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CLOBAZAM: PHARMACOLOGICAL AND THERAPEUTIC PROFILE

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1 Clobazam is a 1,5-benzodiazepine the pharmacological profile of which differs from that of the 1,4 benzodiazepines in that it displays a wide separation of psychosedative or 'tranquillizing' properties from impairment of motor coordination. This is associated with a relative lack of muscle relaxant activity.

2 In man it seems to be an effective anxiolytic agent when given in daily doses of 20–30 mg but produces minimal effects on psychomotor performance at these dose levels.

3 Clobazam has a long elimination half-life of about 18 h; the main metabolite is *N*-desmethylclobazam. Clobazam seems to share the good safety and tolerability characteristics of the 1,4 benzodiazepines.

Introduction

CLOBAZAM was synthesized more than a decade ago in the Maestretti Research Laboratories in Milan (Rossi *et al.*, 1969) and since then the evaluation and development of the drug have been carried out in many different countries.

Considerable published data on clobazam have already accumulated in the literature and there is also a much larger body of unpublished work. This workshop has provided a forum in which to examine in detail and discuss the important experimental work on this drug, and it is appropriate now to review and draw together these data.

Chemistry and animal pharmacology

Clobazam is a 1,5-benzodiazepine and thereby differs structurally from the original members of this group of drugs such as chlordiazepoxide and diazepam, which are 1,4-benzodiazepines. The nomenclature refers to the position of the nitrogen atom in the heterocyclic ring (Figure 1). This confers different chemical properties on the molecule (Kuch, 1979) and more importantly seems also to be reflected in significant pharmacological differences from the 1,4-benzodiazepines.

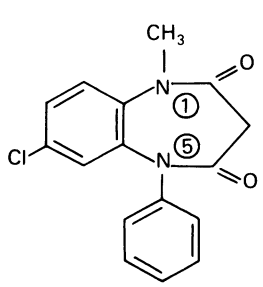

Figure 1 Clobazam (7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione).

The principal pharmacological properties of the 1,4-benzodiazepines are well established (Table 1). Their main therapeutic applications derive from their behavioural, muscle relaxant and anticonvulsant effects.

Table 1 Pharmacological properties of benzodiazepines

Anti-anxiety and behavioural disinhibition
Anticonvulsant
Sedative: Reduction of excessive or normal psychomotor and emotional reactions
Facilitation of sleep behaviour
Anti-aggressive
Potentiation of central depressants
Anterograde amnesia
Muscle relaxant
Virtual lack of direct peripheral effect
Very low toxicity

The pre-clinical assessment of potential anxiolytic drugs has inherent limitations. Anti-anxiety effects cannot be measured directly in animals but there are a variety of pharmacological models for predicting potential anxiety-reducing agents. The basic animal pharmacology of clobazam was first described by Barzaghi *et al.* (1973). Their most significant observation was that there was a wide separation between doses of the drug which would induce a 'tranquillizing' or psychosedative effect and doses necessary to produce ataxia. Clobazam was shown to be generally more active than chlordiazepoxide except in regard to muscle relaxant activity, where the two drugs were approximately equipotent.

These initial findings have been confirmed by other

workers and the data have been comprehensively reviewed (Fielding & Hoffmann, 1979). Using a range of pharmacological models, it has been shown that clobazam produces less disruption of motor coordination than the 1,4 benzodiazepines at doses which are equivalent in terms of tranquillizing activity. This seems to be related to a relative lack of muscle relaxant activity at doses which produce psychosedative effects.

The pharmacological mechanisms involved in the production of central muscle relaxation by drugs, including the benzodiazepines, are not understood. It has been suggested that the benzodiazepines may produce this effect by depression of spinal polysynaptic reflexes. To elucidate the muscle relaxant effects of clobazam, Gerhards (1978) compared the effects of clobazam and diazepam on spinal polysynaptic reflexes in a decerebrate cat model. He has shown that considerably higher doses of clobazam are required to depress these reflexes, compared with diazepam. Depending on the route of administration, clobazam had only 1/7th (intravenously) to 1/30th (intraperitoneally) the potency of diazepam in inhibiting extensor reflexes.

Thus, the animal data demonstrate significant quantitative differences between clobazam and the 1,4-benzodiazepines in the separation of 'taming' effects from central muscle relaxation.

Pharmacokinetics

The kinetics and metabolism of clobazam are complicated and there are important differences between man and certain animal species (Volz *et al.*, 1979), particularly in regard to the number of metabolites and rates of elimination.

