DOSE-DEPENDENCE OF ETHIMIZOLE ABSORPTION FROM THE DOG SMALL INTESTINE

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Despite the widespread clinical use of ethimizole (E) as a respiratory stimulant and nootropic agent, its pharmacokinetics and metabolism have only recently begun to be studied [1, 10, 11, 13]. It has been shown that after peroral administration of E tablets the absolute bioavailability in man varied from 3.6 to 22.2% [13], whereas after peroral administration of E solution to rats it was 32%. The question thus arises whether the low bioavailability of E is linked with its poor absorption from the gastrointestinal tract, or whether it is the result of its rapid metabolism during its first passage through the liver.

In the present investigation a model of a chronic intestinal loop in dogs was used to study the kinetics of absorption of E from the small intestine.

EXPERIMENTAL METHOD

Absorption of E from the small intestine was studied by means of an intestinal loop in chronic experiments [7, 12] on four male mongrel dogs weighing 10-12 kg. An intestinal segment about 30 cm long, with its vascular branches intact, was used for the loop. An anastomosis was formed at the divided ends of the gut to restore the continuity of the small intestine. The ends of the loop were sutured and a small incision made at each end, into which metal cannulas were introduced. The cannulas remained open and experiments to study absorption began 3 weeks after the operation. Before E was injected, the loop was washed with physiological saline (37°C). Next, about 30 ml of a solution of E in physiological saline was injected into the loop. The rate of absorption of E in two concentrations (10 and 1 mg) was studied in each dog at an interval of several weeks. The solution contained 0.33 or 0.033 mg•ml^{-1} of ^{14}C-E (1.66 kBq•ml^{-1}) and an unabsorbed marker ^{14}C-polyethylene-glycol (^{14}C-PEG) in a concentration of 0.62 mg•ml^{-1} (0.5 kBq•ml^{-1}). Samples of 0.5 ml were taken immediately after the injection (zero time) and then at intervals of 3-5 min for 45 min. To each sample 0.5 ml of borate buffer, pH 9.6, and 2 ml of benzene were added. The mixture was shaken for 10 min and centrifuged; samples of 0.5 ml were taken from each phase, transferred into 10 ml of Bray's scintillation solution, and radioactivity was measured on a Packard Tricarb 300 CD liquid scintillation counter. The concentration of E was calculated from activity of the benzene phase, and PEG from activity of the aqueous phase.

^{14}C-E with specific activity of 1.5 kBq•g^{-1} was obtained by the methods described previously [3]. The radiochemical purity of the sample, as shown by thin-layer chromatography, was 99.3%. A mixture of the corresponding amount of labeled and "cold" E and PEG (Amersham International, England) was used.

The fraction of the substance in the samples was calculated by the equation:

$$C_t = \frac{^{14}\text{C-E}_t}{^{14}\text{C-E}_0} \cdot \frac{^{14}\text{C-PEG}_0}{^{14}\text{C-PEG}_t},$$

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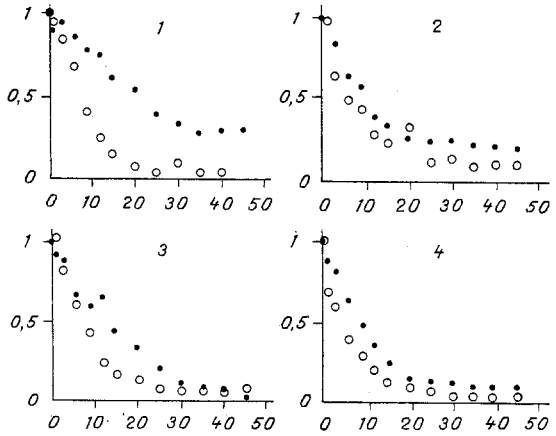

Fig. 1. Changes in concentration of E in intestinal loop with time. Abscissa, time (in min); ordinate, E as a fraction of total dose. Empty circles — E in a dose of 10 mg, filled circles — 1 mg. Data for individual dogs, numbered 1, 2, 3, and 4, are given.

