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Systemic bioavailability of penclomedine (NSC-338720) from oil-in-water emulsions administered intraduodenally to rats

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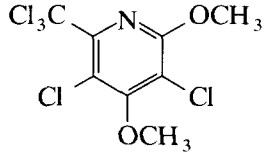
Summary

Penclomedine (NSC-338720) is a low melting point, poorly water-soluble cytotoxic agent with good solubility in triglycerides and a high octanol/water partition coefficient. Its pharmacokinetics in anesthetized rats was studied after i.v. bolus injection of a soybean oil emulsion. Penclomedine displayed biexponential behavior with an apparent $t_{1/2}$ ($\pm$SE) of 1.9 $\pm$ 0.3 h and a clearance of 3.3 $\pm$ 0.1 ml/min per kg. After intraduodenal administration to anesthetized rats as either a 10% o/w emulsion of tributyrin, trioctanoin, triolein, soybean oil or mineral oil, or as a suspension, the rank order of absolute bioavailability was trioctanoin > soybean oil $\approx$ triolein > mineral oil > tributyrin > suspension. The results were rationalized by assuming that drug release from the emulsions was by a combination of vehicle metabolism and diffusional drug release. The poor bioavailability from tributyrin was rationalized by the rapid release of penclomedine resulting in its possible precipitation and subsequent need to redissolve.

Introduction

Penclomedine (NSC-338720; 3,5-dichloro-2,4-dimethoxy-6-trichloromethylpyridine) is a cytotoxic agent with a relatively low melting point (80–80.5 °C), very poor aqueous solubility (< 1 μg/ml), good solubility in triglycerides (180–280 mg/ml), and a high log octanol/water partition coefficient (5.36–5.48). Based on these physicochemical properties, penclomedine was expected to have limited oral bioavailability from a solid or suspension dosage form. This was confirmed in preliminary experiments.



Penclomedine

Crystalline compounds with a very low aqueous solubility have poor or erratic oral bioavailability, e.g., phenytoin (Suzuki et al., 1970; Arnold et al., 1979), griseofulvin (Lin and Symchowics, 1975), and nitrofurantoin (Fincher, 1968). Low melting point compounds with low aqueous solubility but with a good lipid solubility may have

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erratic bioavailability. The bioavailability of these compounds tends to be sensitive to whether the drug is taken in the fed or fasted state (Nakamura et al., 1975; Melander et al., 1977; Martz, 1979; Hasegawa et al., 1981). They may also be good candidates for either a soft gelatin capsule or an emulsion dosage form. Based on its physicochemical properties, penclomedine appears to fit into this category of compounds.

One of the major reasons for the poor intestinal absorption of sparingly water-soluble compounds is the slow dissolution rate in the environment of the gastrointestinal tract. One approach to overcome this problem has been to dissolve the compound in a suitable solvent such as a triglyceride or other lipophilic solvents, or water-miscible solvents like polyethylene glycol (Muranishi et al., 1971; Kincl et al., 1978, 1986; Stella et al., 1978; Yamahira et al., 1979a; Shinkuma et al., 1981; Yamaoka et al., 1983; Muranishi, 1985; Murakami et al., 1986; Palin et al., 1986; Serajuddin et al., 1988) prior to administration.

Oil-in-water emulsion dosage forms have several favorable qualities for the dosing of a lipid phase soluble compound. Not only does the oil keep the lipophilic compound in solution, but also the emulsion, with a small particle size, can provide a large aqueous-to-oil surface area from which the compound may diffuse and removes the problem of oil dispersion. The large surface area also provides a good interface for lipolytic enzymes (Alvarez and Stella, 1989) to digest the oil, if it is a substrate for enzymes such as lipase, so releasing the compound through the digestion process. After release, the lipophilic drug distributes between various phases of the intestinal contents as illustrated in Fig. 1.

Unlike digestible oils, the introduction of a nonabsorbable oil into the lumen of the intestine can alter the normal absorption of lipophilic compounds (Volpenhein et al., 1980; Rozman et al., 1983). Such an oil will remain in the lumen of the small intestine and will tend to retain a portion of the solute.

In the present study, the bioavailability of penclomedine from emulsion dosage forms composed of various digestible and a non-digestible oil and a suspension are compared. The effect of oil surface area was also explored.

Experimental

Materials

Penclomedine (3,5-dichloro-2,4-dimethoxy-6-trichloromethylpyridine; NSC-338720) was supplied by National Cancer Institute, Bethesda, MD.

