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Enhancement of the intestinal absorption of ergot peptide alkaloids in the rat by micellar solutions of polyoxyethylene-24-cholesteryl ether

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The incomplete intestinal absorption of hydrogenated ergot peptide alkaloids as measured in bile duct cannulated rats is much increased when the ergot compounds are administered as micellar solutions together with POE-24-cholesteryl ether. In vitro diffusion experiments with isolated intestinal mucus show that the ergot peptide alkaloids are strongly retained by the mucus layer. It is suggested that the diffusion of the ergot compounds across the mucus barrier is facilitated by micellar entrapment of the drug.

The intestinal absorption of ergot peptide alkaloids is incomplete, the total amount absorbed after oral administration varies between 10–30% for the different hydrogenated compounds (Eckert et al 1978). A potential way to promote the intestinal absorption consists in the simultaneous administration of a surfactant. However, enhancement as well as inhibition of absorption of drugs can be observed in the presence of surfactants (for reviews see Ritschel 1969; Gibaldi & Feldman 1970; Levine 1975). The effect of different non-ionic surfactants of the ether type on the intestinal absorption was studied with the everted sac preparation from rat small intestine by Whitmore et al (1979). The promotion of gastric absorption of water-soluble antibiotics by polyoxyethylene-24-cholesteryl ether (POE-24-cholesteryl ether) was reported by Davis et al (1970). In the work presented here, micellar solutions of POE-24-cholesteryl ether were prepared with different hydrogenated ergot peptide alkaloids. These solutions were administered to bile duct canulated rats.

MATERIALS AND METHODS

Materials

The tritium labelled compounds [9,10-^{3}H]dihydrogotamine, [9,10-^{3}H]dihydroergocristine, [9,10-^{3}H]-dihydroergonine were prepared in the Synthetic Tracer Laboratory of Sandoz Ltd., Basle, The radiochemical purity was at least to 95%. POE-24-cholesteryl ether (Solulan C 24, CTFA adopted name Choleth-24) was purchased from Amerchol, Edison, N. J., Polyethyleneglycol 300 (N.F.), propyleneglycol (U.S.P.), and ethanol (U.S.P.) were used as purchased for the preparation of the micellar solutions. 7-(β-Hydroxypropyl)-theophylline was purchased from Boehringer (Ingelheim). Miglyol, a triglyceride with medium chainlength was purchased from Dynamit Nobel (Witten).

Animals

Male SPF Sprague-Dawley rats of the OFA strain, 250–300 g, were used. Food was withdrawn 20 h before use but there was free access to water. The methods for the surgical preparations of bile duct cannulated rats were those of Weis & Dietschy (1969).

Methods

The micellar solutions were prepared by means of a polytron homogenizer (type PT 20, Kinematica Ltd., Luzern) and were administered as transparent solutions by means of a gastric probe. For the intraduodenal administration to bile duct cannulated rats the aqueous micellar solutions were evaporated to dryness under vacuum. The finely powdered residue was dried and weighed into mini-hard gelatin-capsules (Eli Lilly). The minicapsules containing a reversible solid micellar solution (the addition of water to the residue quickly reconstitutes the original transparent micellar solution) were administered into the duodenum by means of a specially developed flexible double-walled silicone tube. For this purpose the stomach was exposed by a midline incision and the double-walled tube was introduced into the stomach under visual control and then pushed forward into the upper part of the duodenum. There the mini-capsule was released, the tube with-

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drawn and the incision closed by sutures. Up to 15 mg of a dry powder can easily be administered intraduodenally by this method.

Isolation of mucus from rat small intestine and diffusion experiments using a Dianorm Dialyser (Dianorm Ltd., Rüschlikon, Switzerland) with 3 Teflon cells and cellulose membranes with a molecular cutoff of about 10 000 were performed as described by Nimmerfall & Rosenthaler (1980). The 1st compartment was filled with 1 ml of McIlvaine's buffer solution at pH 6·0 containing 30 μg of [^{3}H]-dihydroergonine ml^{-1}. The smaller 2nd compartment contained 0·25 ml of freshly isolated mucus. POE-24-cholesteryl ether was added to the 1st comparment or to the 2nd compartment respectively at a concentration of 10 mg ml^{-1}. 1 ml of McIlvaine's buffer solution was put into the 3rd compartment. Diffusion was allowed for 1 h at 37 °C then aliquots were taken from each compartment and their radioactivity measured. Control experiments, without mucus, were carried out in the central compartment. Results were expressed as the ratio Q of the concentration analysed in a given compartment to the concentration in the 1st compartment. Volume changes in the three compartments did not occur during the experiments.

