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KINETICS OF [^{14}C]PHENAZEPAM EXCRETION IN ALBINO RATS AFTER SINGLE AND REPEATED INJECTIONS OF THE DRUG

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During the 5 days after intraperitoneal injection of [^{14}C]phenazepam into albino rats, both intact animals and animals previously receiving phenazepam injections for 15 days, about 77% of the total radioactivity was excreted with the urine and feces. The excretion processes can be described by a first-order equation. The rate of total excretion of phenazepam was identical after single or repeated injections of the drug. Meanwhile, after a single injection of phenazepam into the animals, it was excreted mainly with the urine, whereas after repeated injections it was excreted mainly with the feces. The process of excretion of phenazepam with the urine after repeated injection is biexponential in character.

KEY WORDS: phenazepam; repeated and single injection; excretion; excretion constants; half-elemination period.

The kinetics of excretion of phenazepam, a tranquilizer of the 1,4-benzodiazepine series [2, 3], with the urine and feces after a single injection or a course of 15 daily injections of the drug is examined in this paper.

EXPERIMENTAL METHOD

Experiments were carried out on two groups of male albino rats weighing 180-200 g. [^{14}C]Phenazepam (1 Ci/mole) in a dose of 14 mg/kg was injected into the animals as a Tween emulsion. Samples of urine collected after 12, 24, 48, 72, and 120 h and of feces collected after 24, 48, 72, and 120 h were investigated. Phenazepam was injected daily for 15 days in a dose of 14 mg/kg into the animals of the second group, and this was followed by a single injection of [^{14}C]phenazepam (1 Ci/mole) in a dose of 14 mg/kg. Samples of urine and feces were collected after 12, 24, 48, 72, 96, and 120 h. The samples of feces were dried in an incubator at 80°C, weighed, and then hydrolyzed, in the same way as the samples of urine, with formic acid for 1 h on boiling water bath. Radioactivity in the biological media was determined by means of an Intertechnique (France) SL-30 liquid scintillation photometer and expressed as percentages of the dose administered to each animal. The excretion data were analyzed by "rate" and "sigma-minus" methods [4] and by Mansgeldorf's method [1].

EXPERIMENTAL RESULTS

The results in Tables 1 and 2 indicate that during the 5 days after intraperitoneal injection of [^{14}C]phenazepam into both groups of experimental animals about 77% of the total radioactivity was excreted with the urine and feces. Calculations showed that the excretion of total radioactivity from the experimental animals can be described by the first-order equation:

$$B_t = B_\infty(1-e^{-kt}),$$

where B_t is the quantity of radioactivity excreted by time t; B_∞ is the quantity of radioactivity excreted in the course of an infinite exposure; and k is the excretion constant.

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TABLE 1. Quantity of [^{14}C]Phenazepam and Its Metabolites Excreted (in % of injected dose) by Albino Rats after a Single Injection of the Drug (M ± m, n = 5)

Process	Time, h				
	12	24	48	72	120
Excretion with urine	21,0±3,4	30,5±4,0	40,2±5,0	43,6±5,1	46,5±5,1
Excretion with feces	—	16,2±2,4	25,6±2,4	28,6±2,3	29,7±2,2
Total excretion	—	46,7±5,0	65,7±4,1	72,2±4,2	76,1±4,6

TABLE 2. Quantity of [^{14}C]Phenazepam and Its Metabolites Excreted by Albino Rats (in % of injected dose) after Preliminary Administration of the Drug for 15 Days (M ± m, n = 5)

Process	Time, h					
	12	24	48	72	96	120
Excretion with urine	15,1±2,0	23,6±3,3	27,8±2,7	31,1±3,2	33,0±3,4	34,2±3,4
Excretion with feces	9,0±4,3	22,0±5,0	36,1±1,5	40,0±0,5	41,9±0,5	42,7±0,2
Total excretion	24,1±6,2	45,6±6,7	64,0±4,4	71,2±3,3	75,0±3,3	76,9±3,4

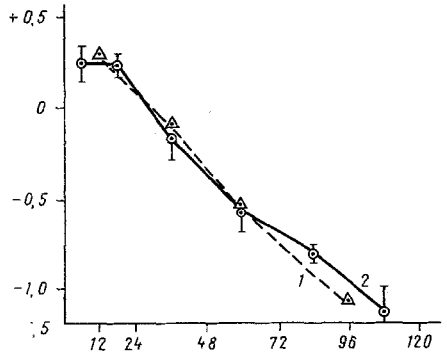

Fig. 1

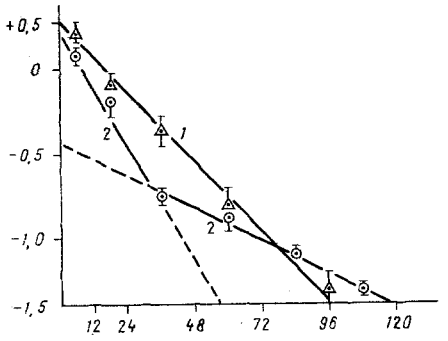

Fig. 2

Fig. 1. Rate of excretion of total radioactivity with urine and feces after a single does and a 15-day course of injections of phenazepam in rats. Here and in Figs. 2 and 3: abscissa, time of experiment (in h); ordinate, logarithm of rate of excretion (in % of injected dose).

