normal food intake does not alter plasma binding of diazepam. The corresponding values for FFA are given in Table 2. The increase in this parameter after lunch was minimal in all patients tested.

The results of this study demonstrate: 1. Food intake does not elevate FFA levels in man as high as was found in experiments with rats to induce changes in drug plasma binding (Gugler, Shoeman & Azarnoff, 1974); 2. food intake does not alter the binding of diazepam in fresh human plasma and fluctuations in diazepam levels as described by Linnoila *et al.* (1975) could not be explained in our experimental design by food-induced changes of plasma binding. The results from our experiments approaching the clinical situation (binding measured at 37°C with genuine fresh human plasma before and after a normal meal, therapeutic concentrations of drugs), are in some contrast to the discussion of a paper recently published by Tsutsumi, Inaba, Mahon & Kalow (1975). This is not too surprising, since their experimental design was 'artificial' from a physiological point of view (binding measured at 22°C with 0.5% human serum albumin solution under the influence of high concentrations of the middle chain fatty acid laurate, the concentration of which is low in normal food). With these experiments we want to emphasize the limitation of extrapolating data from 'nonphysiological' *in vitro* experiments to clinical situations.

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RESIDUAL EFFECTS OF POTASSIUM CLORAZEPATE, A PRECURSOR OF NORDIAZEPAM

Benzodiazepines with nordiazepam as a significant metabolite may be useful in the management of insomnia, though with the overnight ingestion of nordiazepam there may be impaired performance the next day (Tansella, Zimmermann Tansella & Lader, 1974). It is in this context that we have compared the residual effects of potassium clorazepate (15 mg) and diazepam (15 mg), precursors of nordiazepam with hypnotic properties (Nicholson, Stone, Clarke & Ferres, 1976; Nicholson, Stone & Clarke, 1976), on visuo-motor co-ordination in man.

Six healthy volunteers were used. Their ages ranged from 24-42 (mean 36) years, and their weights ranged from 67-84 (mean 73) kg. Instructions were given to all subjects to avoid alcohol for 24 h before and after ingestion of a capsule, but there were no restrictions on the consumption of non-alcoholic beverages. The subjects were not involved in any form of therapy. The task required the subject to position a spot within a randomly moving circle displayed on an oscilloscope (Borland & Nicholson, 1974), and the movement of the spot was controlled by a hand held stick. The difficulty of the task was related to an error signal proportional to the distance between the spot and the centre of the circle, and the signal modulated the mean amplitude of the movement

