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PERFORMANCE STUDIES WITH DIAZEPAM AND ITS HYDROXYLATED METABOLITES

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1 Visuo-motor coordination has been used to study the immediate and residual effects of benzodiazepines on performance in man. The technique provides dose and time response data related to the decrement and the persistence of impaired performance.

2 With the overnight ingestion of flurazepam hydrochloride 30 mg and nitrazepam 10 mg, performance was impaired to 16 h and, at least, 19 h, respectively. Performance was not impaired after the overnight ingestion of diazepam, 5 and 10 mg, temazepam 10, 20 and 30 mg or oxazepam 15 and 30 mg. However, with temazepam 30 mg there was a trend toward impaired performance, and with oxazepam 45 mg, performance was impaired 10 h after ingestion. With morning ingestion, coordination was impaired 0.5 and 2.5 h after diazepam 10 mg, at 0.5 h after temazepam 20 mg, and after oxazepam 30 mg at 2.5 and 4.5 hours.

3 The studies suggest that diazepam 5-10 mg, temazepam 10-20 mg and oxazepam 15-30 mg may be of use in the management of sleep disturbance when impaired performance the next day is to be avoided.

Introduction

RESIDUAL impairment of performance with the overnight ingestion of hypnotics has become of particular interest over the past few years, and it is now evident that such an effect is not an inevitable sequel of a useful drug. However, many of the currently available hypnotics have residual effects on performance in doses within the normally accepted therapeutic range, and so an hypnotic free of residual sequelae would be of considerable value. Many centres have been involved with this problem, and studies have included a variety of tasks. Our work has been concerned mainly with visuo-motor coordination, in which residual and immediate effects related to dose and time have been studied.

Performance has been measured using an adaptive tracking task (Borland & Nicholson, 1974). The task requires the subject to position a spot inside a randomly moving circle displayed on an oscilloscope. The movement of the spot is controlled by a hand-held stick, and an error signal, proportional to the distance between the spot and the centre of the circle, controls the difficulty of the task by modulating the mean amplitude of the movement of the circle. The technique provides the adaptive component which maintains optimum performance of the operator. At the start of each experiment the circle is stationary. The subject positions the spot inside the circle, and with a negative error signal the circle moves away from the spot. When the spot can no longer be maintained inside the target circle due to the increasing difficulty of the task, the task becomes less demanding. At zero error the task requires about 25 s to reach maximum difficulty, whereas a constant displacement between the spot and the centre of the circle of 4 cm reduces the task to zero difficulty within 6 seconds. Subjects are aware of the penalty of error signals, and so they try to avoid all errors, though the task does not permit the maximum performance level to be reached.

Experiments were carried out in sound-attenuated and air-conditioned rooms. The subjects were required to reach a steady level of performance on the task before drug studies were carried out. In subjects familiar with this technique, steady performance was reached within about 5 days' practice, but usually such a level of performance was reached only after 2-3 weeks' practice. Each assessment of performance lasted 10 mins. Trained subjects reached their plateau of performance within the first 100 s of a run. The mean amplitude of the task over the final 500 s was computed, and this was the performance measure. The subjects were informed that this time interval only was used in the assessment of performance, though they were unaware when the period of time commenced. Healthy male subjects were used (age range 21-45 yr). Instructions were

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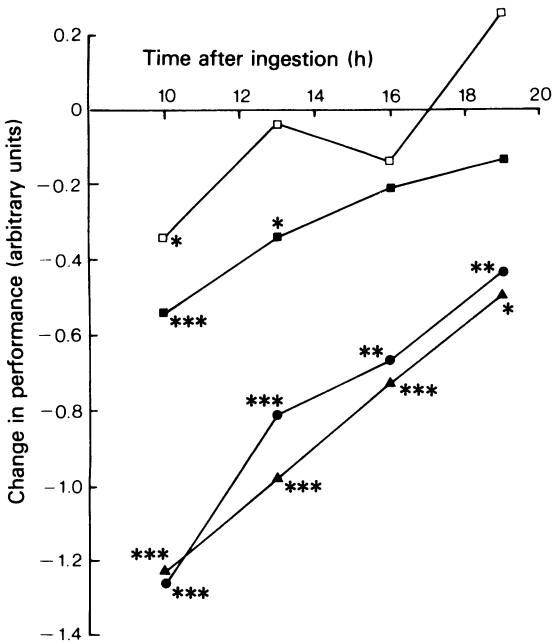

Figure 1 Effect of heptabarbitone 200 (□), 300 (■) and 400 mg (●) pentobarbitone sodium 200 mg (▲) on visuo-motor coordination (arbitrary units). Significance levels: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

given to avoid alcohol, and they were not involved in any other form of therapy. There were no restrictions on the consumption of non-alcoholic beverages.

