Effect of the 1,5-benzodiazepines, clobazam and triflubazam, on the sleep of man

CORAL H. CLARKE, A.N. NICHOLSON & BARBARA M. STONE

Royal Air Force Institute of Aviation Medicine, Farnborough, Hampshire

Many of the 1,4-benzodiazepines used as hypnotics have persistent effects on performance, but it would appear that the 1,5-benzodiazepine, clobazam, has limited residual sequelae (Caille & Bassano, 1974; Borland & Nicholson, 1975). The possibility that 1,5-benzodiazepines may possess less potential for impairing performance in man raises the question of their use as hypnotics for persons involved in skilled activity the next day. It is in this context that we have investigated the hypnotic properties of two members of this group of drugs – clobazam (1-methyl-5-phenyl-7-chloro-1H-1, 5-benzodiazepine-2, 4(3H, 5H)-dione) and triflubazam (1-methyl-5-phenyl-7-trifluoromethyl-1H-1, 5-benzodiazepine-2, 4(3H, 5H)-dione).

The subjects were six healthy male volunteers aged between 21 and 28 years. The assessment of each treatment (matching placebos or dose or a drug) involved four days. For two nights the subjects slept at home and retired at a set time, and for the next two nights they slept in the laboratory. They were requested to refrain from napping and undue exercise, and to abstain from caffeine and alcohol from mid-day on the days which involved recordings. Nine to twelve days separated each assessment. On each occasion the subject ingested two identical capsules, and the study was double blind. Preliminary studies suggested that the appropriate dose ranges to study were clobazam (10–20 mg) and triflubazam (20–40 mg).

The effect of the drugs was limited to the night of ingestion. With both drugs no statistically significant changes were observed in total sleep time or in the duration (min) of each sleep stage. With clobazam (10 & 20 mg) sleep onset latency (SOL) was reduced ($P < 0.05$), and the latency to stage 3 was shortened. There was some evidence of reduced awakenings to stage 0 and stage 1 activity, and with both 10 and clobazam (20 mg) the percentage of total sleep time occupied by stage 1 activity was less ($P < 0.01$). With clobazam (20 mg) there was an increase in the percentage of stage 2 sleep ($P < 0.05$) related to the second two hourly interval of sleep from SOL, and an overall decrease in the percentage of stage 3 ($P < 0.01$) and stage 3 + 4 ($P < 0.05$) sleep. No changes were observed in rapid eye movement sleep.

With triflubazam (20 & 40 mg) there was no change in latencies to sleep stages. There was some evidence of reduced awakenings to stage 0 and stage 1 activity. With 20 mg the percentage of total sleep time occupied by stage 1 activity was less ($P < 0.05$), but this change was not observed with the 40 mg dose. No other changes were observed.

It would appear that the hypnotic activity of the 1,5-benzodiazepines is limited, and that this is particularly so in the case of triflubazam. However, the effect of clobazam on sleep, and its restricted effects on performance (Borland & Nicholson, 1975) suggest that it may be a useful drug in the management of limited sleep difficulties in persons involved in skilled activity.

References

BORLAND, R.G. & NICHOLSON, A.N. (1975). 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.

CAILLE, E.J. & BASSANO, J.-L. (1974). Étude de quatre benzodiazépines au niveau de l'électrogenèse cérébrale, du sommeil, du comportement et de l'humeur. *J. Pharmacol., Clin.*, **4**, 241–255.

Behavioural changes in rats suggesting drug-induced headache

A.P. SILVERMAN

ICI Ltd., Central Toxicology Laboratory

Nitroglycerin and similar organic nitrates lower blood-pressure and are liable to induce headache in man after inhalation or skin contact. If rats also get headaches, they would be expected to show: (1) Conditioned taste aversion; drugs like lithium producing unpleasant symptoms in man often cause rats to avoid novel but otherwise attractive bait (Nachman & Hartely, 1975). (2) An unspecific reduction in spontaneous behaviour (whereas strongly conditioned behaviour, e.g. to avoid shock, might overcome a mild deficit).

Twenty-four albino rats were caged in pairs, separated for 6 h each week day, and given water for 2 h daily while separated. Social behaviour was observed on return to the home cage (Silverman,