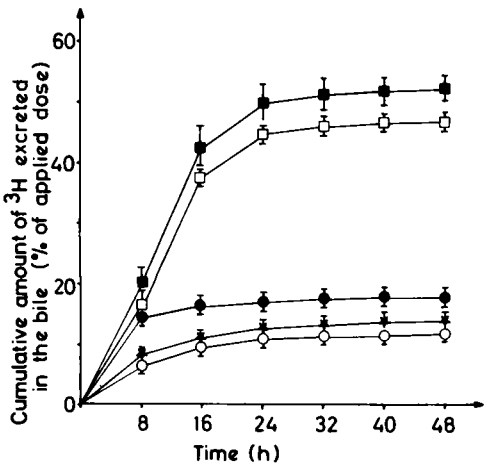

FIG. 1. Cumulative excretion of radioactivity in bile after oral administration of [^{3}H]dihydroergonine ([^{3}H]DN) with different solvents in bile duct cannulated rats. ○ 0·05 mg [^{3}H]DN-hydrochloride in 0·5 ml water; ★ 0·05 mg [^{3}H]DN-hydrochloride in 0·5 ml PEG-300; ● 0·05 mg [^{3}H]DN-base in 0·5 ml PEG-300; □ 0·05 mg [^{3}H]DN-base +50 mg POE (24)-cholesteryl ether in 0·5 ml propylene glycol; ■ 0·05 mg [^{3}H]DN-base +50 mg POE(24)-cholesteryl ether in 0·5 ml PEG-300. Each value represents the mean of 5 rats ± s.e.m.

RESULTS AND DISCUSSION

Animal experiments

Fig. 1 presents the excretion of radioactivity in the bile after oral administration of [^{3}H]dihydroergonine in different solvents to bile duct-cannulated rats. The threefold increase in absorption achieved by the micellar solution, as shown by increased excretion, is remarkable, whereas the influence of the solvent or the salt form of the drug on the amount absorbed is negligible.

Similar results were obtained with [^{3}H]dihydroergotamine and [^{3}H]dihydroergocristine (Table 1). Fig. 2 shows the elimination of radioactivity in the bile after intraduodenal administration of [^{3}H]-dihydroergotamine to cannulated rats. The simultaneous administration of the surfactant leads to a fourfold increase of the total amount absorbed. β-Hydroxypropyltheophylline, a well-known absorption promoter of ergot peptide alkaloids (Berde et al 1970) also produces an enhancement of the intestinal absorption of dihydroergotamine but less so than POE-24-cholesteryl ether (Table 2).

Diffusion experiments

If an aqueous solution of [^{3}H]dihydroergonine is placed in the 1st compartment, after 60 min 40% of

