

Effect of Fat Substitutes, Sucrose Polyester and Tricarallylate Triester, on Digitoxin Absorption in the Rat

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Abstract—The effect of non-absorbable fat substitutes (sucrose polyester (SPE) and tricarallylate triester (TCTE)) on [^3H]digitoxin intestinal absorption was studied in the rat using a small intestine in-situ perfusion technique. The effect of SPE and TCTE was compared with that of sunflower oil, oleic acid, and saline. After 120 min perfusion, 5% SPE emulsion significantly reduced ($P < 0.001$) digitoxin absorption compared with all other treated groups. Five per cent TCTE emulsion had a less marked effect than SPE ($P = 0.0002$) and did not differ from sunflower oil. No difference was found between saline and 5% oleate emulsion, which did not reduce digitoxin absorption compared with other treated groups ($P < 0.02$). When taurocholic acid and lipase were added, results for the saline-, TCTE-, and SPE-treated groups were similar to those above, but the sunflower oil-treated group showed significantly enhanced ($P < 0.01$) digitoxin absorption. Thin-layer chromatography of the lipid phases showed hydrolysis of sunflower oil in the presence of taurocholic acid and lipase, but not of TCTE or SPE. The inhibitory effect of the non-absorbable fat substitutes on digitoxin absorption could be related to drug sequestration by the persistent oil phase constituted by the undigested and then unabsorbed fat substitutes. That part of digitoxin dissolved in the undigested oil phase is consequently unavailable for intestinal absorption.

Increased risk for cardiovascular diseases has been attributed to high dietary fat content (Lipid Research Clinics Program 1984; Bergholz 1991). Non-nutritive fat substitutes have been developed that have the same functional and organoleptic properties as fat (Sommerkamp & Hesser 1990; Bergholz 1991). Sucrose polyester (SPE) is a fat-like material consisting of a mixture of hexa-, hepta-, and octa-esters of sucrose (Mattson & Volpenheim 1972; Rizzi & Taylor 1978).

SPE provides no calories because of its resistance to lipolysis which prevents its intestinal absorption (Mattson & Volpenheim 1972; Sommerkamp & Hesser 1990). Unabsorbable SPE thus provides a persistent oil phase in the lumen of the intestinal tract (Jandacek 1982; Bernhardt 1988). Fat-soluble materials that are retained in this phase are subsequently eliminated in the stool along with intact SPE (Jandacek 1982). This mechanism explains the hypocholesterolaemic effect of SPE in that absorption of dietary cholesterol is decreased (Glueck et al 1979; Jandacek 1982; Bernhardt 1988).

Several studies (Fallat et al 1976; Crouse & Grundy 1979; Glueck et al 1979; Mattson et al 1979) have shown that SPE reduces absorption of vitamins A and E, and diet supplementation with these vitamins has been proposed when SPE is administered to man (Bernhardt 1988; Bergholz 1991). Jandacek (1982) suggested that the effect of SPE on cholesterol and vitamins could be extrapolated to lipophilic drugs. The effect of SPE on lipid-soluble drugs, particularly those used to control serious medical conditions, has been suggested to have possible clinical implications (Munro 1990). Although Roberts & Leff (1989) observed no statistical differences in the absorption of lipophilic drugs when administered with SPE, triglyceride oil, or water in man, a large inter-subject variability was noted. The present study

investigates the effect of two fat substitutes (SPE and tricarallylate triester (TCTE)) on the intestinal absorption of a lipophilic drug (digitoxin) using the in-situ perfused intestine of the rat.

Materials and Methods

Materials

Digitoxin (0.2 mg mL^{-1}) was from Nativelle (France). Polyethylene glycol (PEG 4000) was from Merck Clevenot (France). [^3H (G)]Digitoxin (sp. act. $26.1 \text{ Ci mmol}^{-1}$, purity: 99%) and [$1,2^{14}\text{C}$]PEG (sp. act. 13.0 mCi g^{-1}) were obtained from New England Nuclear-Du Pont de Nemours (Paris, France). Perfusion solutions were prepared with 0.9% NaCl (saline). Oleic acid was from Merck Clevenot (France). Sunflower oil was from Lesieur (France). Sucrose polyester (Lipochim, Marseille, France) was prepared as described by Rizzi & Taylor (1978) with D-(+)-sucrose (Fluka, France) and sunflower oil of the following fatty acid composition: 10% C16:0, 0.1% C16:1, 3.7% C18:0, 24% C18:1, 62% C18:2, and 0.1% C18:3. Tricarallylate triester (Lipochim, Marseille, France) was prepared by esterification of tricarallylic acid (Fluka, France) with sunflower fatty alcohols obtained by reduction of sunflower methyl esters. Fatty alcohol composition was 9.2% C16:0, 0.1% C16:1, 3.9% C18:0, 24.1% C18:1, and 61.5% C18:2. Lipase and taurocholic acid (sodium salt) were from Sigma (Verpillière, France). All other chemicals were of analytical grade.