Results

Studies with barbiturates

Initial studies were carried out with the barbiturates, heptabarbitone and pentobarbitone sodium. With heptabarbitone decrements in performance were observed 10 h after 200 mg, 10 and 13 h after 300 mg and 10, 13, 16 and 19 h after 400 mg (Borland & Nicholson, 1974), and with pentobarbitone sodium the residual effects during the day after overnight ingestion of 200 mg were very similar to those observed with heptabarbitone 400 mg (Borland *et al.*, 1975). Residual effects on visuo-motor coordination were related to dose both in their persistence and in the decrement at a given time interval (Figure 1), and in this way the studies supported previous investigations (Von Felsinger *et al.*, 1953; Malpas *et al.*, 1970; Bond & Lader, 1972) and showed, as did Kornetsky *et al.* (1959), that impaired performance may persist longer with higher

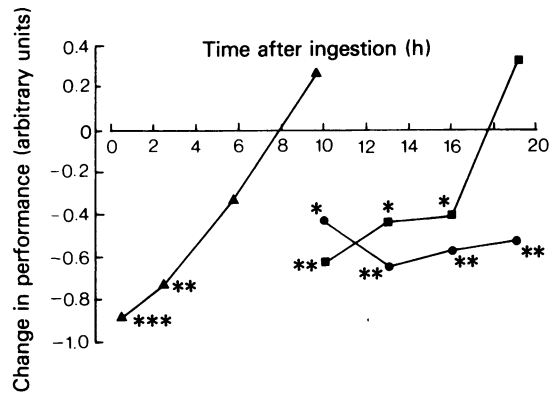

Figure 2 Effect of diazepam 10 mg (▲) ingested in the morning, and nitrazepam 10 mg (●) and flurazepam hydrochloride 30 mg (■) ingested overnight on visuo-motor coordination (arbitrary units). Significance levels: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

doses which are still within the usually accepted therapeutic range.

Studies with 1,4-benzodiazepines

The preliminary studies with barbiturates established the sensitivity of a tracking task to the residual effects of drugs both in relation to time and to dose, and so the technique was used in the investigation of residual effects of the benzodiazepines, diazepam, flurazepam hydrochloride and nitrazepam (Borland & Nicholson, 1975; Borland *et al.*, 1975). It was found that, although performance was impaired to 16 h after flurazepam hydrochloride 30 mg and to, at least, 19 h after nitrazepam 10 mg, the effects with diazepam 10 mg were more limited (Figure 2). Studies on the immediate effects of diazepam 10 mg showed that impaired performance was limited to a few hours after ingestion and that there was little likelihood of residual impairment with overnight ingestion, as long as the dose did not exceed 10 mg (Borland & Nicholson, 1977).

It was with these findings that the studies turned to a detailed analysis of the effects of diazepam and its metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy, N-desmethyldiazepam (oxazepam) (Clarke & Nicholson, 1978). Performance was observed from 10-16 h after overnight ingestion of diazepam 5 and 10 mg, temazepam 10, 20 and 30 mg and oxazepam 15, 30 and 45 mg, and from 0.5-6.5 h after morning ingestion of diazepam 10 mg, temazepam 20 mg and oxazepam 30 mg. Coordination was not impaired with the overnight ingestion of diazepam 5 and 10 mg (Figure 3), temazepam 10, 20 and 30 mg

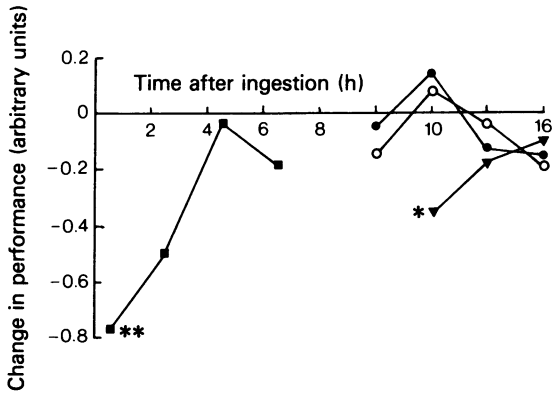

Figure 3 Effect of diazepam 10 mg (■) ingested in the morning and diazepam 5 (●), 10 (○) and 15 mg (▲) ingested overnight on visuo-motor coordination (arbitrary units). Significance levels: $*P < 0.05$; $**P < 0.01$.

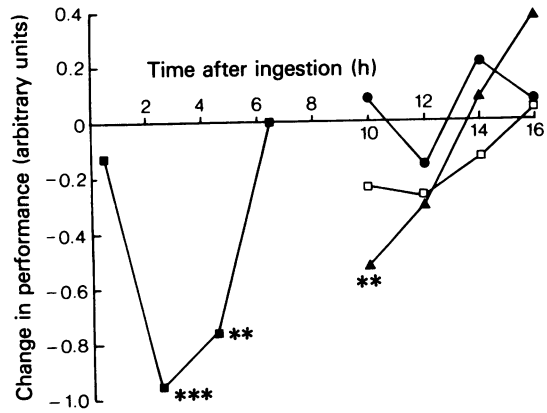

Figure 5 Effect of oxazepam 30 mg (■) ingested in the morning, and oxazepam 15 (●), 30 (□) and 45 mg (▲) ingested overnight on visuo-motor coordination (arbitrary units). Significance levels: $**P < 0.01$; $***P < 0.001$.

