Rectal diazepam in the treatment of absence status: a pharmacodynamic study

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SUMMARY Rectal administration of diazepam is highly effective in terminating absence status as judged by reduction of spike-wave activity in the EEG. Pharmacokinetic studies indicate that diazepam can have antiepileptic properties at serum levels well below those previously reported as being necessary to achieve a therapeutic effect.

Intravenous diazepam is regarded by most as the drug of first choice in the treatment of status epilepticus.^{1,2} Situations where facilities for intravenous administration are not available necessitate either an alternative route of administration of the same drug or an alternative therapy. For cases less extreme than tonic-clonic status, diazepam given via a route other than intravenous may be appropriate.

Pharmacokinetic studies have shown that absorption of diazepam following intramuscular injection is poor and erratic due to precipitation in the tissues³ and is related to the technique of administration.⁴ This route is therefore unsuitable when a rapid therapeutic effect is required. Rectal administration of diazepam solution in children produces peak serum concentrations within 10-20 min⁵ and is of value in preventing recurrent febrile convulsions.⁶ However, the use of such therapy in adults has been little explored. The value of this alternative route of administration of diazepam is illustrated in a patient prone to frequent absence status where quantification of spike-wave activity in the EEG provided an accurate assessment of a therapeutic response.

Patient and methods

The patient studied was a 35-year-old man, resident at the Chalfont Centre for Epilepsy, who has had epilepsy from the age of 2½ years. He suffered from tonic-clonic fits and frequent absences during which his EEG exhibited generalised atypical 2-2.5 Hz spike-wave activity. The

duration of his absences was highly variable and on occasions they were very prolonged lasting several hours. These were often succeeded by tonic-clonic seizures. EEG monitoring was achieved using the Oxford Medical Systems ambulatory EEG cassette tape recorder (Medilog 4) to which the patient was electively connected whilst well. This he wore continually, though not operating, until an absence status occurred. EEG monitoring was then initiated and treatment given under EEG control. The timing of equipment placement was aided by the clinical course of his epilepsy and the duration of the waiting period ranged from 1-7 days. On two occasions only was the equipment removed without the patient having an absence status.

During prolonged absences the following treatments were administered rectally on six occasions each: diazepam solution (20 mg); diazepam suppository (20 mg); saline. Diazepam (Valium, Roche) solution for intravenous injection and placebo (an equivalent volume of saline) were each injected into the rectum using a 5 ml syringe to which was attached a plastic catheter lubricated with K-Y jelly. The suppositories were an experimental formulation having rapid release characteristics produced by Dr B Winsley, John Radcliffe Hospital, Oxford. Blood samples were withdrawn from an indwelling intravenous catheter at intervals over a 3 hour period for measurement of serum concentrations of diazepam. The procedure was identical for all treatments (including placebo) and the study was conducted single blind. Each taped EEG recording was subsequently coded and analysed blind. Ten min epochs of EEG (5 min either side of the blood sampling times) were written out on paper using the Oxford Medical Systems play back unit (PMD-12) connected to a 4 channel Mingograf ink-jet EEG recorder equipped with a high paper speed facility (30 cm/s). Spike-wave activity was quantitated by eye and the effectiveness of treatment was evaluated on the basis of the amount of

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spike-wave activity in each of the 10 min epochs of EEG after treatment compared to that in 10 min of control EEG before treatment. To obtain a detailed time-course of the onset of action of active treatment each tape was written out on paper continually from 0-30 min and divided into 1 min epochs, spike-wave activity being quantified and expressed as above. The control values were taken as 1/10th of the original 10 min control EEG.

The initial six active treatments were each preceded by a 3 hour placebo study in order to ensure that cessation of absences did not occur spontaneously. Thereafter, it became clear that the course of the type of absences under study was long and continuing. The remaining six active treatments were given only when it was felt that spontaneous cessation was unlikely as judged by continuance of fitting over a period of observation (usually more than 1 hour). The interval between active treatments ranged from 2-34 days (median 7 days) and the duration of the study was 6½ months. Chronic AED therapy was continued unchanged throughout. The significance of differences between treatments was determined using the Mann-Whitney U test and differences between mean serum diazepam concentrations were assessed using Student's *t* test.

Results

Figure 1 shows the results of the spike-wave analysis over a 3 hour period. Both active treatments markedly reduced spike-wave activity, diazepam solution having a more dramatic effect. Unlike the suppository, the effect of the solution tended to wane after 90 min although the values were still significantly different from placebo (table).

Changes in spike-wave activity following both active treatments reflected differences in the rate of rise of diazepam serum concentration (fig 2). The mean serum level at 15 min after the solution was 194 ng/ml (SD ± 66 ng/ml) compared to 58 ng/ml (SD ± 19 ng/ml) after the suppository (*p* < 0.01). Peak serum levels were higher and attained more rapidly after solution (mean 323 ± 107 ng/ml at 50 min) than after suppository (mean 257 ± 50 ng/ml at 58 min) though differences were not significant. The mean serum level at 180 min after the solution (142 ± 28 ng/ml) was significantly lower than after suppository (177 ± 33 ng/ml) (*p* < 0.05) and this corresponded to a significant increase in spike-wave

Fig 1 Results (means of six treatments) of spike-wave analysis over a 3 h period after rectal administration of saline (●—●), diazepam solution 20 mg (▲—▲) and an experimental diazepam suppository 20 mg (△—△). Assessment was by counting spike-wave activity in 10 min of control EEG and in seven 10 min periods following treatment (5 min either side of times shown). Differences from saline (*p* < 0.01) except at 120 min after diazepam solution (*p* < 0.05). Differences between diazepam solution and diazepam suppository at 15 min and 180 min (*p* < 0.05; Mann-Whitney U test).

activity (*p* < 0.05). Differences among serum concentrations at other times were not significant.