Emulsion preparation and stability control

Five perfusion solutions of 5 mg mL^{-1} ($4.5 \text{ } \mu\text{Ci mg}^{-1}$) PEG and $0.5 \text{ } \mu\text{g mL}^{-1}$ ($23.5 \text{ } \mu\text{Ci } \mu\text{g}^{-1}$) digitoxin were prepared in physiological saline: 0.9% NaCl, 5% (v/v) oleic acid, 5% (v/v) sunflower oil, 5% sucrose polyester (v/v) or 5% (v/v) tricarallylate triester.

Each oil was mixed with physiological saline containing

the drug using a bladed stirrer and then sonicated (Labsonic 2000, B. Braun, Les Ulis, France). Emulsion stability was ensured by 0.6% (w/v) of either a sorbitan mono-oleate: polyoxyethylene-20 sorbitan mono-oleate mixture (0.8:0.2, Seppic, Paris, France) for oleic acid, or egg lecithin (Lipoid E80, Seppic, Paris, France) for the other oils. The surface-active agents were previously dissolved in the lipid phase at 70°C. The diameter and dispersion of the lipid particles in the emulsion were checked with an autolite submicron particle sizer (Nicomp 370, Hiac/Royco, Palaiseau, France).

Perfusion solutions were also prepared with taurocholic acid and lipase. Lipase was added at 0.6% (w/v), a concentration recommended by Watanabe et al (1990). Taurocholic acid was added at a physiological concentration of 10 mM (Poelma et al 1989).

Partition coefficient determination

The digitoxin partition coefficient between the lipid phase and aqueous phase was determined at 37°C by shaking 2.0 mL of the aqueous phase (saline) and 2.0 mL of lipid phase for 90 min. The aqueous phase contained digitoxin at a concentration similar to that used in the absorption experiments. The lipid phase was either sunflower oil, oleic acid, SPE or TCET. After centrifugation, digitoxin concentration in the aqueous and lipid phases was determined by measuring [³H]digitoxin radioactivity. The partition coefficient (P) was calculated from

$$P = C_{lip}/C_{aq}$$

where C_{lip} is the digitoxin concentration in the lipid phase and C_{aq} the concentration in the aqueous phase.

Experimental procedures

Sprague-Dawley male rats (Iffa Credo, Lyon, France), 280 ± 21 g (n = 54), were fasted with free access to water 16–20 h before experimentation. The rats were anaesthetized with 55 mg kg⁻¹ intraperitoneal 6% pentobarbitone (Clin Midy, St Jean de la Ruelle, France). All experiments were performed between 1000 and 1800 h.

The in-situ perfused intestine model was adapted from that described by Hayton & Levy (1972). The abdomen was opened by a midline incision. A polyethylene cannula (i.d. 3.5 mm, Biotrol, Paris, France) was inserted through a small transverse incision in the intestine 4.6 ± 0.7 cm distal to the pylorus and tied in place with a silk suture. The proximal cannula was inserted below the ampulla to avoid the biliary excretion of the drug in the intestinal segment. A second cannula was placed 40 ± 6.3 cm below the first. The proximal cannula was connected, via a peristaltic pump (P1, Pharmacia, Les Ulis, France), to a 20 mL reservoir. The distal cannula ensured perfusate recirculation in the reservoir. The recirculation technique allowed us to determine the kinetics of digitoxin by measuring levels in the reservoir.

Physiological temperature and moisture of the intestine were preserved by covering it with saline-soaked gauzes at 37°C. Body temperature was also maintained at 37 ± 1°C by a heating lamp and monitored by a rectal probe (Ellab Thermometer model TE 3, Copenhagen, Denmark).

Before perfusing the drug solution, the intestinal segment was flushed with saline until the effluent was clear. The perfusion solution, under magnetic stirring and maintained

at 37°C in a water-bath, was circulated through the intestinal segment at a rate of 0.8 mL min⁻¹, in the range of the optimal perfusion rate determined by Savina et al (1981).