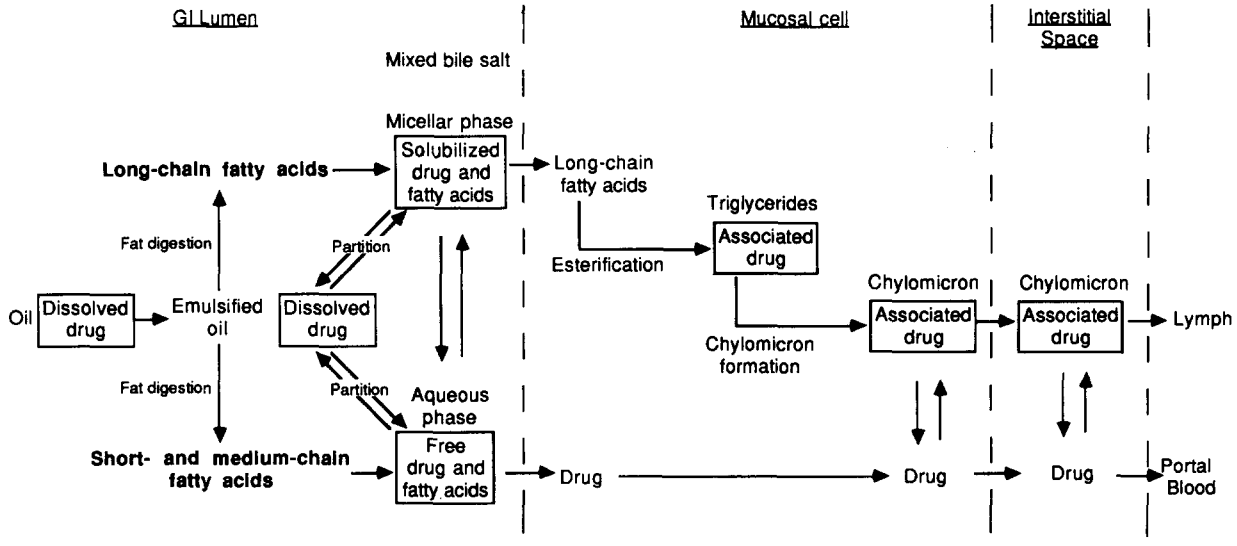

Fig. 1. Luminal and mucosal processing of an administered oil containing dissolved drug.

Soybean oil, triolein (95%), trioctanoin (97–98%), tributyrin (99%), and light mineral oil were all obtained from Sigma Chemical Co., St. Louis, MO. All oils used in the emulsion preparation were used without further purification.

The L-α-phosphatidylcholine (lecithin, type IX-E from egg yolk, 60%) obtained from Sigma Chemical Co. (St. Louis, MO) was used without further purification as was glycerol (99.5%, Aldrich Chemical Co., Milwaukee, WI). The water used in all experiments was deionized and filtered through charcoal prior to distillation from an all-glass still (Corning Mega-Pure System MP-1, Corning, NY).

Male Sprague-Dawley rats weighing from 300 to 350 g were obtained from SASCO (Omaha, NE). Three types of cannulas were used in the experiments. The duodenal and intraperitoneal cannulas, each beveled to a 45° angle, were composed of 15 cm and 7 cm pieces of polyethylene tubing (0.5 mm i.d., 0.8 mm o.d., Dural Plastics, Auburn, NSW, Australia), respectively. The tracheal cannula was composed of a 4 cm piece of polyethylene tubing (1.67 mm i.d., 2.42 mm o.d., Clay-Adams, Parsippany, NJ) also beveled to a 45° angle.

Methods

Dosage form preparation

The emulsions used were composed of a 10% oil phase and a 90% aqueous phase (w/w). The emulsions varied only in the type of oil used. Soybean oil, triolein, trioctanoin, tributyrin, and light mineral oil were used as the oil phases. Penclomedine (PCD) was dissolved in the appropriate oil to a concentration of 100 mg/g before the formation of the emulsion. The aqueous phase of the emulsions was composed of a suspension of 1.2 g lecithin and 4.5 g glycerol in 84.3 g distilled water. The emulsions were formed by placing 1 g of oil and 9 g of the lecithin suspension into a 20 ml vial. This mixture was cooled in an ice bath and sonicated (Heat Systems-Ultrasonics Inc., model W-385, Farmingdale, NY) in 3-min increments for 9–12 min until all visible oil droplets had gone. Particle size analysis was performed on all emulsions using a sub-micron particle sizing apparatus (Nicomp 370, Nicomp Instruments Inc., Goleta, CA) and found to be between 0.2 and 0.4 μm diameter for all emulsions. The final concentration of penclomedine in the emulsions was 10 mg/g, which was checked by HPLC. Penclomedine is chemically very stable in various emulsions (Prankerd et al., 1988), although all emulsions used in this study were freshly prepared.

For the suspension, penclomedine was finely ground in an agate mortar and pestle. This powder was added to an aqueous mixture of 2% methylcellulose (1500 cps, Fisher Scientific, Pittsburgh, PA).

