CLOBAZAM: ANTICONVULSANT ACTION IN ANIMAL MODELS OF EPILEPSY

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THE 1,4-benzodiazepines include the most potent anticonvulsant agents in clinical use. However, the clinical value of, for example, diazepam and clonazepam is not as great as might be expected from their potency in acute test systems. This is because of (a) neurological side-effects, which include psychomotor impairment, apathy and muscular hypotonia and (b) re-appearance of seizures after a few weeks or months of therapy (Browne, 1976; Edwards & Eadie, 1973; Korttila & Linnoila, 1975).

Several studies in man and experimental animals suggest that the neurological effects of the 1,5 benzodiazepine, clobazam (1-phenyl-5-methyl-8-chloro-1,2,4,5-tetrahydro-2,4-diketo-3H-1,5-benzodiazepine) differ from those of the corresponding 1,4 benzodiazepine, diazepam (Borland & Nicholson, 1975; Rigal & Savelli, 1975; Hindmarch *et al.*, 1977; Nicholson, 1979; Fielding & Hoffmann, 1979). In particular, the impairment of performance in complex psychomotor tasks observed after diazepam is less, or absent, after clobazam. Thus we need to know if the anticonvulsant properties of clobazam are equal to those of diazepam. If so, it may be advantageous to utilize a 1,5 benzodiazepine rather than a 1,4 benzodiazepine in the therapy of epilepsy.

In their original report on the pharmacology of clobazam, Barzaghi *et al.* (1973) showed that it was active in mice against the tonic phase of seizures induced by pentylenetetrazol, or by maximal electroshock, respective oral ED₅₀s being 1.6 and 23.0 mg/kg. Diazepam and clobazam are equipotent against pentylenetetrazol (threshold) seizures in mice; clobazam is slightly more active than diazepam against the tonic extensor phase of the electroshock response (Fielding & Hoffmann, 1979). We have studied two types of reflex epilepsy: sound-induced seizures in DBA/2 mice, and photically induced seizures in baboons, *Papio papio*, from the Casamance region of Senegal (Chapman *et al.*, 1978). In mice,

maximal protection against seizures was observed 1 h after intraperitoneal injection of clobazam. The ED₅₀ for blockade of 'wild running' (the initial and minimal component of the response) was 2.1 mg/kg. The ED₅₀ for blockade of tonic extension was 1.1 mg/kg.

In baboons with photosensitive epilepsy, myoclonic responses to stroboscopic stimulation were absent 5 min to 3 h after clobazam 2 mg/kg intravenously, and 5 min to 6 h after clobazam 4–12 mg/kg. In baboons pretreated with a subconvulsant dose of D,L-allylglycine (2 amino-4-pentenoic acid, 170–185 mg/kg), clobazam 1 mg/kg intravenously produced a transient, partial protection against myoclonic responses, and 2 mg/kg a transient (5–60 mins) complete protection. A total and sustained (up to 6 h) protection was seen after clobazam 6 mg/kg.

A plasma concentration of clobazam greater than 0.45 µg/ml was associated with protection against myoclonus in the unmodified syndrome in the baboons. After allylglycine pretreatment, substantial protection was seen with plasma clobazam levels above 0.6 µg/ml, and total protection with plasma levels above 2.0 µg/ml.

Signs of neurological toxicity were absent or minimal (very transient nystagmus) after clobazam 2–6 mg/kg, but there was a loss of muscle tone (facial, limb and trunk) after clobazam 12 mg/kg.

These results indicate that the anticonvulsant potency of clobazam (in mice and baboons) is very similar to that of diazepam (Meldrum *et al.*, 1975a) but less than that of clonazepam (Meldrum *et al.*, 1975b).

Two other 1,5 benzodiazepines (BAU 500 and BAU 426; Meldrum & Horton, 1979) have been shown in animal test systems to possess anticonvulsant properties comparable to those of clonazepam.

Only careful clinical trials will permit a conclusion as to the therapeutic advantage of 1,5 benzodiazepines in the various forms of epilepsy.

