Prazepam metabolism in female subjects

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The benzodiazepine prazepam has been suggested to be metabolized first via hydroxylation followed by *N*-dealkylation (DiCarlo et al 1970; Viau et al 1973). However, more recently Greenblatt & Shader (1978) reported that *N*-desalkylprazepam (*N*-desmethyldiazepam) was the only metabolite detected in the plasma of subjects given a single oral dose of 20 mg of prazepam. The parent drug was not detected. Our findings are in accord with those of Greenblatt & Shader (1978)

We have administered prazepam (3 × 10 mg capsules, batch no. X05050, kindly supplied by William R. Warner & Co. Ltd., Eastleigh, Hants) to fasting female volunteers (56–64 kg, aged 20–41 years, all non-smokers), under conditions similar to those described by Brodie et al (1981). Blood samples were withdrawn from arm veins during 11 days and the plasma separated and assayed for *N*-desalkylprazepam by gas chromatography using a nitrogen selective detector (Brodie et al 1981). Urine was also collected for 24 h and similarly assayed for prazepam, *N*-desalkylprazepam, oxazepam and 3-hydroxyprazepam.

The peak mean concentration of *N*-desalkylprazepam of 235 ng ml^{-1} occurred at 12 h (Table 1) but the plasma concentrations were maintained at almost this value over 5–24 h. They then declined with a mean half-life of 107 h (Table 2) (but only 82 h if the results of Subject 5 are ignored). The mean apparent plasma clearance of *N*-desalkylprazepam calculated from the expression dose/area assuming complete absorption of prazepam and conversion to the desalkyl metabolite was 0·92 litres h^{-1}. These values of plasma half-life and clearance are similar to those calculated from data obtained after oral doses of clorazepate (Wretlind et al 1977; Carrigan et al 1977) which is converted to *N*-desmethyldiazepam (*N*-desalkylprazepam) in the acid milieu of the stomach (Baselt 1978) or of *N*-desmethyldiazepam itself (Klotz et al 1976).

The calculated plasma clearances were not corrected for the proportion of the dose (about 11%) that may be converted to 3-hydroxyprazepam (Viau et al 1973) and, therefore, unavailable for conversion to *N*-desalkylprazepam.

Neither prazepam nor *N*-desalkylprazepam were detected in the 24 h urine of any of the subjects above a limit of detection of 2 ng ml^{-1} urine. 3-Hydroxyprazepam (4·3% s.d. 3·0, range 0·5–7·3% dose) and oxazepam (1·3% s.d. 1·0, range 0·3–3·0% dose) were present, almost totally conjugated. Extensive studies (Chang et al 1978) suggest that more rigorous hydrolysis of conjugates results in a greater accountability of the excreted dose in 5-day urine as oxazepam than as 3-hydroxyprazepam (ratio 1:0·2–0·3). About 4% of the dose was excreted as conjugated oxazepam in 0–24 h urine. As in their studies of urinary metabolites, DiCarlo et al (1970) and Viau et al (1973) had found mainly 3-hydroxyprazepam and oxazepam as their glucuronides, the hydroxy compound being present in greater proportions in early urine, those authors suggested that the major metabolic pathway for prazepam differed from that of diazepam in that prazepam was first hydroxylated to 3-hydroxyprazepam which was then *N*-dealkylated to oxazepam. It was also inferred that *N*-dealkylation of the cyclopropylmethyl group of prazepam was less facile than that of the methyl group of diazepam (DiCarlo et al 1970; Schallek et al 1972). However, as *N*-desalkylprazepam is the only major metabolite and drug-related substance detected in plasma, it is probable that the major metabolic route of prazepam is essentially similar to that of diazepam, namely *N*-dealkylation followed by hydroxylation, i.e. prazepam → *N*-desalkylprazepam → oxazepam. The relatively long action of prazepam must be a consequence of this pathway. Some direct hydroxylation of prazepam also occurs and the resultant product, 3-hydroxyprazepam, is more rapidly cleared from the plasma of man, as is oxazepam (Wretlind et al 1977), and, therefore, neither of these metabolites would be able to contribute as much to the pharmacological action of doses of prazepam as does *N*-desalkylprazepam (*N*-desmethyldiazepam) which is known to be active in man (Randall et al 1965).