After 120 min, the rats were killed and the intestinal segment lengths measured. Each group consisted of six rats.

Collection of samples and analytical methods

Fifty microlitre samples (in duplicate) were drawn from the reservoir at 0, 10, 20, 30, 45, 60, 90 and 120 min of perfusion and were mixed with 3 mL Pico-Fluor 40 scintillation liquid (Packard, Rungis, France) in a minivial. Radioactivity was measured by double-label (¹⁴C/³H) liquid scintillation counting with a beta-counter (Tri-Carb 4530, Packard, Les Ulis, France) using automatic external standardization for the quenching correction.

Thin-layer chromatography of lipid phases

At the end of perfusion, the perfusate was collected in a test tube and centrifuged until the lipid phase was separated from the aqueous phase. After dilution in chloroform (1/100, v/v), aliquots of the lipid phase were applied to 20 × 20 cm pre-coated silica gel plates (60 F-254, Merck, France). Chromatography was performed at room temperature (21°C) with the solvent mixture hexane/ethyl ether/acetic acid (90:30:1, v/v). Lipids were visualized by staining with iodine.

Data analysis

PEG was used as a non-absorbable marker to verify any transfer of water into or out of the intestinal lumen (Blanchard et al 1990).

³H measurements were converted to digitoxin concentrations and corrected for water movements measured by [¹⁴C]PEG using the equation:

$$C_{corr} = C_{init} \cdot R_{digit} \cdot R_{PEG}$$

Where C_{corr} is the corrected concentration (μg mL⁻¹), C_{init} the initial digitoxin concentration (μg mL⁻¹), R_{digit} the ratio of [³H]digitoxin (d min⁻¹/50 μL) to the initial radioactivity, and R_{PEG} the [¹⁴C]PEG radioactivity ratio.

The percentage of initial concentration remaining in the reservoir was plotted against time. Pharmacokinetic parameters of digitoxin elimination from the reservoir were calculated using the SIPHAR pharmacokinetics computer program (Simed, Creteil, France) as follows: half-life $t_{1/2}$ (min) calculated by linear regression using the least-squares method;

$$CL = k_e \cdot V \cdot L \text{ (mL min}^{-1} \text{ cm}^{-1}\text{)}$$

where k_e is the elimination rate constant ($k_e = \ln 2/t_{1/2}$), V the perfusate volume, and L the length of the intestinal segment (Hayton & Levy 1972).

Results are expressed as mean ± s.e.m. (n = 6). Statistical analysis was performed using one-way analysis of variance. Significance was set at $P < 0.05$.

Results

Quality controls of emulsions showed a mean oil particle diameter of 276.5 ± 142.4 nm (mean ± s.d.) with 0.3% over 1 μm. The emulsions were stable even in the reservoir and during storage at 4°C for at least one week. These character-

Table 1. Kinetic parameters of [3 H]digitoxin in saline, or in emulsion with oleic acid, sunflower oil, tricarballate triester or sucrose polyester.

Parameters	Saline	Oleic acid	Sunflower oil	Tricarballate triester	Sucrose polyester
Remaining after 120 min (% dose)	43 $\pm$ 3.9 ^a 49 $\pm$ 2.2 ^b	39 $\pm$ 2.6 ^b —	57.8 $\pm$ 3.5 [*] 36.8 $\pm$ 3.5 [§]	59 $\pm$ 2.7 [*] 60.8 $\pm$ 2.2 [‡]	77.7 $\pm$ 1.9 [†] 76.6 $\pm$ 2.7 [†]
Half-life (min)	106.7 $\pm$ 13.6 ^a 122.4 $\pm$ 8.4 ^b	89 $\pm$ 5.9 —	170.8 $\pm$ 14.8 [*] 92.5 $\pm$ 8.6 [§]	178 $\pm$ 18.9 [*] 178 $\pm$ 12.4 [‡]	347.9 $\pm$ 37.5 [†] 349.6 $\pm$ 55.8 [†]
Clearance (μ L min ⁻¹ cm ⁻¹)	3.1 $\pm$ 0.36 ^a 3.2 $\pm$ 0.55 ^b	3.8 $\pm$ 0.48 —	2.13 $\pm$ 0.17 [*] 4.4 $\pm$ 0.2 [§]	1.95 $\pm$ 0.12 [*] 2.2 $\pm$ 0.16	0.98 $\pm$ 0.11 [†] 1.3 $\pm$ 0.16 [†]

^aWithout taurocholic acid and lipase. ^bWith taurocholic acid and lipase. The results are expressed as mean $\pm$ s.e.m. (n=6). *P<0.05 compared with the saline or oleate-treated groups. †P<0.05 compared with the other four groups. ‡P<0.05 compared with saline and sunflower oil-treated groups. §P<0.05 compared with sunflower oil-treated group without taurocholic acid and lipase.