Fig. 2. Rate of excretion of total radioactivity with urine after single and repeated doses of radioactive phenazepam in rats. Legend as in Fig. 1.

Comparison of the rate of excretion of the drug in albino rats after a single or repeated injections showed (Fig. 1) that the processes were identical in both cases. The "rate" method of determination of the parameters of excretion illustrated in Figs. 1-3 is limited by certain disadvantages, for T 0.5 is less than the interval of taking samples of urine and feces (Table 3), and this inevitably leads to errors (overestimation) during the determination of k. The "sigma-minus" method also leads to successive accumulation of error during analytical determination of k, for it is assumed that $B_{120} = B_\infty$. These limitations do not extend to Mansgeldorf's method when B_∞ is determined directly (by plotting a graph with coordinates B_t and $B_t + \Delta t$). By using 24 and 48 h as Δt, the value of B_∞ was determined for both groups of animals, and was found to be 78% of the administered dose. In both cases the excretion constant was determined by the equation:

$$k = \frac{2.303}{t} \cdot \frac{B_\infty}{B_\infty - B_t}.$$

However, if the rate of excretion of total radioactivity is examined separately with the urine and feces, differences can be observed for the groups of animals receiving phenazepam as a single dose or repeatedly. For instance, after a single dose of phenazepam the total radioactivity was excreted by the rats mainly with the urine, whereas in the case of repeated injections it was excreted mainly with the feces (Tables 1 and 2). This change in the excretion of phenazepam and its metabolites is probably the result of intensification of their elimination with the bile.

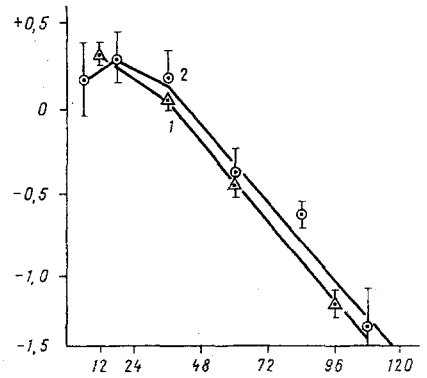

Fig. 3. Rate of excretion of total radioactivity with the feces after single and repeated doses of radioactive phenazepam in rats. Legend as in Fig. 1.

TABLE 3. Kinetic Parameters of Excretion of [^{14}C]Phenazepam and Its Metabolites by Albino Rats

Process	Time of process, D		
	$T_{0,5}$, h	k, h^{-1}	B_∞, %
	After single dose of drug		
Excretion with urine	17	0,040	47
Excretion with feces	22	0,032	31
Total excretion	19	0,037	78
	After repeated doses of drug		
Excretion with urine			
fast phase	9	0,077	29
slow phase	38	0,018	17
Excretion with feces	18	0,038	45
Total excretion	19	0,036	78

In animals receiving a single dose of phenazepam the excretion of total radioactivity both with the urine and with the feces was exponential over the whole range of values of t investigated (Table 3). In animals receiving diazepam for 15 days, however, the character of excretion of radioactivity with the urine was biexponential (Fig. 2). Excretion of radioactivity with the feces remained exponential in character between 24 and 120 h (Fig. 3). Determination of B_∞ of the feces, and also of the "fast" and "slow" phases of excretion of radioactivity with the urine, a value in excess of 78% of the injected dose was obtained (Table 3), on the assumption that excretion was exponential in character.

After both single and repeated doses of the drug, 0.6 B_∞ of radioactivity was excreted by the albino rats in the course of 24 h. It can thus be concluded that no change took place in the function of the systems of the body leading to phenazepam excretion. On the basis of the two series of experiments the following model can be proposed to represent the change in the content of the drug in the body during prolonged administration to animals:

$$D_{ef} = D_{dd}(e^{-kT} + e^{-2kT} + \ldots + e^{-knT}),$$

where D_{ef} is the content of the drug and its metabolites in the body; D_{dd} the daily dose of the drug; T the time between injections.

Despite the relatively long half-elimination time of phenazepam and its metabolites in rats, their accumulation is a limited process and reaches a steady state. If the daily dose is taken as 100, during the first 24 h the content of radioactive material falls to 40%, and when the steady state is reached, it fluctuates between 67 and 167%.

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