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# CLINICAL EXPERIENCES WITH CLOBAZAM

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NORMAL feelings and behaviour depend on the balance of the various biogenic amines throughout the nervous system. Various factors may disturb this balance: (1) defective synthesis of catecholamines or indolamines (in parkinsonism, for example, there is dopamine depletion due to tyrosine hydroxylase insufficiency); (2) increased turnover of biogenic amines; and (3) a shift of transmitters to the wrong neurones (toxic delirium following L-DOPA).

These biochemical imbalances are caused sometimes by genetic factors and sometimes by the environment. Stress, excessive strain, unresolved conflicts, overcrowded home circumstances, and so on, can disturb the balance. This results in affective-vegetative decompensation which is an expression of inadequate adaptation. We have termed this pattern of clinical disturbance the "vegetative-affective stimulus syndrome". It is characterized by sleeplessness, restlessness, agitation, excited mood, anxiety, outbreaks of perspiration and palpitations.

The syndrome is characterized by three phenomena: (1) a lowering of the general stimulus threshold (normally subliminal stimuli – climate, alcohol, overwork – may trigger off symtoms); (2) prolongation of reactions (a pathogenic stimulus – for example, trivial family quarrel – is not neutralized by feedback mechanisms, but triggers off symptoms for hours or days afterwards); (3) accumulation effect (anxiety causes tachycardia which increases the anxiety and leads to sleeplessness, and so on).

The great importance of the psychotropic drugs, particularly the tranquillizers, lies in man's need for rapid recompensation. For a tranquillizer to be clinically useful, the desired target effect must far outweigh the side-effects.

Over the past 4 years we have tested clobazam in 380 patients with vegetative-affective stimulus syndrome. The dosage has been 10 or 20 mg three times daily. The psychogalvanic reflex (PGR) was used to demonstrate objectively the patients' emotional responses, both before and after 4 weeks on clobazam 10 mg three times daily.

There were considerable variations in amplitude as an expression of reaction prolongation: the emotional tension created by an acoustic stimulus did not diminish. A second curve, 4 weeks later, showed much smaller and less frequent amplitude deflections, a sign of reduced oscillation.

The level of vigilance was measured by critical flicker fusion (CFF). In this technique, flickering light stimuli are altered until the subject perceives a steady light. The critical point is higher in adolescents than in the elderly. The CFF is an objective measure of clarity of consciousness. Clarity of consciousness can be modified by tranquillizers. Three hours after clobazam 20 mg the values for five patients showed no change. After 5 min of mental arithmetic the CFF increased, as it did in control subjects. Three hours after clobazam 40 mg there was a decline in activation values indicative of a reduction in clarity of consciousness.

When testing a tranquillizer, it is recommended that several methods be used to monitor objectively any sedative effect. Precise experimental results indicate the direction and degree of such an effect and obviate the need for time-consuming double-blind studies. We consider it imperative that the PGR test be carried out to measure affective responsiveness. Measurement of CFF provides an objective indication of clarity of consciousness and any changes in it.

We also recommend a motor testing apparatus to measure reaction speed so that the precision and speed of motor performance can be assessed. Clobazam 20 mg produced no change in the movements tested and caused only slight slowing of performance in the tapping test.

Clobazam is therefore a tranquillizer which alleviates affective tension and sleep disturbances. Moderate doses (10–20 mg three times daily) do not alter clarity of consciousness or motor reaction speeds, either subjectively or objectively.

In addition to its sedative effect in the vegetative-affective stimulus syndrome, clobazam can also be used successfully as a sleep-promoting evening medication in patients with agitated depression.

Abstract translated from the German by David Beattie.

## Discussion

DR H. JESSEL (Hamburg), commenting on Professor Birkmayer's experience, described the results of an open dose ranging study with clobazam. Total daily doses of 40 mg or 60 mg produced effective anxiety reduction and were very well tolerated by the patients. No tachyphylaxis was observed and follow-up of these patients had shown them to be well maintained on this dosage, and able to continue with their normal daily activities. Particularly notable was the lack of daytime sedation, an important consideration for outpatient