As shown in fig 3, both active treatments produced an effect much earlier than 15 min. Reduction of spike-wave activity occurred within the first 5 min, differences between treatments becoming significant at 8 min and persisting until 16 min (*p* < 0.05). Figure 4 shows the same data with serum levels emphasising the relationships between rate of change in serum concentration and reduction of spike-wave activity. Following diazepam solution, spike-wave activity fell to 46% of the control at 5 min (mean serum level 30 ± 15 ng/ml; *n* = 3). A comparable serum concentration was achieved at 10 min after the suppository (mean 34 ± 21 ng/ml) when spike-wave activity was reduced to 24% of the control. Clearly an effect was evident before this time at which point serum levels would have been lower (mean at 5 min 18 ± 11 ng/ml).

Table Spike-wave activity (mean ± 1 SD) in seconds before and after rectal administration of saline and diazepam. Differences from saline (*p* < 0.01) at all points except * (*p* < 0.05; Mann-Whitney U test). Differences between diazepam solution and diazepam suppository † (*p* < 0.05; Mann-Whitney U test). Statistics were done using percentage data

	Control	10-20 min	25-35 min	40-50 min	55-65 min	85-95 min	115-125 min	175-185 min
Saline	371 ± 69	398 ± 163	446 ± 171	347 ± 169	375 ± 204	489 ± 124	368 ± 229	443 ± 175
Diazepam suppository (20 mg)	418 ± 155	67 ± 36	17 ± 24	30 ± 39	32 ± 48	29 ± 47	23 ± 34	18 ± 16
Diazepam solution (20 mg)	537 ± 26	†8 ± 13	24 ± 47	23 ± 32	14 ± 10	26 ± 20	*164 ± 157	†130 ± 131

Fig 2 Spike-wave activity with serum levels of diazepam (means of six treatments) after diazepam solution 20 mg (top) and diazepam suppository 20 mg (bottom). Mean serum levels ($\square$ — $\square$) at 15 min and 180 min significantly different ($p < 0.01$ and $p < 0.05$ respectively; unpaired t test). The lower mean serum concentration at 180 min after diazepam solution coincided with a significant increase (top) in spike-wave activity ($p < 0.05$; Mann-Whitney U test).

Fig 3 Spike-wave activity (means of six treatments) in 1 min epochs from 0-30 min each expressed as a % of the control. The control was 1/10 of the original 10 min control EEG. Diazepam solution ($\blacktriangle$ — $\blacktriangle$) was superior to the suppository ($\triangle$ — $\triangle$) in reducing spike-wave activity between 8 and 16 min ($p < 0.05$; Mann-Whitney U test).

Discussion

Absence seizures have a reputation for being particularly sensitive to benzodiazepines, intravenous diazepam being effective in 93% of cases of absence status compared to 88% of tonic-clonic

Fig 4 Spike-wave activity 0-30 min with serum concentrations of diazepam ($\square$ — $\square$) following the 20 mg solution (top) and the 20 mg suppository (bottom). Serum levels are mean values (diazepam solution 5 min $n = 3$; 10 min $n = 4$; others $n = 6$). Differences between mean serum levels ($p < 0.01$; unpaired t test).

status and 75% of complex partial status.² These results show that rectal administration of diazepam, either as a rapid release suppository or as a solution, is highly effective in terminating absence status as judged by reduction of spike-wave activity in the EEG. Pharmacokinetic studies indicate that diazepam solution is rapidly absorbed from the rectum and an antiepileptic effect is evident within 5 min. Serum concentrations of N-desmethyldiazepam were negligible indicating that the results were not due to a cumulative effect. Diazepam suppositories provide a more convenient mode of administration but serum levels are lower and rise more slowly than after an equivalent dose of the solution even with the rapid release formulation used. It should be noted that the wax-based suppositories now commercially available (Valium, Roche) are very slowly absorbed and are unsuitable for clinical use when a rapid therapeutic effect is required.

Administration of both agents per rectum to volunteer patients with epilepsy show marked variations in serum diazepam levels achieved between subjects (Dhillon *et al*, unpublished) and this may prove a limiting factor in their use. The bio-availability of diazepam solution given rectally is almost complete,⁷ although others express a more conservative estimate and suggest that adsorption to

faeces or loss of the drug through the anus may account for incomplete absorption.³ The serum level of diazepam required to achieve an antiepileptic effect is uncertain, however, and interpretation of serum levels achieved is difficult as the benzodiazepines are lacking a well established therapeutic range. The minimum effective serum concentration has been variously estimated, values between 150-500 ng/ml being suggested as therapeutic,⁸⁻¹⁰ although the methods of determination are open to criticism. Such estimates have often been based on recurrence of seizures or interictal epileptiform abnormalities in the EEG following initial suppression with intravenous diazepam. The results of our study show that diazepam can have antiepileptic properties at serum levels well below those previously reported. However, there was no clear relationship between therapeutic effect and serum concentration. The point at which spike-wave activity reappeared occurred at serum levels well above those necessary to induce an effect. It is perhaps the rate of increase in serum concentration, and therefore rapid penetration into the brain, which is more important than the concentration *per se*. Previous estimates of a minimum effective serum concentration based on recurrence of EEG abnormalities may therefore not be truly representative. Evaluation of the subjective sedative effects of the drug in other studies^{11 12} tend to support this view. Our results, however, are limited in that this is a single case study. The difficulties in obtaining pharmacodynamic data during clinical seizures are self evident. Whether this form of treatment will be of value to other patients with different seizure types requires further work. Studies along these lines are in progress.

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