TABLE 1. Mean Time of Absorption of E from Isolated Intestinal Loop in Dogs

Dog No.	MTA (± standard deviation)	
	dose of E, mg	
	10	1
1	30,12±8,06	9,26±0,89
2	20,97±2,60	4,00±1,02
3	16,81±0,90	9,48±0,63
4	12,37±0,71	7,62±0,63
Mean	20,07±3,07	7,59±0,79

where C_t is the fraction of the original quantity of the preparation remaining in the segment at time (t), ^{14}C-E_0 and ^{14}C-PEG_0 denote radioactivity of ^{14}C-E and ^{14}C-PEG in the samples at zero time (t = 0), and ^{14}C-E_t and ^{14}C-PEG_t denote radioactivity at time t. To analyze the data for each dog a single-term exponential function was used:

$$f(t) = P(1) \cdot e^{-P(2)t},$$

where $P_{(1)}$ and $P_{(2)}$ are parameters of the exponential function. The mean time of absorption (MTA) of E on the isolated segment and the asymptote of the standard deviation SD_{MTA} were calculated [14, 15]:

$$MTA = 1/P(2), \quad SD_{MTA} = 1/P(2)^2 \cdot SD_{P(2)},$$

where $SD_{P(2)}$ is the asymptote of the standard deviation of parameter $P_{(2)}$. Statistical differences between the pharmacokinetic parameters were assessed by the t test.

EXPERIMENTAL RESULTS

The concentration of E in the intestinal loop fell exponentially with time in both doses (Fig. 1). The MTA of E from the intestinal loop, after injection in two different doses (1 and 10 mg) is given in Table 1.

The absorption time of E was appreciably longer when the higher dose was injected. Consequently, the kinetics of absorption of E from the gastrointestinal tract is dose-dependent. In both doses E was absorbed comparatively quickly from the isolated segment of small intestine, and for that reason the low bioavailability of the drug [13] is linked with its rapid metabolism before entering the systemic circulation.

Because pK_A of E is 1.75 ± 0.05 [2], and considering the partition coefficient of octanol—phosphate buffer (pH 7.38), good absorption of E from the gastrointestinal tract would be expected. The data given above show that absorption of at least part of the dose of E is dose-dependent, for its velocity decreased with an increase in the dose injected. This is evi-

dence of the existence of a specialized transport process, characterized by saturation. Several transport systems are known to exist in the small intestine, each of them specific for the absorption of a concrete class of natural compounds: monosaccharides, amino acids, pyrimidines and purines [6]. E is structurally similar to the xanthines, and its molecule, moreover, is similar to that of adenine [4]. The existence of two processes, responsible for transport through the intestinal epithelium, has been demonstrated for purine and pyrimidine bases: 1) a specialized transport process characterized by saturation and competition with certain other substances; 2) passive diffusion, the rate of which is unaffected by the presence of other compounds [8, 9]. It can be tentatively suggested that in dogs at least some E passes through the intestinal epithelium by means of the specialized transport system for structurally similar natural compounds, most probably purine bases.

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EFFECT OF β-ENDORPHIN AND MYELOPEPTIDES ON cAMP LEVEL AND PROLIFERATION OF LYMPHOCYTES IN VITRO

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Endogenous opioids, and β-endorphin in particular, are secreted into the blood stream and take part in regulating the functional state of immunocompetent cells [1, 3, 10], although data on this matter are highly contradictory [10, 11, 14]. Meanwhile there are grounds for considering that opioids synthesized actually in the cells and organs of the immune system participate in the regulation of immunogenesis. In particular, myelopeptides (MP), which are produced by bone marrow cells and stimulate antibody production [1, 7], contain substances capable of interacting with opiate receptors [8] and with sera against α-, β-, and γ-endorphins, and β-lipotropin [4]. There is also evidence suggesting that opioids are synthesized in the thymus [5], spleen [13], and circulating leukocytes [9].

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