The results summarized in Table 1 are expressed as activity relative to atropine sulphate. All compounds were administered as their salts.

The pronounced central activity of BRL 1288 relative to its peripheral anticholinergic activity indicates that the compound has great potential in the treatment of Parkinsonism.

The effect of chronic barbitone administration and withdrawal on the sensitivity of the central nervous system to barbiturate

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We have previously reported the effect of chronic barbitone administration and withdrawal on hexobarbitone sleeping time and hepatic drug-metabolizing enzyme activity. During barbitone treatment, rats were found to be tolerant to hexobarbitone and the ability of liver microsomal preparations to oxidize hexobarbitone *in vitro* was increased. Three weeks after withdrawal a hypersensitivity to hexobarbitone, associated with decreased activity of drug-metabolizing enzymes, was found (Stevenson & Turnbull, 1968). These experiments, however, provided no indication as to whether brain sensitivity to barbiturates had altered during barbitone administration and withdrawal. Information on this has now been obtained from studies in which the tissue barbiturate concentration on awakening from a hypnotic dose of labelled barbiturate has been determined.

Female Wistar rats were made dependent on barbiturate by the administration of barbitone sodium in the drinking water (Stevenson & Turnbull, 1968). Barbitone-treated, withdrawn and control animals were killed on awakening following intraperitoneal administration of [^{3}H]-hexobarbitone sodium (150 mg/kg), [^{14}C]-pentobarbitone sodium (40 mg/kg) or [^{14}C]-barbitone sodium (225 mg/kg) and the brain, liver and serum level of labelled barbiturate and metabolites was measured. In addition, the total barbiturate concentration was determined spectrophotometrically, thus enabling the tissue level of unlabelled barbitone (i.e. that taken in the drinking water) to be calculated.

Animals chronically treated with barbitone awoke with a lower tissue concentration of [^{3}H]-hexobarbitone or [^{14}C]-pentobarbitone, but when tissue barbitone was taken into account, the total barbiturate concentration was higher than that found in control rats, indicating a central nervous tolerance. Furthermore, the total brain barbiturate concentration on awakening was found to be higher in rats which had been given barbitone for five weeks than in animals which had received barbitone for only a few days, indicating a gradual development of tolerance throughout the period of barbitone administration. The tissue concentration of labelled barbiturate metabolites, with the exception of the brain level of pentobarbitone metabolites, was higher than that found in control rats. The tissue levels of [^{14}C]-barbitone were found to be the same in barbitone-dependent as in control animals, showing that prolonged treatment with barbitone does not significantly affect the metabolism of this drug.

Our results show that after withdrawal, central nervous tolerance is gradually lost until three weeks after withdrawal animals awoke with the same brain barbiturate level as control rats.

The duration of anaesthesia produced by an intraventricular injection of 500 μg pentobarbitone sodium to rats withdrawn for 48 hr following various periods of barbitone administration has also been determined. The changes in sensitivity of the central nervous system indicated by this method were similar to those described above, tolerance being indicated by a markedly reduced sleeping time.

REFERENCE

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Behaviour and EEG are affected on the day after hypnotic doses of nitrazepam and amylobarbitone sodium

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Five and 10 mg nitrazepam have more pronounced effects on certain behavioural tasks than 100 and 200 mg of amylobarbitone sodium during the 3 hr immediately after daytime administration (Malpas & Joyce, 1969), as well as upon changes in the resting EEG (Volavka, Joyce, Maloney, Brawn, Summerfield, Topham & Scott, 1969). Over a longer period of time similar doses of pentobarbitone or quinalbarbitone cause statistically significant impairment on other psychomotor tasks (Goodnow, Beecher, Brazier, Mosteller & Tagiuri, 1951; Kornetsky, Vates & Kessler, 1959), but Ditt (1964) was unable to demonstrate any impairment in performance 10 to 16 hr after treatment with 5 or 10 mg of nitrazepam. We have now compared some behavioural and EEG effects of amylobarbitone and nitrazepam in the day following their administration as hypnotics in a double-blind cross-over trial.

Ten healthy male medical students took nitrazepam 5 or 10 mg, amylobarbitone sodium 100 or 200 mg, or placebo orally just before going to bed and were tested 13 and 17 hr later. Speed of motor performance and time to reach decisions at various information loads were estimated by means of a card sorting task (Crossman, 1953). All ratings of performance and EEG were completed before judges were informed of the treatments given. At 13 hr after treatment both doses of nitrazepam caused significant slowing of motor performance compared with placebo, but only the higher dose of nitrazepam significantly slowed information processing. Neither dose of amylobarbitone had significant effects on motor performance as compared with placebo, but the larger dose significantly lengthened decision time at all information loads and the lower dose did so at high information loads only. At 17 hr after treatment the effects were still apparent and in the same direction as before, but did not reach the 5% level of significance in any case. At 17 hr subjects were more likely to show the electrical changes associated with drowsiness and sleep after treatment with nitrazepam than with the barbiturate: changes with the latter were in turn more marked than those with placebo.

The subjects were apparently unaware that their performance was less efficient than usual. They considered themselves to be more alert at 13 hr after any drug treatment than at the same time after placebo and they did not report more subjective " hangover " effects after drug than after placebo.