Table 1. Mean plasma concentrations of *N*-desalkylprazepam after single oral doses of prazepam (30 mg) to human subjects.

Time (h)	Concentrations (ng ml^{-1}) (s.d.)
·75	151 (100)
1·5	185 (59)
3	194 (70)
5	216 (75)
8	233 (100)
12	235 (68)
24	215 (58)
48	179 (33)
96	125 (46)
168	85 (52)
216	54 (47)
264	44 (38)

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Table 2. Half-lives ($t_{\frac{1}{2}}$), areas under the plasma concentration-time curves (AUC) and apparent plasma clearances (Clp) of *N*-desalkylprazepam after single oral doses of prazepam (30 mg ≡ 25 mg *N*-desalkylprazepam) to human subjects.

Subject No.*	$t_{\frac{1}{2}}$ (h)	AUC (μg h ml^{-1})	Clp† (litres h^{-1})
1 (41)	109	26·22	0·95
2 (27)	91	29·99	0·83
3 (20)	63	24·93	1·00
4 (23)	63	18·69	1·34
5 (39)	208‡	50·61	0·49
Mean (s.d.)	107 (60)	30·09 (12·17)	0·92 (0·31)

* The ages (years) of the subjects are shown in parentheses.
† Uncorrected (See text).
‡ On another occasion when this volunteer was dosed with prazepam, the measured half-life of *N*-desalkylprazepam was shorter, 96 h, and the clearance higher, 0·57 litres h^{-1}.

We are grateful to Dr C. White for medical supervision of the subjects and to William R. Warner & Co. Ltd for their support of these studies.

March 12, 1980

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Naloxone fails to block amphetamine-induced anorexia and conditioned taste aversion

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Some behavioural effects of amphetamine can be antagonized by naloxone (Holtzman & Jewett 1973; Holtzman 1974; Holtzman 1976; Dettmar et al 1978; Haber et al 1978). Such findings suggest that endorphin/catecholamine interactions may be important in the control of behaviour (Dettmar et al 1978; Haber et al 1978). However, naloxone/amphetamine interactions are *not* simple phenomena, having been reported to be species specific (Holtzman 1974, 1979a), although other data cast doubt on this notion (Dettmar et al 1978). They have also been reported to be behaviourally specific (Haber et al 1978) although this conclusion is also questionable (cf. Segal et al 1977; Dettmar et al 1978); and to occur only with low ($\leqslant$3 mg kg^{-1}) doses of naloxone (Dettmar et al 1978). Other authors have reported antagonism with much higher doses (Holtzman & Jewett 1973). Clearly, the data available on amphetamine/naloxone interactions are inconsistent. Nevertheless, much evidence supports the idea that catecholamine/endorphin interactions are important in mediating behaviour (e.g. Harris et al 1977; Iwamoto & Way 1977; Broekkamp et al 1979; Belluzi & Stein 1977; Katz & Carroll 1979; Amir et al 1979; Kelley et al 1980). The work reported here has further investigated naloxone/amphetamine interactions to clarify the significance of contradictory earlier reports. The first study described examined naloxone effects on amphetamine anorexia.

Female albino rats (200–250 g) housed in a light and temperature controlled room were habituated to an 18-h food deprivation schedule for 28 days, during which they received six i.p. injections of 0·9% NaCl (saline) to adapt them to handling and injection stress. They were then allocated to ten groups (n = 8) making up a complete 2 × 5 factorial design, all subjects receiving two injections on the day of anorexia testing. The first injection was saline or (+)-amphetamine 2·0 mg kg^{-1}. The second was either one of four doses of naloxone hydrochloride: 0·3 (n_1), 1·0 (n_2), 3·0 (n_3) and 10 mg kg^{-1} (n_4) or a saline control. Injection pairs were administered i.p. (2 ml kg^{-1}) within one minute, 30 min before food access. Amounts of food (lab chow) eaten were recorded 1, 2, 4 and 6 h after access. Some of the behavioural effects of the 2·0 mg kg^{-1} dose of (+)-amphetamine used have previously been reported to be antagonized by naloxone (Holtzman 1976; Segal et al 1977; Dettmar et al 1978).

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