In man the drug is virtually completely absorbed after oral administration and peak plasma levels are achieved within 1–4 hours. The terminal half-life of elimination of the parent compound is about 18 hours. However, [^{14}C]-labelled studies have indicated a terminal elimination half-life of total radioactivity of 2.7–5.9 d, indicating the presence of a metabolite with a much longer half-life than the unchanged drug (Rupp *et al.*, 1979). Clobazam is present in the serum mainly as parent compound and is about 90% protein bound; the major metabolite is *N*-desmethylclobazam. Other metabolites which have been identified in man include 4′-hydroxyclobazam and 4′-hydroxydesmethylclobazam (Figure 2); these hydroxylation products represent an important difference in the metabolism of clobazam from that of the 1,4 benzodiazepines. In the latter, hydroxylation occurs at the 3 position of the heterocyclic ring, whereas this does not occur with the 1,5 benzodiazepines (Volz *et al.*, 1979). The desmethyl metabolite of clobazam is active but with considerably less potency than the

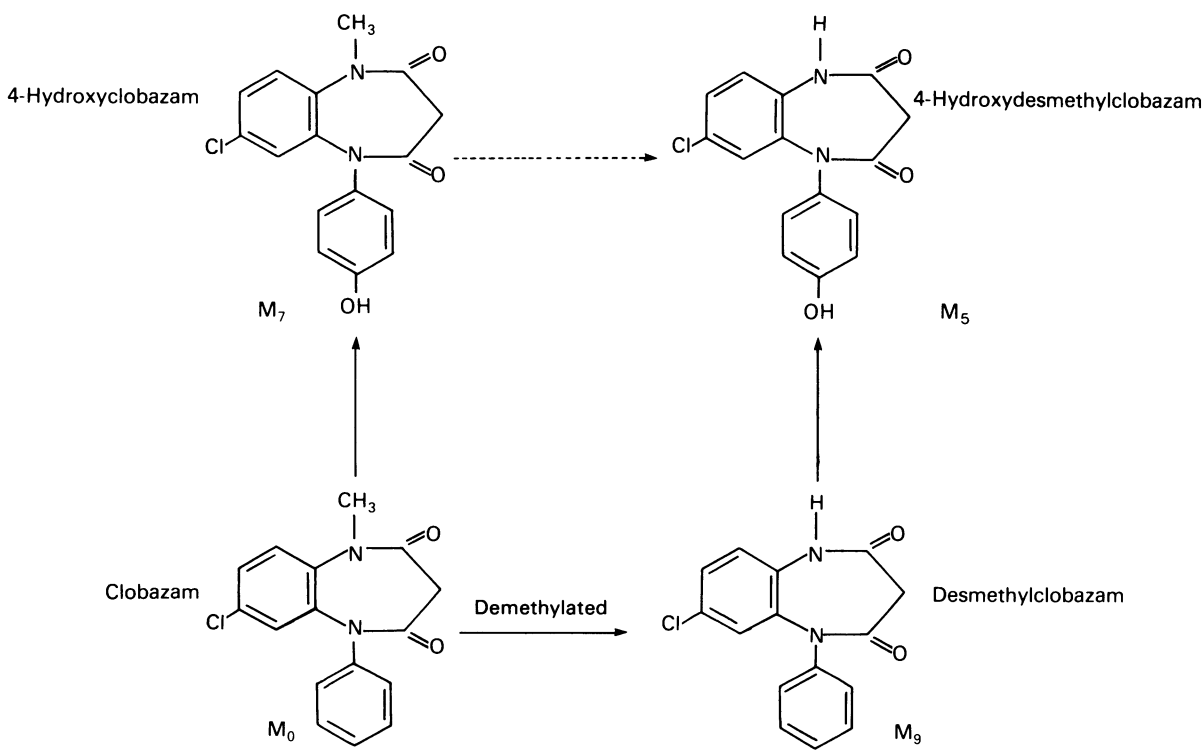

Figure 2 Major metabolites of clobazam.

parent compound (Fielding & Hoffmann, 1979) and with a much longer half-life (Rupp *et al.*, 1979).

The kinetics of clobazam therefore exhibit similarities to the 1,4 benzodiazepines, in particular with regard to the long overall elimination half-life. This has significant implications for rational dosage regimens in clinical practice.

Toxicology

The benzodiazepines are an exceptionally safe group of drugs and are remarkable for the low incidence of adverse effects associated with their use and their low potential for drug interactions (Byck, 1973; Van Der Kleijn *et al.*, 1977). Extensive toxicological evaluation of clobazam in animals has shown that this drug shares the very wide safety margin of the 1,4 benzodiazepines (Schütz, 1979).

One area of concern with this group of drugs, in view of their very widespread use, has been the possiblility of physical dependence and withdrawal effects. The matter is still controversial (*Drug and Therapeutics Bulletin,* 1977) but there have been several reports of severe withdrawal effects, notably convulsions and psychosis, occurring in patients receiving chronic high dose treatment, particularly after abrupt withdrawal.

There is evidence from long-term animal (dog) studies that withdrawal phenomena may occur with clobazam in this species (Schütz, 1979) but no such effects have yet been observed in man. In this context it is important to note that clobazam has a much shorter elimination half-life in dogs and that this may account for these findings, as on abrupt withdrawal of the drug elimination will be much more rapid than in man.