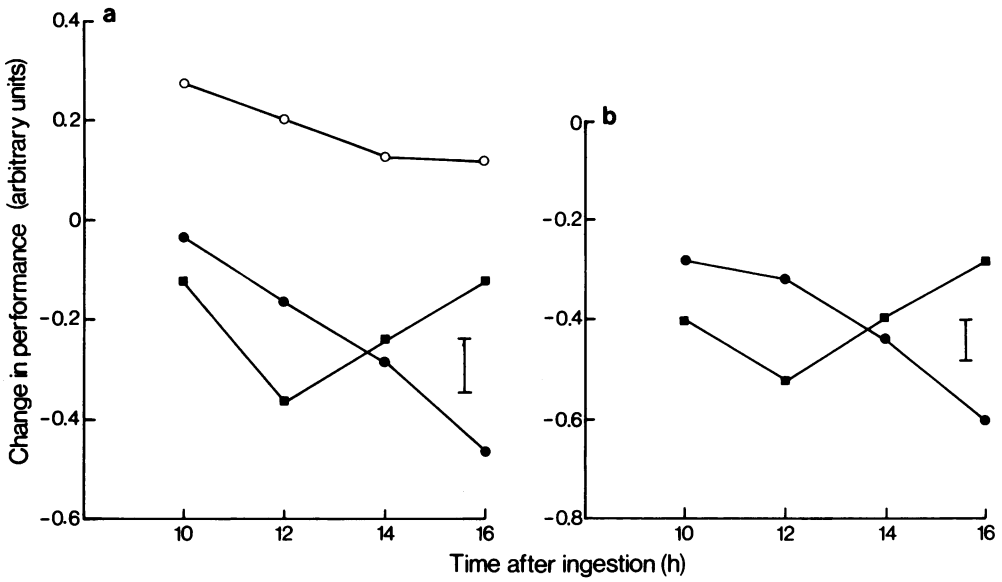

Figure 1 Change in performance (arbitrary units) on adaptive tracking after placebo, diazepam (15 mg) and potassium chlorazepate (15 mg). (a) Change in performance compared with performance unrelated to ingestion of capsule. (b) Change in performance related to ingestion of placebo. ○ placebo; ● potassium clorazepate; ■ diazepam. Vertical bar is the standard error (a: 0.12 arbitrary units. b: 0.08 arbitrary units).

Table 1 Analysis of variance and significance levels for performance change after placebo and drugs compared with control on adaptive tracking (arbitrary units) (mean for six subjects)

Source	*Degrees of freedom*	*Mean squares*	*F*	*Significance levels*
Subjects (S)	5	0.756076		
Drugs (D)	2	1.322471 (S x D)	5.21	*
Time (T)	3	0.132163		
S x D	10	0.254082	4.10	***
S x T	15	0.403388	6.50	***
D x T	6	0.090054		
S x D x T	30	0.062020		

	Time after ingestion			
Treatment	09° 00 h (+ 10 h)	11° 00 h (+ 12 h)	13° 00 h (+ 14 h)	15° 00 h (+ 16 h)
Placebo	0.27 *(*)	0.20 (*)	0.13 NS	0.12 NS
Potassium clorazepate (15 mg)	−0.03 NS	−0.17 NS	−0.29 **	−0.46 ***
Diazepam (15 mg)	−0.13 NS	−0.37 ***	−0.24 **	−0.12 NS

Least significant differences from zero for means of 6 were
5% = 0.21; 1% = 0.28; 0.1% = 0.37. (* = 5%; ** = 1%; *** = 0.1%).

of the circle. Trained subjects reached a plateau level of performance within the first 100s of each assessment. The mean amplitude of the task over the final 500s of a 10 min run was used as the performance measure, but, though the subjects were informed that the final 500s was used in the assessment of their performance, they were unaware when the interval commenced.

Performance was measured at 09.00, 11.00, 13.00 and 15.00 h during a day when no capsule was ingested the previous night (control), and during days when a capsule (placebo, diazepam (15 mg), or potassium chlorazepate (15 mg) was ingested the night before at 23.00 h. At least 7 days separated each experiment. The trial was double blind, and the order of the experiments (control, placebo or drugs) was random. Placebo and drugs were prepared as identical capsules, and two capsules were ingested on each occasion with water.

Performance at 09.00 h after placebo or drug was compared with performance at the same time of the day when no capsule was ingested the previous night, but as there were no differences between performance at 11.00, 13.00 and 15.00 h during the day when no capsule was ingested the previous night, the mean of the performances at these times was compared with each performance after a capsule. Performance at 09.00 h after drugs was compared with performance at the same time of the day after placebo, and the separate performances at 11.00, 13.00 and 15.00 h after drugs were compared with the mean of the performances at 11.00, 13.00 and 15.00 h after placebo. Analysis of variance was used. The results are given in Tables 1 and 2 and illustrated in Figure 1. At 09.00 h no change in performance was observed with diazepam or potassium clorazepate, but there was a subsequent impairment of performance with both drugs. The progressive impairment from 09.00 to 15.00 h with potassium clorazepate was a linear effect ($P = 0.01$). The return of performance to control levels during the day with placebo, and the progressive improvement from 11.00 to 15.00 h with diazepam were also linear effects ($P = 0.01$ and 0.05 respectively).