Animal experimental protocol

Intravenous bolus administration of a soybean oil emulsion formulation of penclomedine was given to anesthetized rats weighing approx. 300 g. Following the injection, successive blood samples were taken and analyzed for drug content. This information was used as a control for the intraduodenal bioavailability studies.

Anesthetized rats weighing approx. 300 g were dosed with the emulsions via intraduodenal infusion at a rate of 0.85 ml/h (Syringe pump, Sage Instruments, model 341A, Cambridge, MA). Following the start of the infusion, successive blood samples were taken and analyzed for drug content.

Specific procedures

All rats used in the experiments were fasted for 24 h prior to each experiment with free access to water. The animals were anesthetized for the duration of the experiment using 50 mg/kg sodium pentobarbital given by an intraperitoneal injection. Although gastrointestinal function is impaired by anesthesia, an anesthetized animal model was used to facilitate intraduodenal infusion of the emulsions and lymph sampling as part of a larger matched study to be presented in another paper. Additional injections were given as needed (at approx. 2-h intervals). The animals were shaved from ventral midline to dorsal midline on the animals' right side and also on the ventral side of the neck and upper chest.

The duodenal cannula was attached to a trocar and externalized through the abdominal wall. It was then inserted into a small hole made in the duodenum approx. 1 cm from the pylorus. The cannula was secured with one drop of superglue (cyanoacrylate adhesive, Duro, Locktite Corp., Cleveland, OH). The intraperitoneal cannula was inserted between sutures after the closing of the animal's abdominal muscle layers. The application of superglue during the skin layer closure secured the cannula.

A tracheotomy was performed by cutting a 5×5 mm hole in the skin above the trachea. The muscle layers were separated with two pairs of 4 inch tissue forceps to expose the trachea. A pair of 4 inch curved tip forceps were inserted under the trachea and a small incision was made on the top of the trachea and the cannula was inserted about 1.5 cm. Surgical suture was tied around the trachea to secure the cannula. The trachea was realigned to its original position and the skin was closed with superglue.

The jugular veins were exposed to ease blood sampling and intravenous administration. Two incisions were made in the skin approx. 3 mm anterior to the clavicle and 5 mm each side of center. A small amount of fat and tissue were cleared to expose the vein just as it meets the pectoral muscle.

Drug administration

In all cases, a period of at least 1 h was allowed after surgery prior to the administration (either intravenous or intraduodenal) of the drug formulations. This time was allowed to aid the recovery of the animals from the surgical procedures and let the intestinal motility return to as close to normal as possible.

Intravenous administration was achieved by a direct bolus injection of 0.5 g of emulsion into the jugular vein. The intraduodenal administration of 0.5 g of emulsion was performed by a Sage infusion pump at a rate of 0.85 ml/h through the duodenal cannula.

The intraduodenal administration of 5 mg of penclomedine in 50 μl oil from a 250 μl syringe followed by 450 μl of the lecithin suspension from a 1 ml syringe was performed by a Sage infusion pump at a rate of 0.85 ml/h through the duodenal cannula. This procedure was performed to determine the effect of oil droplet size.

Sampling

Blood samples were taken directly from the jugular vein by venous puncture. This is accomplished by inserting the syringe needle into the pectoral muscle and then into the vein in an anterior direction. This method prevents blood leakage from the vein and can be used for multiple venous punctures. The intravenous samples were taken from the vein not used in the intravenous bolus administration to prevent any local contamination. The samples for the intravenous bolus experiments were taken at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, and 12 h post drug administration while samples for the intraduodenal experiments were taken at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h after starting the drug infusion.

Sample work-up and analysis

From the blood samples, a 150 μl aliquot was taken into a 15 ml glass centrifuge tube. An appropriate internal standard spike, DDT, in acetonitrile was added to each sample. After the internal standard spike, 1 ml of normal saline and 5 ml distilled diethyl ether were added. The tubes were then vortexed for 1 min. To separate the aqueous and organic layers, the tubes were centrifuged for 3 min at $850 \times g$. The tubes were then placed into a dry ice/acetone bath to freeze the aqueous layer. After a 30 s centrifugation, the ether layer was decanted into a clean 5 ml centrifuge tube and evaporated to dryness with a nitrogen stream. The sample were reconstituted with 100 μl of 75% acetonitrile in water and analyzed by HPLC.

A 20 μl aliquot of the reconstituted sample was injected onto a modular HPLC system. The HPLC system used for analysis included a Beckman 110B pump, a Perkin-Elmer ISS-100 Auto injector, and a Kratos 757 variable-wavelength detector operated at 243 nm. The separation of penclomedine from the biological matrix was accomplished by using a reversed-phase C_8 column (15 cm $\times$ 4.6 mm, 5 μm particle size) with a mobile phase of acetonitrile : water (75 : 25) at a

flow rate of 2.0 ml/min. Peak area measurements were performed by a Shimadzu CR-6A integrator. The peak area ratio of the compound of interest to the internal standard was determined and compared to the standard curve to determine the concentration of the sample.