Clinical pharmacology

The benzodiazepines have become one of the most widely prescribed groups of drugs in clinical medicine today and the reasons for their popularity with prescribing physicians are well known: they are effective anxiolytic agents with few unwanted effects. However, one area where they do produce adverse effects of clinical importance is in relation to sensorimotor function and the performance of skilled tasks. A wide range of 1,4-benzodiazepines has been shown to impair mental functioning and psychomotor performance (Wittenborn, 1979) and this seems to be an inevitable concomitant of their action at therapeutic doses.

Evidence from animal pharmacological studies with clobazam has indicated that the drug does not seem to produce impairment of motor coordination at doses which were 'anxiolytic'. Early human studies have examined the effects of clobazam on simple reaction time and showed that, unlike diazepam and chlordiazepoxide, it produced no impairment in this test at comparable acute doses (Borland & Nicholson, 1974; Berry *et al.*, 1974). These results were followed up by a large number of investigations into the effects of clobazam on laboratory tests of psychomotor function and on the performance of skilled tasks, including driving motor cars (Biehl, 1974; Hunt *et al.*, 1974; Caille & Bassano, 1975; Fernández-Guardiola *et al.*, 1975; Leygonie *et al.*, 1975; Parrott & Hindmarch, 1975a and b; Rigal & Savelli, 1975; Hindmarch *et al.*, 1977; Parrott & Hindmarch, 1977; Doongaji *et al.*, 1978; Parrott & Hindmarch, 1978; Salkind *et al.*, 1979; Wittenborn *et al.*, 1979). Most of these studies were carried out using normal volunteers but two were specifically designed to investigate performance effects in clinically anxious patients (Doongaji *et al.*, 1978; Salkind *et al.*, 1979). A large variety of performance tasks have been used in the various studies and the detailed results are discussed elsewhere (Hindmarch, 1979; Nicholson, 1979; Wittenborn *et al.*, 1979).

Overall, the results of these investigations have been remarkably consistent. The evidence suggests that, in single doses of up to 20 mg, clobazam produces no immediate or delayed effects on psychomotor performance. Acute doses of 30 mg do seem to affect sensorimotor function deleteriously at 2–3 h after administration, corresponding to the time of maximum serum levels. However, repeated administration of clobazam in divided doses of 30 mg or 40 mg daily for up to 2 weeks does not seem to impair psychomotor function in either volunteers or patients.

Clinical efficacy

Koeppen (1979) has summarized the results of the worldwide clinical evaluation of clobazam, reviewing the published literature and the results of unpublished clinical trials. A large number of open and double-blind trials, placebo-controlled trials and trials in which clobazam has been compared with standard therapy have been completed. Clobazam has been used for up to 42 months and in doses of up to 120 mg daily in these studies. The data show that, in daily doses of 20–30 mg, clobazam is an effective anxiolytic (with an effect 'equivalent' to diazepam 15 mg daily). Clobazam is well tolerated and there have been few reported side-effects, the only one of any significance being drowsiness. These results have been confirmed in ordinary clinical practice in France and South America where clobazam has been generally available for up to 3 years.

Conclusions

Sternbach's discovery of chlordiazepoxide and the development of this drug in the late 1950s began what

has been described as the 'benzodiazepine bonanza' (Tyrer, 1974). Today these drugs are prescribed probably more widely than any other group, yet we are still a long way from understanding how they work. The central physiological and biochemical basis of anxiety, the mechanisms by which drugs may influence this and the relationships between anxiety, arousal, anxiety-reduction and sedation still need to be defined. It is possible that drugs such as clobazam may hasten the elucidation of some of these problems. Clobazam seems to be a drug in which effective anxiety-reduction may be separated from measurable effects on arousal and performance. However, the pharmacodynamic profile of clobazam seems to be qualitatively very similar to that of the 1,4-benzodiazepines: anxiety-reduction with drowsiness as a subjectively reported side-effect (Koeppen, 1979); anticonvulsant activity (Meldrum & Horton, 1979); effects on sleep with a reduction in sleep onset latency (Hindmarch *et al.*, 1977; Kesson *et al.*, 1978; Nicholson *et al.*, 1977); and low toxicity.

The one significant pharmacodynamic difference is the relative lack of muscle relaxant activity with clobazam (Barzaghi *et al.*, 1973; Fernández-Guardiola *et al.*, 1975; Fielding & Hoffmann, 1979; Gerhards, 1978). However, this is clearly not the only explanation for the minimal effects on psychomotor performance produced by clobazam. Hindmarch (1979) has suggested that clobazam and the 1,4-benzodiazepines have different effects on cortical arousal (as measured by critical flicker fusion threshold) and that this may be the reason for its failure to produce impairment of performance. This is an area which needs further exploration in view of the important clinical implications, not only for an understanding of the drugs used to treat anxiety but for an understanding of anxiety itself.

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