the drug industry, but because of their likely economic benefits it seems a pity they should have to be abandoned for lack of immediate resources.

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ACTIVITY OF FOSAZEPAM, A SOLUBLE ANALOGUE OF DIAZEPAM

In a previous paper we reported the effects of fosazepam (7-chloro-1-(dimethylphosphinylmethyl)-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-on), a soluble analogue of diazepam, on sleep in man (Nicholson, Stone & Clarke, 1976). Both diazepam and fosazepam have short plasma half times (equilibration phase), but fosazepam, unlike diazepam, modifies the sleep of the recovery night. Similar observations were reported by Allan & Oswald (1976), and it has been suggested that the hypnotic effect of fosazepam may be due to its long acting metabolite, nordiazepam, which is known to modify the sleep wakefulness cycle of man for about 28–30 h after ingestion (Nicholson, Stone, Clarke & Ferres, 1976). However, though the metabolism of both diazepam and fosazepam in man involves significant plasma levels of nordiazepam (Hoechst AG—Internal Report) it would appear that nordiazepam is a relatively unimportant metabolite of fosazepam in the monkey, and we have used this species difference to investigate the behavioural activity of fosazepam and its principal metabolite, 3-hydroxyfosazepam, uncomplicated by the activity of nordiazepam (Figure 1).

The pharmacokinetic studies were carried out with a colony of six male monkeys (*Macaca mulatta*) weighing between 5.4 and 6.2 kg (mean 5.8 kg). Each animal was injected intraperitoneally on separate occasions with 3.0 mg/kg diazepam and 3.0 mg/kg fosazepam. Blood samples were obtained at 0.5, 1, 2, 4, 8 and 24 h after injection and plasma prepared. Diazepam and nordiazepam were measured by the gas chromatographic method of Hart, Hill, Bye, Wilkinson & Peck (1976). Fosazepam was extracted from acidified plasma with dichloromethane and assayed by high pressure liquid chromatography. Nitrazepam was the internal standard. Analysis was on a Spherisorb 5 μ silica column with a mobile phase of 9% methanol/91% methylene chloride, and detection was by UV absorption at 236 nm. The mean plasma concentrations are given in Table 1, and illustrated in Figure 2. The plasma concentrations of nordiazepam during the first 6 h after injection were above 1.0 μg/ml after diazepam, and below 0.1 μg/ml after fosazepam.

The behavioural studies were carried out with a separate colony of five male monkeys weighing

Table 1 Mean plasma concentrations (μg/ml) after intraperitoneal injection of 3.0 mg/kg of diazepam and 3.0 mg/kg fosazepam. The results are the mean for six monkeys

Drug	*Compound measured*	*Time after injection (h)* 0.5	1	2	4	8	24
Diazepam	Diazepam	0.48	0.29	0.11	0.05	0.03	0.00
	Nordiazepam	2.02	2.45	1.58	1.44	0.90	0.20
Fosazepam	Fosazepam	1.18	1.14	0.52	0.20	0.08	0.05
	Nordiazepam	0.04	0.04	0.04	0.05	0.03	0.02

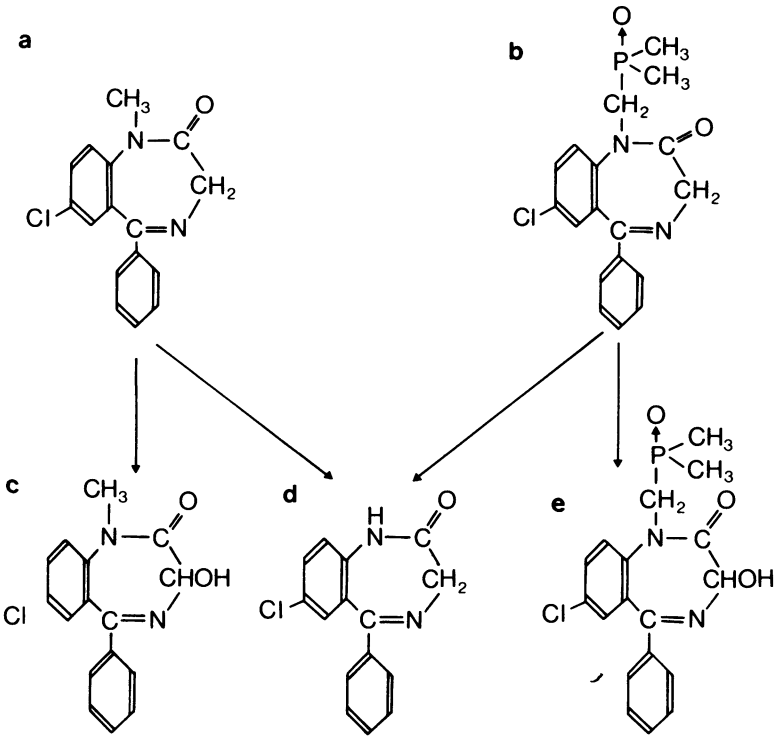

Figure 1 Structural formulae of (a) diazepam and (b) fosazepam, and their principal metabolites ((c) 3-hydroxydiazepam, (d) nordiazepam and (e) 3-hydroxyfosazepam).

