(95% confidence limits 3·7–9·9) mg/kg. These doses are anorectic in the rat and show that fenfluramine, like amphetamine, produces changes in the behaviour of rats which are indicative of central nervous system stimulation.

REFERENCES

ALPHIN, R. S., FUNDERBURK, W. H. & WARD, J. W. (1964). Anorexigenic activity of N-ethyl-2-methyl-trifluoromethylphenylethylamine hydrochloride. *Tox. appl. Pharmac.*, **6**, 340.

LE DOUAREC, J. C., SCHMITT, H. & LAUBIE, M. (1966). Étude pharmacologique de la fenfluramine et de ses isomères optiques. *Archs int. pharmacodyn. Thér.*, **161**, 206.

TEDESCHI, D. H., FOWLER, P. J., CROMLEY, W. H., PAULS, J. F., EBY, R. Z. & FELLOWS, E. J. (1964). Effects of centrally acting drugs on confinement motor activity. *J. Pharm. Sci.*, **53** (9), 1046.

YELNOSKY, J. & LAWLOR, R. B. (1970). A comparative study of the pharmacologic actions of amphetamine and fenfluramine. *Archs int. pharmacodyn. Thér.*, **184**, 374–388.

Residual effects of a new benzodiazepine: flurazepam

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Persistent behavioural and physiological effects after hypnotic doses of barbiturates and nitrazepam have been described by Malpas, Rowan, Joyce & Scott (1970). In a study using normal subjects with two doses of nitrazepam (5 and 10 mg) and amylobarbitone sodium (100 and 200 mg), electroencephalographic changes were apparent 18 h after ingestion. These changes were found on visual examination of paper records of the electroencephalogram (e.e.g.) taken while the subjects relaxed in a quiet, darkened room.

In a previous study we found e.e.g. changes and behavioural impairment 12 h after nitrazepam and butobarbitone sodium (Lader & Walters, 1971). We have extended this work to study the residual effects of a new benzodiazepine, flurazepam, in doses of 15 and 30 mg compared with those of butobarbitone sodium 150 mg and a placebo. Eight normal subjects received all four treatments at weekly intervals as part of a balanced design, using double-blind procedures. The drug was taken at 22.00 or 23.00 h and the psychological and physiological tests were carried out 12, 15 and 18 h later. The physiological tests consisted of e.e.g. recordings during an auditory reaction time task and the electroencephalographic averaged evoked response (A.E.R.) to the auditory stimuli (clicks) was also quantified. All experiments were carried out on-line, in real-time using a PDP-12A computer. The e.e.g. was analysed on-line by passing it through four broad wave band filters: 2·4–4·0 Hz, 4·0–7·5 Hz, 7·5–13·5 Hz and 13·5–26·0 Hz. The computer sampled each wave band at intervals between the auditory stimuli and calculated the mean rectified voltage in each wave band. The A.E.R. was computed using thirty-two epochs and the variance was calculated to check for artifacts. The main peaks had mean latencies of: P_1, 75 ms; N_1, 123 ms; P_2, 197 ms; N_2, 285 ms. Peak-to-peak amplitudes were computed in microvolts.

All wave bands showed significant changes which persisted through the day up to 18 h after the drug; for example, the 4·0–7·5 Hz wave band was significantly decreased by both drugs. A particularly sensitive measure was the mean voltage of the wave bands calculated as a percentage of the total voltage. Two components of the A.E.R.: P_1-N_1 and N_1-P_2 were significantly diminished. However, reaction time was not affected.

These results confirm the persistent physiological changes which occur after single doses of hypnotics and emphasize the need for caution in evaluating studies of psychiatric patients receiving night sedation compared to normal controls not taking sleeping-tablets.

REFERENCES

LADER, M. H. & WALTERS, A. J. (1971). Hangover effects of hypnotics in man. *Br. J. Pharmac.*, **41**, 412.

MALPAS, A., ROWAN, A. J., JOYCE, C. R. B. & SCOTT, D. F. (1970). Persistent behavioural and electroencephalographic changes after single doses of nitrazepam and amylobarbitone sodium. *Br. med. J.*, **2**, 762–764.

Iontophoretic study of the central anticholinergic properties of BRL 1288

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The new anti-Parkinson drug BRL 1288 (2[ethyl-n-propylamino]ethyl-α-α-diphenylglycollate hydrochloride) appears to have new features compared with many existing anti-Parkinson drugs in that it has very little peripheral anticholinergic activity though it abolishes oxotremorine-induced tremors in mice (Hughes & Spicer, 1969; Brown, Hughes & Mehta, 1969; Leslie & Conway, 1970). It thus seemed important to obtain more direct information about the possible anticholinergic activity of BRL 1288 in the central nervous system.

The action of BRL 1288 has been compared with those of atropine and procaine on acetylcholine—and L-glutamate-excited neurones using microiontophoretic techniques. Seven barrelled glass microelectrodes of overall tip diameter 4–10 μm containing the drug solutions were placed in the postcruciate cortex of cats anaesthetized with nitrous oxide-halothane. Extracellular action potentials recorded from one barrel were displayed on an oscilloscope and electronically counted.

BRL 1288 (cationic current 25–100 nA) reduced the excitant action of acetylcholine. However, this action of BRL was not specific for acetylcholine since the excitatory effect of L-glutamate was also reduced. Moreover, BRL 1288 was more effective against glutamate, the EC50 (effective current) being $30{\cdot}5 \pm 9{\cdot}1$ compared with $65{\cdot}0 \pm 17{\cdot}5$ against acetylcholine-induced excitation.

Atropine was at least twice as effective as BRL 1288, on a current basis, in reducing the excitant action of acetylcholine and, unlike BRL, it produced a long lasting effect. However, atropine had only half the activity of BRL 1288 against neurones excited by L-glutamate and recovery was rapid.

Structurally, BRL 1288 has features in common with the local anaesthetic, procaine. Comparisons between these drugs on neurones excited by acetylcholine or L-glutamate showed that both agents often caused a reduction in the amplitude of the extracellular action potential at similar ejecting currents. Furthermore, BRL and procaine were equipotent in antagonizing glutamate excitation although BRL was more effective in antagonizing acetylcholine excitation.

In view of these findings, the local anaesthetic potencies of BRL 1288, procaine and atropine were determined on the isolated frog sciatic nerve. The results obtained indicated that, on a molar basis, BRL was 2–3 times as potent as procaine and one hundred times as potent as atropine.