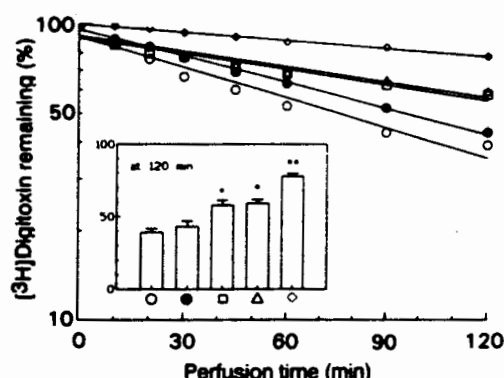


FIG. 1. Percentage of [3 H]digitoxin remaining in the reservoir during the in-situ intestine perfusion of digitoxin in saline (●), or in emulsion with either oleic acid (○), sunflower oil (□), tricarballate triester (△), or sucrose polyester (◇). Results are expressed as mean for six rats. The histograms show the results at 120 min. Vertical lines show s.e.m. *P<0.05 compared with saline- and oleate-treated groups, **P<0.05 compared with all other groups.

istics indicate a good emulsion quality (Hazane et al 1983). The digitoxin partition coefficient with oleic acid was equal to 14.06 ± 1.68 ($\pm$ s.e.m., n=3). This value was significantly greater than with sunflower oil (1.00 ± 0.17 , $P=0.0015$),

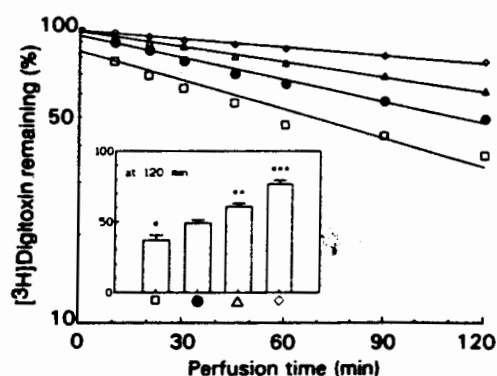


FIG. 2. Percentage of [3 H]digitoxin remaining in the reservoir during the in-situ intestine perfusion of digitoxin with taurocholic acid and lipase. For details see Fig. 1. *P<0.05 compared with saline-treated group, **P<0.05 compared with saline- and sunflower oil-treated group, ***P<0.05 compared with all other groups.

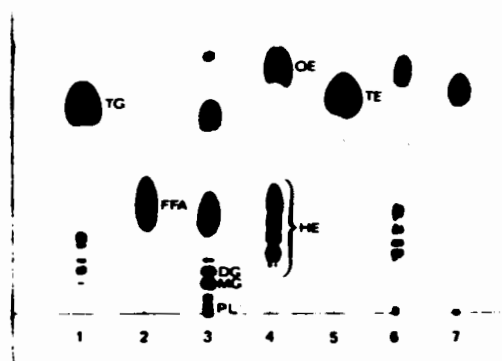


FIG. 3. Qualitative one-dimensional TLC in the solvent mixture hexane/diethyl ether/acetic (90:30:1) of sunflower oil (1), oleic acid (2), sunflower oil with taurocholate and lipase (3), SPE (4), TCCTE (5) and SPE (6) and TCCTE (7) with taurocholate and lipase. TG triglycerides, DG diglycerides, MG monoglycerides, FFA free fatty acids, PL phospholipids, OE octaesters, HE heptaesters, TE triesters.

TCCTE (1.04 ± 0.21 , $P=0.0015$), or SPE (1.53 ± 0.04 , $P=0.002$). [14 C]PEG measurements were constant, indicating that water transfers were minor despite the hypotonicity of saline compared with plasma, which could lead to an absorption of water and sodium. The egg lecithin and sorbitan mono-oleate/polyoxyethylene-20 sorbitan mono-oleate mixture showed no difference in digitoxin absorption even when added to sunflower oil or TCCTE (data not shown).

