Behavioural activity in the monkey *(Macaca mulatta)* of the metabolites of diazepam in man

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In previous studies in the monkey *(Macaca mulatta)* we showed that diazepam (3.0 mg/kg) increased total response time and impaired accuracy of response on a delayed differentiation task (Nicholson & Wright, 1974). In the present studies we have examined the activity of the principal metabolites of diazepam, N-desmethyldiazepam (nordiazepam), 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-desmethyldiazepam (oxazepam), using both delayed differentiation and spatial delayed alternation. Five monkeys were trained on each task. The four drugs (diazepam and its three metabolites) were given by intraperitoneal injection (1.8 and 3.0 mg/kg) in 5 ml polyethylene glycol. Delayed differentiation was tested 2 and 6 h after injection, and delayed alternation was tested 2 h after injection. The data were analysed by analysis of variance.

With differentiation there were no effects after temazepam or oxazepam, and effects with diazepam and nordiazepam were observed at 2 h only. Both doses of diazepam and nordiazepam increased total response time ($P < 0.01$). Diazepam impaired accuracy of response to matching on NO-GO responses ($P < 0.001$), and nordiazepam impaired accuracy of response to matching on both GO ($P < 0.05$) and NO-GO ($P < 0.05$) responses. With alternation there were no effects after temazepam or oxazepam. Both doses of diazepam impaired behaviour ($P < 0.01$), but the effect of nordiazepam $P < 0.05$) was limited to the higher dose.

In further experiments alternation was tested 4 and 6 h after 3.0 mg/kg nordiazepam. The mean plasma level (1.84 μg/ml) of nordiazepam 4 h after 3.0 mg/kg nordiazepam is similar to that (1.57 μg/ml) of nordiazepam 2 h after 3.0 mg/kg diazepam (Curry, Nicholson & Whelpton, 1976), but no impairment was observed. These findings, together with the observation that the activity of diazepam is changed by demethylation, suggest that the effect of diazepam is unlikely to be due solely to nordiazepam. With temazepam and oxazepam the absence of behavioural effects may have been related to their fast equilibration half times — 0.60 and 0.57 h respectively. However, no impairment was observed with alternation 1 h after 3.0 mg/kg temazepam or oxazepam. Mean plasma levels of temazepam and oxazepam are 0.46 and 0.87 μg/ml at 1 h compared with 0.17 and 0.39 μg/ml respectively at 2 h (Curry *et al.*, 1976).

These studies using identical doses of diazepam and its principal metabolites indicate that, though behavioural activity persists after demethylation (nordiazepam), hydroxylation (temazepam and oxazepam) is accompanied by a loss of, or a considerable reduction in, activity. Diazepam, nordiazepam and temazepam (each 10 mg orally) are hypnotics in man (Nicholson & Stone, 1976; Nicholson, Stone, Clarke & Ferres, 1976), and so behavioural activity represented by impaired differentiation and alternation is not an inevitable property of such benzodiazepines.

References

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