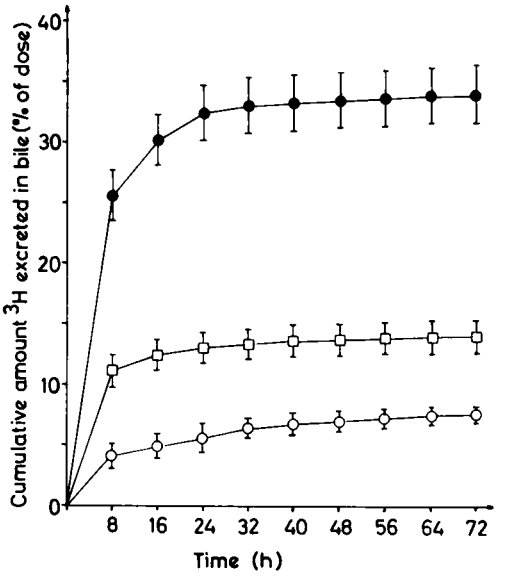

FIG. 2. Cumulative excretion of radioactivity in bile after intraduodenal administration of [^{3}H]dihydroergotamine-mesylate (DHE-ms) with different absorption promoters in bile duct cannulated rats. ○ 0·05 mg [^{3}H]DHE-ms +10 mg sorbitol; □ 0·05 mg [^{3}H]DHE-ms + 10 mg β-hydroxypropyl-theophylline; ● 0·05 mg [^{3}H]DHE-ms + 10 mg POE(24)-cholesteryl ether. Each value represents the mean of 5 rats ± s.e.m.

Table 1. Cumulated percentage of radioactivity excreted in 48 h with the bile and the urine after oral administration of some tritiated ergot peptide alkaloids in different solutions, in bile duct cannulated rats.

Sample administered*	Number of rats	% of dose in the urine (mean ± s.e.m.)	% of dose bile + urine (mean ± s.e.m.)
0·05 mg[^{3}H]DN-hydrochloride in 0·5 ml water	5	4·6 ± 0·7	15·6 ± 0·8
0·05 mg [^{3}H]DN-hydrochloride in 0·5 ml PEG-300	5	4·6 ± 0·7	18·8 ± 0·8
0·05 mg [^{3}H]DN-base in 0·5 ml PEG-300	5	2·0 ± 0·4	20·1 ± 1·5
0·05 mg [^{3}H]-DN-base + 50 mg POE(24)-cholesteryl ether in 0·5 ml propylene glycol	5	3·0 ± 0·9	50·2 ± 3·0
0·05 mg [^{3}H]DN-base + 50 mg POE(24)-cholesteryl ether in 0·5 ml PEG-300	5	5·1 ± 1·3	57·5 ± 3·3
7·15 mg [^{3}H]DCS-mesylate in 0·5 ml water	8	2·0 ± 0·5	12·1 ± 0·7
7.15 mg [^{3}H]DCS-base + 88 mg POE(24)-cholesteryl ether + 15 mg Miglyol 812 + 180 mg PEG-300 + 0·2 ml water	10	6·8 ± 1·6	75·4 ± 3·3
0·05 mg [^{3}H]DHE-mesylate in 0·5 ml water	6	1·4 ± 0·3	6·4 ± 0·4
0·05 mg [^{3}H]DHE-base + 25 mg POE(24)-cholesteryl ether in 0·5 ml ethanol	10	4·4 ± 0·5	35·4 ± 0·7

* DN, DCS, and DHE represent dihydroergonine, dihydroergocristine, and dihydroergotamine respectively.

the total amount is found in the 2nd compartment where it is almost completely retained by the mucus, as indicated by the high ratio of Q in the 2nd and the very low ratio of Q in the 3rd compartment (Fig. 3). However, if the 1st compartment is filled with a micellar solution of the drug then only about 12% of the total amount is found in the 2nd compartment where the ratio of Q is $<$ one. It seems therefore that the micellar aggregates formed from dihydroergonine (mol. wt 549·6) and from POE-24-cholesteryl ether (mol. wt 1400) are too big to be able to penetrate the diffusion membrane which has a molecular cutoff of about 10 000. When the surfactant is incorporated together with the mucus in the 2nd compartment, the drug can diffuse more easily from the 1st into the 2nd compartment where it is retained less by the mucus, probably because of the micellar entrapment which impedes the interaction of the drug with the mucus environment. Furthermore, the surfactant may influence the three-dimensional structure of the mucus gel altering its permeability for the solute.

The interpretation of the results obtained by administration of micellar solutions of ergot peptide alkaloids with POE-24-cholesteryl ether is complicated by the fact that surfactants can exert different effects including solubilization of water-insoluble drugs by entrapment within micelles, reduction of interfacial tension and promotion of wetting (which favours the contact of the drug with the absorbing epithelium), and also direct interactions with biological membranes. The results of the oral administrations in rats indicate that neither the salt form of the drug nor the solvents have any remarkable influence on the intestinal absorption of dihydroergonine. However, the results are in accordance with the findings of Davis et al (1970), who reported that POE-24-cholesteryl ether induces a completely

Table 2. Cumulated percentage of radioactivity excreted in 72 h with the bile and the urine after intraduodenal administration of [^{3}H]dihydroergotamine (DHE) and [^{3}H]dihydroergonine (DN) in combination with different promoters, in bile duct cannulated rats.

