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A CLINICAL VIEW OF CLOBAZAM

H. H. WIECK, L. BLAHA & B. HEERKLOTZ
Universitäts-Nervenklinik mit Poliklinik, Schwabachanlage 6 u 10, 8520 Erlangen, West Germany

1 The results so far published in the literature, together with our own results, show that in clobazam (Frisium) we have a daytime tranquillizer which is comparable to the newest benzodiazepine derivatives.

2 It is particularly indicated in disorders of the sleeping–waking rhythm, and sometimes also in psychovegetative disorders associated with epilepsy.

3 Its tranquillizing profile of action, the low incidence of side-effects and the absence of interactions with other drugs mean that its applications are varied, not only in neuropsychiatry but also in other medical disciplines.

4 The fact that therapeutic doses do not seem to impair driving ability or render patients incapable of carrying on their profession, means that it is suitable for the treatment of outpatients.

Introduction

CLOBAZAM is the first example of a 1,5-benzodiazepine—that is, the two nitrogen atoms in the heterocyclic ring of the molecule are at positions 1 and 5. This modification of the chemical structure and the results of pharmacokinetic and pharmacodynamic studies in animals (Barzaghi *et al.*, 1973) made the compound seem attractive for clinical use. It was introduced in Germany in January 1978.

The present paper intends to establish from previous studies and our own experience whether clobazam is in fact a modern tranquillizer as defined by Wieck (Wieck, 1977*a*; Wieck & Heerklotz, 1978) and where it stands among the number of new and relatively new benzodiazepine derivatives, and also to define specific differential indications for the use of clobazam, in so far as present knowledge permits.

Clobazam: a modern tranquillizer?

Wieck (1979) has already defined precisely the ethical principles of tranquillization. A drug that is to achieve this desirable effect must possess the properties given in the following table.

Tranquillizing effect
Antinociceptive
Protective
Aiding sleep
Redressing balance of moods
Indirect anxiolytic activity
Indirect antidepressant activity
No impairment of daytime function.

The most important of these is the antinociceptive effect (Wieck, 1977*b*). We consider that anxiolysis and elevation of mood are only indirectly connected, despite the fact that it is usually these symptoms which are named as target symptoms in clinical trials, as these are the symptoms which can best be assessed with the objective and subjective rating scales at present available.

Clinical activity of clobazam

A number of double-blind trials have shown that doses of clobazam between 20 and 60 mg daily reduce hyperactivity and significantly improve emotional disorders (Martin, 1975; Devanthan & Channabasavanna, 1977; Laudano *et al.*, 1979). The symptoms 'inner unrest', 'anxiety' and 'increased irritability', in particular, usually respond to treatment after only 2–3 d (Grenier & Rolland, 1975; Moreau, 1976; Rochiccioli, 1977) but 'dejection', 'dysphoria' and 'depression' also improve after clobazam therapy (Baudet *et al.*, 1976; Devanthan, 1977; Radmayr & Koeppen, 1977).

Most studies assess the degree of intensity of symptoms in psychovegetative disorders of extremely varied origin, under treatment with clobazam. In partial disorders such as functional disorders of the gastrointestinal, urogenital or respiratory tracts, disorders of the cardiovascular system, sleep disturbance, and disorders of sexual function, the therapeutic result is almost always good or very good (Arioni Faccini *et al.*, 1971; Freche, 1975; Roger *et al.*, 1975; Foucaud, 1977). Not only is the localized discomfort improved but the emotional disorder is also normalized. The ages of the patients studied range from infants to geriatric, but even in these extreme age groups no serious intolerance has been observed (Mises, 1975; Moreau, 1976; Lajouanine, 1977).

The therapeutic success in disorders of the sleeping–waking rhythm has been repeatedly stressed. Studies in healthy volunteers and in patients have shown that clobazam does not impair normal sleep, but that there is a trend towards normalization where the EEG sleep pattern is disturbed (Caille & Bassano, 1975; Leygonie *et al.*, 1975; Clarke *et al.*, 1977).

Side-effects of clobazam

The frequency of side-effects has been extremely low in controlled studies so far. There have been no occurrences of serious side-effects. In a few cases, particularly in very old and very young patients, slight drowsiness and dizziness, and dryness of the mouth were reported at the beginning of treatment, but these subsided during the course of treatment without the necessity for a reduction in dose. Cognitive performance, coordination and psychomotor speed were hardly impaired under clobazam treatment, unlike other benzodiazepines, and there was no impairment at doses of clobazam 40 mg and less. Even long-term use of clobazam did not induce organic disorders or affect orthostatic tolerance. No effect was observed on the newborn babies of women who had been treated with clobazam during the last 3 months of pregnancy, compared with a placebo sample (Baudet *et al.*, 1976).