Digitoxin concentration decreases in the reservoir are summarized in Table 1 and Figs 1, 2.

The decrease in digitoxin concentration in the reservoir was considered to be due to intestinal absorption. The absorption of digitoxin proceeded by first-order kinetics under the experimental conditions.

Thin-layer chromatography of the lipid phases showed an apparent digestion of sunflower oil in the experiment with taurocholic acid and lipase since mono- and di-glycerides, and free fatty acids are revealed (Fig. 3). SPE and TCCTE remained undigested as shown by the identical separations both with and without taurocholate and lipase: octa-esters and chain of hepta-esters for SPE, and triesters for TCCTE. The low amounts of phospholipids are due to egg lecithin added for the emulsion.

Discussion

Absorbable dietary fats have been demonstrated to enhance absorption of lipophilic drugs (Walter-Sack 1987). Absorption of a lipophilic drug requires its dissolution in the micellar aggregates resulting from fat digestion (Eldem & Speiser 1989). Since some fat substitutes are neither digested (Mattson & Volpenheim 1972) nor absorbed (Mattson & Nollen 1972), it might be expected that these reduce the absorption of lipophilic drugs (Fallat et al 1976; Jandacek 1982).

The results reported here demonstrate an inhibitory effect of SPE and TCTE on digitoxin absorption, the effect of SPE being more marked. The digitoxin partition coefficient with SPE was greater than with TCTE, suggesting a greater drug sequestration which could also explain the effect on digitoxin absorption. This effect can be attributed to the resistance of SPE and TCTE to hydrolysis and their subsequent non-absorption (Hamm 1984; Roberts & Leff 1989). Thin-layer chromatography of lipid phases showed apparent resistance of SPE and TCTE to pancreatic lipase hydrolysis. The digitoxin dissolved in the oil phase of the fat substitutes is reduced in the aqueous micellar phase from which absorption proceeds (Fallat et al 1976; Jandacek 1982) and this results in reduced absorption as shown for cholesterol (Fallat et al 1976; Mattson et al 1976; Crouse & Grundy 1979), vitamins A and E (Fallat et al 1976; Crouse & Grundy 1979; Glueck et al 1979; Mattson et al 1979), and DDT (Volpenheim et al 1980). Other studies have shown that a lipid-like agent (methyl polysiloxane) reduced absorption of lipophilic drugs (warfarin and phenindione) significantly in man (Talbot & Meade 1971) and that a non-digestible lipid (oleyl alcohol) decreased significantly the rate of absorption of acetyl sulphafurazole, dicoumarol, and griseofulvin in rats (Bloedow & Hayton 1976). On the other hand, the results of studies carried out in man (Roberts & Leff 1989) using oral administration with other lipophilic drugs such as propranolol, diazepam, norethisterone and ethinyl oestradiol showed that SPE was equivalent to glyceride oil (partially hydrogenated soybean oil) in its effect on drug absorption, with a large between-subject variability.

TCTE had a less marked effect on digitoxin absorption than SPE. We have found no mention of an effect of TCTE on lipophilic compound absorption in the literature. We think that the different effect of TCTE on digitoxin absorption compared with SPE could be related to the structural difference due to the number of ester bonds, TCTE's steric bulk being smaller and its sequestration ability less pronounced than that of SPE.

The undigested sunflower oil acted in the same manner as TCTE, as indicated by the identical kinetics. We did not observe any statistically significant difference in digitoxin absorption when administered with sunflower oil or TCTE. This could be related to the close structural resemblance between sunflower oil and TCTE (the two compounds are triesters) and the non-digestion of sunflower oil which was due to the absence of bile salts and pancreatic lipase. The perfusion technique used here does not involve the bile ducts and avoids biliary excretion of the drug. Addition of the bile salt taurocholic acid and lipase to the perfusate gave results which confirm that absorbable lipids enhance lipophilic drug

absorption and that non-absorbable fat substitutes significantly reduce it. The effect of sunflower oil with taurocholic acid and lipase did not differ from that of oleate without these additions. This may be related to the absorbability of the digested triglyceride and the free fatty acid.

In conclusion, the present study shows that the non-absorbable fat substitutes, SPE and TCTE, decreased intestinal absorption of digitoxin, a lipophilic drug. In addition, it shows that bile salts and pancreatic lipase must be considered in the study of the effects of lipid compounds on intestinal absorption.

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