sudden worsening of seizure frequency, though a single patient who reported no benefit from the addition of lorazepam had two seizures within a week of completing the study.

We appreciate that this is a relatively small and heterogenous sample of seizure patients but in spite of this, benefit has accrued and has persisted for some up to a year following the end of the formal study. In conclusion, it appears that lorazepam, as with other benzodiazepines, such as clobazam[6] is useful in the management of chronic epilepsy and particularly for those with partial complex or other focal seizures, who are rightly regarded as the most difficult group to control.

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References

[1] Feldman RG, Paul NL. Identity of emotional triggers in epilepsy *J. Nerv Ment Dis* 1976;**162**:345–53.
[2] Yorka JE, Homan RS, Vasco MR, Crawford IL, Bow RD, Tarska WG. Lorazepam in status epilepticus. *Ann Neurol* 1979;**6**:207–13.
[3] Scott DF, Moffett A. Lorazepam: its effect on the EEG paroxysmal activity in patients with epilepsy. *Acta Neurol Scand* 1981;**64**:353–60.
[4] Crown S, Crisp AH. A short clinical diagnostic self-rating scale for psychoneurotic patients. *Br J Psychiatry* 1966;**112**:917–23.
[5] Crown S, Crisp AH. The Middlesex Hospital Questionnaire clinical research. In: Pichot P, ed. *Psychological Medicine and Psychopharmacology* Basle: Kager, 1974;111–24.
[6] Feely M, Calvert R, Gibson J. Clobazam in catamenial epilepsy: a method of evaluating anticonvulsants. *Lancet* 1982;**2**:71–3.