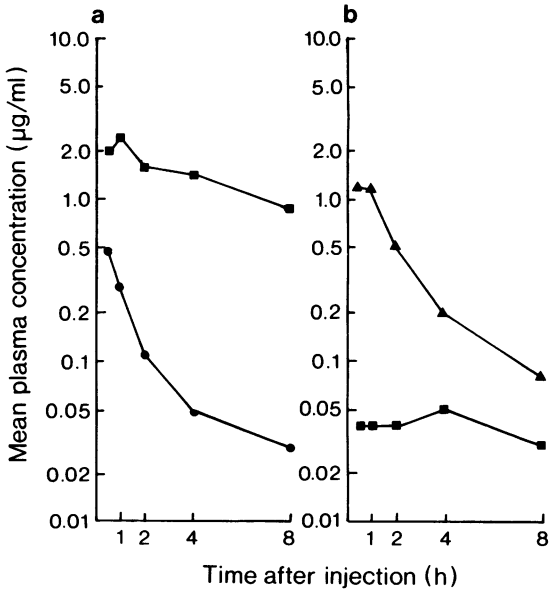

Figure 2 Mean plasma concentrations (μg/ml) in the monkey of (a) diazepam (●) and nordiazepam (■) and (b) fosazepam (▲) and nordiazepam (■) after intraperitoneal injection of diazepam (3.0 mg/kg) and fosazepam (3.0 mg/kg) respectively.

between 6.8 and 15.2 kg (mean 11.6 kg), trained on delayed differentiation. The details of the task, experimental procedure and techniques for analysis of the results are given elsewhere (Nicholson, Wright & Ferres, 1973; Nicholson & Wright, 1974). Diazepam was given by intraperitoneal injection at 1.8 and 3.0 mg/kg body weight in 5 ml polyethylene glycol, and fosazepam and 3-hydroxyfosazepam were injected at 18.0 and 30.0 mg/kg in water. The effect of these drugs on total response time and accuracy of matching are given in Tables 2 and 3. With diazepam total response time was increased and accuracy of matching impaired, but with fosazepam and 3-hydroxyfosazepam no change in total response time and accuracy of response was observed.

These studies suggest that substitution of the methyl group of diazepam by a dimethyl-phosphinylmethyl group reduces markedly the behavioural activity of the molecule. In the monkey, diazepam (1.8–3.0 mg/kg) increases total response time and impairs differentiation, whereas fosazepam and its metabolite, 3-hydroxyfosazepam (each 18.0–30.0 mg/kg) have no behavioural effects. This would be in accord with the conclusion from sleep studies in man that the activity of fosazepam may be due to that of its metabolite, nordiazepam (Nicholson, Stone & Clarke, 1976). The suggestion that the hypnotic effect of fosazepam in

Table 2 Change in total response time (ms) after drugs. The results are the mean for five monkeys

Time after injection (h)	*Diazepam (mg/kg)* 1.8	3.0	*Fosazepam (mg/kg)* 18.0	30.0	*3-Hydroxy fosazepam (mg/kg)* 18.0	30.0
2	119 ***	188 ***	29 NS	−19 NS	−15 NS	−17 NS
6	53 **	93 ***	17 NS	−28 NS	−16 NS	22 NS

NS = Not significant.
Least significant differences; * 36, ** 53, *** 77.

Table 3 Change in accuracy of response to matching on delayed differentiation after drugs. The results are the mean for five monkeys

Time after injection (h)	*Diazepam (mg/kg)* 1.8	3.0	*Fosazepam (mg/kg)* 18.0	30.0	*3-Hydroxy fosazepam (mg/kg)* 18.0	30.0
2	−2.2 *	−3.4 **	0.2 NS	−1.2 NS	−0.8 NS	0.0 NS
6	−0.2 NS	0.2 NS	−0.8 NS	−1.6 NS	−0.8 NS	−1.0 NS

NS = Not significant.
Least significant differences; * 2.2, ** 3.2, *** 4.6.

man does not depend on the activity of the parent drug, which is highly water soluble, but is related to its metabolite would also explain the higher dose of fosazepam, compared with diazepam, necessary to produce an equivalent increase in total sleep time.

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