Studies which directly or indirectly investigated the effect of clobazam on driving ability have shown that impairment is unlikely at a dose of clobazam 20 mg (Berry *et al.*, 1974; Biehl, 1974; Borland & Nicholson, 1974; Fernandez-Guardiola *et al.*, 1975; Rigal & Savelli, 1975; Hindmarch *et al.*, 1977). Nevertheless, for reasons of safety, driving should be forbidden during the first few days of treatment, as has been repeatedly recommended in the case of other daytime tranquillizers. The dangers attendant in individual cases of intolerance are thereby excluded (Blaha & Heerklotz, 1978; Wieck, 1976).

Our own experience

Our clinical experience so far, based on individual observations, can be summed up briefly in the statement 'Clobazam is a daytime tranquillizer'.

We have used this new 1,5-benzodiazepine derivative particularly in patients with psychovegetative general disturbances and, in combination with antidepressives, in manic-depressive psychoses. Most patients stated that they felt more balanced and calmer, and that they felt better overall, after only 2 or 3 days' treatment. We did not observe any strong sedative or hypnotic effect, and no such effect was reported by any patient. No adverse effect was observed on the cardiovascular system, and there was no interaction with other drugs. Doses of clobazam up to 60 mg daily were tolerated by outpatients without any adverse reactions.

We too must stress the particularly good effect of clobazam on sleep disorders, which most patients mentioned spontaneously. Even persistent sleep disorders were improved or completely abolished by clobazam. One example of clobazam's success may be seen in the case of a 56-y-old teacher who had had chronic sleep disorders for more than 6 years. Barbiturates had not proved satisfactory, and the patient eventually became dependent on them. His condition was worsened by increasing anxiety and depressive mood. On the second night after commencement of treatment with clobazam the patient was able to get to sleep easily, and slept through the night. This normalization of the sleeping rhythm continued for the rest of the treatment period.

Clobazam's place among the benzodiazepines

As has been reported in the literature, and as we ourselves have observed, clobazam has a positive effect on both isolated psychosomatic disorders and on the psychovegetative system as a whole.

Clobazam relieves discomfort and malaise. In addition it has an indirectly relaxing effect which results in direct anxiolysis and antidepressant activity. The disorders in question frequently include sleep disturbances, which respond particularly well to clobazam. Clobazam's activity here is not sedative but antinociceptive in protecting sleep.

In addition to this, clobazam exercises a balancing and harmonizing effect on the psychovegetative system as a whole. As the substance is not known to induce marked sedation and hangover, or to impair cognitive performance, and as there is hardly a danger of dependency, it fulfils most of the requirements of a daytime tranquillizer.

Thus, as far as is at present known, clobazam is just as effective as dipotassium clorazepate and prazepam in its activity as a daytime tranquillizer (Skupin & Franzke, 1975) and equivalent to lorazepam as an indirect anxiolytic. Its activity in normalizing sleep is stronger and can best be compared with that of bromazepam. Oxazepam has a more potent sedative activity.

As is the case with the other benzodiazepine tranquillizers, the contraindications for clobazam must be seen as relative, except in the case of direct hypersensitivity to the substance. Despite this, patients with myasthenia gravis or ataxia should only be treated with clobazam in hospital conditions. Although no teratogenic effect has been observed in animal studies, the use of substances of this nature should be avoided in the first 3 months of pregnancy.

Possible future uses of clobazam

Although experience with clobazam is still limited, as

it has only recently been available for clinical evaluation, we shall attempt to define its indications with the aid of published results.

Clobazam is a daytime tranquillizer and is thus suitable for the treatment of outpatients and working patients. The main area indicated is psychovegetative disorders of all origins, including psychosomatic conditions. Its use is particularly successful in patients in whom sleep disorders are the major symptom.

Clobazam is particularly suitable in combination therapy, as it is well tolerated and does not interact with other drugs. On the one hand it can be used in combination with neuroleptics in psychiatric indications, and on the other it is particularly useful in combination with antidepressants. As it can soothe or completely relieve not only emotional discomfort but also organic disorders such as post-myocardial infarction, angina pectoris, hiatus hernia, and so on, it is also indicated in a number of medical disciplines.

One specific indication for clobazam is in the treatment of convulsions, which are frequently associated with psychovegetative disorders. Animal studies have shown an anticonvulsant effect comparable to that of diazepam and superior to that of chlordiazepoxide (Barzaghi *et al.*, 1973). Clobazam's profile of action, which is otherwise tranquillizing, improved the subjective condition of patients suffering from convulsions, but was also able simultaneously to reduce the necessity for anticonvulsants. Controlled studies designed to test this aspect seem to be scientifically acceptable.

Clobazam's balancing and harmonizing effect is definitely responsible for the good results achieved in the treatment of children with behaviour disorders. Its activity in normalizing sleeping–waking rhythms is probably also a contributing factor. The use of clobazam in these indications is justified by the fact that it is well tolerated.

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