NEUROPHARMACOLOGICAL PROFILE OF CLOBAZAM, A NEW 1',5'-BENZODIAZEPINE

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THE effects of the new 1',5'-benzodiazepine, clobazam, on visual evoked potentials (VEP) and spontaneous EEG in conscious rabbits and on spinal polysynaptic reflexes in the decerebrate cat were studied and compared with diazepam (Gerhards, 1978). The relative abilities of clobazam and diazepam to depress the slow negative wave (SNW) in the VEP in the rabbit proved to be a very stable and easily accessible parameter for measuring the central effects of these anxiolytics.

The results obtained point to definite differences between clobazam and diazepam in dynamic and kinetic aspects. Regarding the peak effect of pharmacological action, diazepam is about twice as potent as clobazam, that is the maximum effect induced by diazepam 1 mg/kg is about equivalent to the effect induced by clobazam 2.5 mg/kg. After clobazam, however, this peak effect has a plateau between 1 and 6 h after administration whereas the diazepam effect is already declining after 1 h. Thus, with respect to the area under the curve, clobazam is more effective than diazepam in reducing SNW amplitude in the VEP of rabbits.

Power spectrum density analysis of spontaneous

EEG in rabbits revealed, after both clobazam and diazepam, a significant increase in β -activity in the cortical lead and a decrease of power in the α and θ bands, mainly in the hippocampal lead. Furthermore, a decrease in the dominant frequency in the hippocampus of 0.5–0.8 Hz was regularly observed.

These changes are very similar to the alterations found by Itil (1974) in the computer-analyzed human EEG after treatment with anxiolytic drugs.

The central muscle relaxant effects of clobazam, assessed by inhibition of spinal reflexes in the decerebrate cat, seemed to be much weaker than those of diazepam. Clobazam had about one-seventh to one-eighth the potency of diazepam in inhibiting extensor reflexes after intravenous application and one-thirtieth the potency of diazepam after intraperitoneal application.

Clobazam was found to be much less effective than diazepam in inhibiting polysynaptic spinal reflexes, whereas their effects on late components of the VEP were at least equivalent. This indicates a better split between the tranquillizing and the muscle relaxant properties of clobazam.

References

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ITIL, T.M. (1974). Quantitative pharmaco-electro-encephalo-

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Discussion

PROFESSOR H. WIECK (Erlangen) asked about the implications of the decrease in amplitude of the slow negative wave (SNW) of the visual evoked potentials (VEPs).

DR GERHARDS replied that anxiolytics are known to induce significant alterations in the pattern of VEPs and somatosensory evoked potentials (SEPs) in animals and in humans. These changes are characterized by attenuation of amplitudes and decreases of latencies of late peaks (peak latencies > 150 ms) (Saletu, 1974). Concerning the actual mode of action of anxiolytics on the evoked potential, various investigators have shown that the primary

response (peak latencies < 50 ms) may be related to impulses arriving at the cortex through specific thalamocortical pathways, whereas the secondary response (peak latencies 50–500 ms) is derived from collaterals to the midbrain reticular formation (MRF) and/or other brain areas including the limbic system, and thus through diffuse thalamic projections to the cortex.

Our results, showing attenuated amplitudes of peaks with latencies of 150–200 ms might indicate a reduced extralemniscal conduction to the cortex, suggesting that one of the principal sites of action of anxiolytics is the MRF and/or the limbic system.