It is considered that with both placebo and drugs the enhanced or preserved performance of the early part of the day was related to the response of the subjects to ingestion of a capsule which could have impaired their performance. Enhanced performance after placebo and the apparent absence of an effect after drugs during the early part of the day, together with subsequent impairment, reflected a poorly sustained increase in effort. With placebo and diazepam performance returned to control levels during the experiment (Table 1), and so it is considered that performance 16 h after ingestion reflected that uninfluenced by increased effort. The studies suggest that the evaluation of residual effects should involve comparisons with performance unrelated to capsule ingestion as well as with performance related to placebo. In the present experiments

Table 2 Analysis of variance and significance levels for performance change after drugs compared with placebo on adaptive tracking (arbitrary units) (mean for six subjects)

Source	*Degrees of freedom*	*Mean squares*	*F*	*Significance levels*
Subjects (S)	5	1.138707		
Drugs (D)	1	0.005941		
Time (T)	3	0.022002		
S x D	5	0.128379	3.70	*
S x T	15	0.165394	4.76	**
D x T	3	0.169049	4.87	*
S x T x D	15	0.034742		

		Time after ingestion		
Treatment	09° 00 h (+ 10 h)	11° 00 h (+ 12 h)	13° 00 h (+ 14 h)	15° 00 h (+ 16 h)
Potassium clorazepate (15 mg)	−0.29 **	−0.32 ***	−0.44 ***	−0.61 ***
Diazepam (15 mg)	−0.40 ***	−0.52 ***	−0.39 ***	−0.27 **

Least significant differences from zero for means of 6 were
5% = 0.16; 1% = 0.22; 0.1% = 0.31. (* = 5%; ** = 1%; *** = 0.1%).

absence of measures unrelated to capsule ingestion would have led to the conclusion that performance after both drugs was impaired throughout the next day. It would appear that the residual effects of potassium clorazepate and diazepam are limited, and that, though the effect of potassium clorazepate is more persistent than that of diazepam, subjects are able to overcome the residual impairment of both drugs at the 15 mg dose.

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PHARMACOKINETIC INTERPRETATION OF STEADY STATE CONCENTRATION OF ANTIPYRINE AND OTHER DRUGS IN PLASMA

The biotransformation rate of antipyrine is a widely used index of hepatic microsomal drug metabolizing activity in man. It is customary to determine either the biological half-life or the body clearance of antipyrine following administration of a single dose of the drug. Alternatively, one can determine the steady state concentration of antipyrine in plasma during prolonged administration of constant doses at fixed intervals of time and use this as a measure of the biotransformation kinetics of the drug (Davis, Simmons, Dordoni & Williams, 1974). Typically, the steady state concentration of a drug in plasma is determined by drawing one blood sample at a fixed time after a maintenance dose and repeating this procedure one or more times to ascertain that a steady state has, in fact, been reached. The purpose of this communication is to point out some potential problems in the pharmacokinetic interpretation of such data, using antipyrine as an example.

The elimination kinetics of antipyrine are adequately described by mathematical expressions based upon a one-compartment pharmacokinetic model with first-order elimination (Greisen & Andreasen, 1976). The plasma concentration at the steady state (C_∞) produced by repeated,

Table 1 Relationship between elimination rate constant and steady state concentrations of antipyrine in plasma*

		Steady state antipyrine concentration (μg/ml)				
Elimination rate constant (h^{-1})	*Biological half-life (h)*	*0 h (maximum)*	*2 h*	*8 h*	*12 h (minimum)*	$\bar{C}_\infty$ *('mean')*
0.03	23.1	47.5	44.7	37.3	33.2	39.8
	(2.0)†	(1.70)	(1.8)	(2.2)	(2.4)	(2.0)
0.06	11.6	27.9	24.8	17.3	13.6	19.9
	(1.0)	(1.0)	(1.0)	(1.0)	(1.0)	(1.0)
0.09	7.70	21.7	18.1	10.6	7.38	13.3
	(0.67)	(0.78)	(0.73)	(0.61)	(0.54)	(0.67)
0.12	5.78	18.8	14.8	7.19	4.45	9.95
	(0.5)	(0.67)	(0.60)	(0.42)	(0.33)	(0.50)

* Based on 8.6 mg/kg every 12 h and an apparent volume of distribution of 600 ml/kg.

† Values in parentheses are normalized relative to the respective values when the elimination rate constant is 0.06 h^{-1}.