References

- BARZAGHI, F. FOURNEX, R. & MANTEGAZZA, P. (1973). Pharmacological and toxicological properties of clobazam (1-phenyl-4-methyl-8-chloro-1, 2, 4, 5-tetrahydro-2,4-diketo-3H-1,5-benzodiazepine) a new psychotherapeutic agent. *Arzneimittel-Forsch.*, **23**, 683–686.
- BORLAND, R.G. & NICHOLSON, A.N. (1974). Immediate effects on human performance of a 1,5-benzodiazepine (Clobazam) compared with the 1,4 benzodiazepines chlordiazepoxide hydrochloride and diazepam. *Br.J.clin. Pharmac.*, **2**, 215–221.

- BROWNE, T.R. (1976). Clonazepam. *Arch. Neurol.* **33**, 326–332.
- CHAPMAN, A.G., HORTON, R.W. & MELDRUM, B.S. (1978). Anticonvulsant action of a 1,5 benzodiazepine, Clobazam, in reflex epilepsy. *Epilepsia*, **19**, 293–299.
- EDWARDS, V.E. & EADIE, M.J. (1973). Clonazepam – a clinical study of its effectiveness as an anticonvulsant. *Proc. Aust. Assoc. Neurol.*, **10**, 61–66.
- FIELDING, S. & HOFFMANN, I. (1978). Pharmacology of anti-anxiety drugs with special reference to clobazam. *Br. J. clin. Pharmac.*, **7**, 7S–16S.
- HINDMARCH, I., HANKS, G.W. & HEWETT, A.J. (1977). Clobazam, a 1,5-benzodiazepine, and car-driving ability. *Br. J. clin. Pharmac.*, **4**, 573–578.
- KORTTILA, K. & LINNOILA, M. (1975). Psychomotor skills related to driving after intramuscular administration of diazepam and meperidine. *Anaesthesiology*, **42**, 685–691.
- MELDRUM, B.S. & HORTON, R.W. (1979). Anticonvulsant activity in photo-sensitive baboons, *Papio-papio*, of two new 1,5 benzodiazepines. *Psychopharmacology* (in press).
- MELDRUM, B.S., HORTON, R.W. & TOSELAND, P.A. (1975a). A primate model for testing anticonvulsant drugs. *Arch. Neurol.* **32**, 289–294.
- MELDRUM, B.S., ANLEZARK, G., BALZAMO, E., HORTON, R.W. & TRIMBLE, M. (1975b). Photically induced epilepsy in *Papio-papio* as a model for drug studies. In *Advances in Neurology*, Vol. 10. Ed. Meldrum, B.S. & Marsden, C.D. Pp 119–128. New York: Raven Press.
- NICHOLSON, A.N. (1978). Differential effects of the 1,4 and 1,5 benzodiazepines on performance in healthy man. *Br. J. clin. Pharmac.*, **7**, 825–835.
- RIGAL, J. & SAVELLI, A. (1975). Clobazam, fonctions de vigilance et conduite automobile. *Gaz. med. Fr.*, **82**, 3908–3914.

Discussion

DR W. RUPP (Frankfurt) asked whether there was any correlation between the drug plasma levels in Dr Meldrum's baboon model and therapeutic plasma levels in man.

DR MELDRUM replied that in general the plasma levels did correspond. With diazepam, for example, 0.5 µg/ml is accepted as being in the therapeutic range in man and also seemed to be an effective level in the baboon. The same is true for barbiturates and the hydantoin. An exception is sodium valproate (di-*n*-propylacetate) in which higher plasma levels are required in the baboon than are normally achieved in man.

PROFESSOR D. LAWSON (Glasgow) asked if there was any evidence as to whether the activity shown in the baboon model was due to the parent compound or to the desmethyl metabolite.

DR MELDRUM replied that the assays carried out by Dr Hill utilized a GLC method which is specific

for the parent compound. No measurements of the plasma levels of the metabolites were made and he had not tested the activity of the metabolites. However, as the most pronounced effects were seen directly after the injection, and as they then progressively declined, it is likely that clobazam itself is the active principal. As he had commented in his paper, there was a slight lack of correlation late in the procedure (5–6 h after giving clobazam) between the plasma levels and the apparent anticonvulsant effect. This may suggest that at this stage there is an active metabolite present.

DR W. BOGIE (London) asked whether, in view of the potential usefulness of clobazam as an anticonvulsant, a parenteral formulation would be available for the treatment of status epilepticus.

DR RUPP replied that there were considerable difficulties in producing a suitable formulation for parenteral use. These problems were still not resolved.