Sample administered	Number of rats	% of dose in the urine (mean ± s.e.m.)	% of dose bile + urine (mean ± s.e.m.)
0·05 mg [^{3}H]DHE-mesylate + 10 mg sorbitol	5	2·2 ± 0·6	9·9 ± 0·6
0·05 mg [^{3}H]DHE-mesylate + 10 mg]β-hydroxypropyl-theophylline	8	3·2 ± 0·5	17·4 ± 1·3
0·05 mg [^{3}H]DHE-mesylate + 10 mg POE(24)-cholesteryl ether	6	6·6 ± 1·6	40·7 ± 1·2
0·05 mg [^{3}H]DN-hydrochloride + 10 mg sorbitol	5	6·3 ± 1·0	23·9 ± 2·1
0·05 mg [^{3}H]DN-hydrochloride + 10 mg β-hydroxypropyl-theophylline	5	3·7 ± 0·8	30·7 ± 1·4
0·05 mg [^{3}H]DN-hydrochloride + 10 mg POE(24)-cholesteryl ether	5	3·4 ± 0·2	58·6 ± 3·6

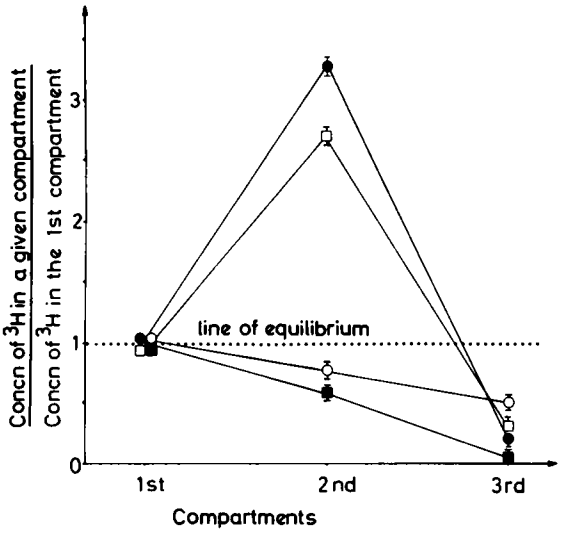

FIG. 3. Distribution of radioactivity in the different compartments after diffusion of [^{3}H]dihydroergonine through a mucus layer during 1 h at 37 °C, expressed as a function Q of the concentration in the 1st compartment. ○ [^{3}H]Dihydroergonine ([^{3}H]DN) in the 1st compartment, buffer solution in the 2nd and 3rd compartment; ● [^{3}H]DN in the 1st compartment, mucus in the 2nd compartment, and buffer solution in the 3rd compartment; ■ [^{3}H]DN + POE(24)-cholesteryl ether in the 1st compartment, mucus in the 2nd compartment, and buffer solution in the 3rd compartment; □ [^{3}H]DN in the 1st compartment, mucus + POE(24)-cholesteryl ether in the 2nd compartment, and buffer solution in the 3rd compartment. Each value represents the mean of three experiments ± s.e.m.

reversible hyperabsorption state of the gastric diffusion barrier.

As described earlier by Franz et al (1980) the rate of disappearance of ergot peptide alkaloids from the lumen of the intestinal tract of rats, in situ, is increased considerably by addition of mucolytic enzymes. Furthermore, the mucus layer seems to be a general rate-limiting barrier for drugs depending on their molecular weight as reported by Nimmerfall & Rosenthaler (1980). It is therefore suggested that the diffusion of ergot peptide alkaloids across the mucus barrier is facilitated by the micellar entrapment which shields the drug molecules from the mucus environment. The elucidation of the exact nature of the absorption promoting effect of the micellar solution needs further investigation.

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