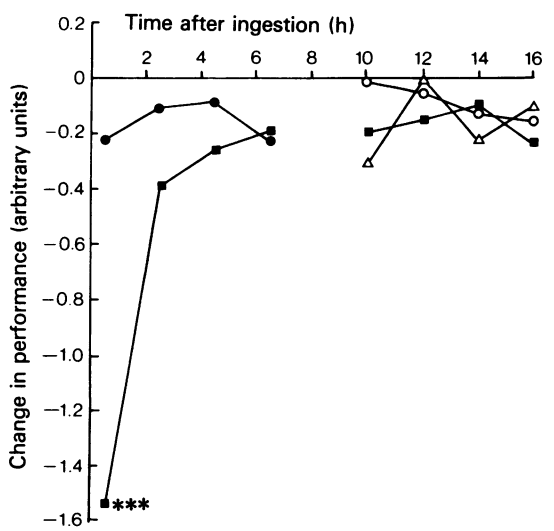

Figure 4 Effect of temazepam 10 (●) and 20 mg (■) ingested in the morning, and temazepam 10 (○), 20 (□) and 30 mg (▲) ingested overnight on visuo-motor coordination (arbitrary units). Significance level: $***P < 0.001$.

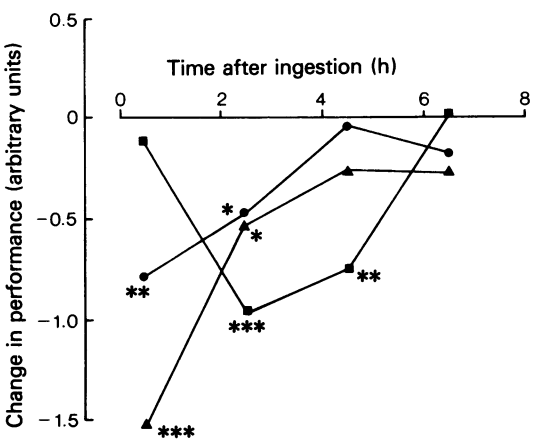

Figure 6 Effect of diazepam 10 mg (●), temazepam 20 mg (▲) and oxazepam 30 mg (■) ingested in the morning on visuo-motor coordination (arbitrary units). Significance levels: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

(Figure 4) or oxazepam 15 and 30 mg (Figure 5). However, with temazepam 30 mg there was a trend toward impaired performance, and with oxazepam 45 mg there was impaired performance 10 h after ingestion. With morning ingestion visuo-motor coordination was impaired at 0.5 and 2.5 h after diazepam 10 mg, at 0.5 h after temazepam 20 mg, and at 2.5 and 4.5 h after oxazepam 30 mg (Figure 6).

These observations were in broad agreement with other studies. Similar results with diazepam have been reported by Seppälä *et al.* (1976) with coordination skills and visual functions related to driving. Recovery from impaired performance within

a few hours after ingestion of diazepam has been observed by Hart *et al.* (1976) with a variety of tasks including auditory vigilance, reaction time, short-term memory and digit symbol substitution. With temazepam our results were comparable with those of Hindmarch (1975), and so suggested a residual effect on performance with the 30 mg dose. Other workers have observed the slow onset of impaired performance with oxazepam, and Molander & Duvhök (1976) have recorded maximum depression of critical flicker fusion frequency 3.0 h after ingestion of oxazepam 20 and 40 mg and impaired coordination with oxazepam 40 mg.

It is evident that diazepam and its hydroxylated metabolites may be free of residual effects within certain dose ranges. However, there are certain points which have to be taken into consideration with the use of these drugs by persons involved in skilled activity. With diazepam 10 mg daily, accumulation of its long-acting metabolite, nordiazepam, is a possibility, and so diazepam is more appropriate for occasional use as an hypnotic. Temazepam and oxazepam have the advantage over diazepam that their metabolism is not complicated by a long-acting metabolite, and so daily ingestion of these drugs would not be contraindicated. The relatively slow absorption of oxazepam indicated by the delayed appearance of impaired performance could reduce its usefulness as an hypnotic, although otherwise it would seem to be an effective drug. Nevertheless, even with these provisos, diazepam, temazepam and oxazepam, are likely to be of use in the management of sleep disturbance when impaired performance the next day is to be avoided. Diazepam 5-10 mg, temazepam 10-20 mg and oxazepam 15-30 mg are, in this context, useful drugs, and studies on the effects of these drugs on sleep in man, reviewed elsewhere (Stone & Nicholson, 1979), have indicated their place in the management of sleep disturbance.

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