Statistical analysis

Statistical analysis for experimental results where more than two sets of data are compared was performed by use of the GT2 method (Hochberg, 1974). This method is used to compare means of multiple data sets of unequal sample sizes. In all cases, except where noted, statistical significance was determined at the 95% confidence limit ($p = 0.05$).

Statistical analysis for experimental results where only two sets of data were compared was performed by use of the F-distribution method (Sokal and Rohlf, 1981). This method is used to compare means of two data sets of unequal sample sizes. In all cases, except where noted, statistical significance was determined at the 95% confidence limit ($p = 0.05$).

Results and Discussion

Intravenous penclomedine soybean oil emulsion was used as a control for the intraduodenal bioavailability studies. Fig. 2 shows a plot of the average penclomedine blood concentration (with standard error bars) vs time after intravenous bolus dosing of 0.5 g of a 10 mg/g penclomedine soybean oil emulsion (5 mg penclomedine per 300 g rat). The solid squares are the experimental points for the average of seven rats. The line through the data in Fig. 2 was generated from the average of fitted parameters for each rat determined by a computer fit of the data to a bi-exponential equation using PC-NONLIN® (Statistical Consultants Inc., Lexington, KY). The following bi-exponential equation was determined:

$$C_p = 66.8e^{-2.10t} + 18.2e^{-0.40t} \quad (1)$$

where C_p is the concentration of penclomedine (in μg/ml) in whole blood and t is time (in h). Mean pharmacokinetic parameters generated by the computer fit are listed in Table 1.

Drug release from an emulsion in the blood may affect the pharmacokinetics of the intravenous bolus dosing of penclomedine. If the drug is released very slowly from the emulsion, there may be a delay in the overall distribution of the drug. Since whole blood was assayed for drug, the actual concentration of drug in the blood should be detected even if the drug is still associated with the oil. In an effort to detect drug release from the emulsion, the following experiment was performed. After intravenous bolus administration of 0.5 g of a 10% o/w soybean emulsion (10

TABLE 1

Mean pharmacokinetic parameters determined after i.v. administration of 5 mg penclomedine (16.7 mg/kg) in a 10% o/w soybean oil emulsion to rats (n = 7)

Parameter	Value ± SE [a]
$t_{1/2\beta}$	1.9 ± 0.3 h
MRT	1.8 ± 0.2 h
AUC	82.3 ± 4.5 μg h ml^{-1}
AUMC	153 ± 18 μg h^2 ml^{-1}
V_d	0.56 ± 0.1 l kg^{-1} (169 ± 24 ml)
CL_{TB}	3.3 ± 0.1 ml min^{-1} kg^{-1} (1.0 ± 0.04 ml min^{-1})

[a] Standard error of the mean.

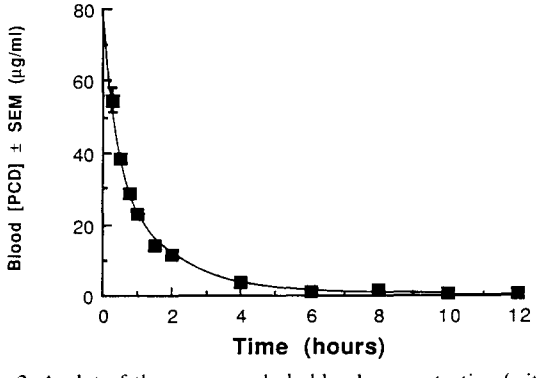

Fig. 2. A plot of the average whole blood concentration (with standard error bars) vs time obtained following intravenous bolus adminstration of 5 mg penclomedine (PCD) in a 10% o/w soybean oil emulsion (10 mg/g) to rats (experimental, ■; calculated, –; $n = 7$).

mg/g), blood samples were taken at 5-min intervals for 30 min. A portion of the whole blood was assayed for penclomedine whereas the remainder was centrifuged at $850 \times g$ for 15 min to allow any oil in the sample to rise to the surface. The top layer as removed and assayed for penclomedine and the remainder was resuspended and reassayed for penclomedine content. Qualitatively, a cloudy layer (oil) did not persist after the 15 min sample. Quantitatively, there was no difference between the whole blood sample concentration and the resuspended blood. However, there was a significant difference between these levels and the top layer in all of the blood samples. Although this may be indicative of the affinity of penclomedine to the red blood cell fraction of whole blood, it does show that the drug rapidly dissociates from the oil after intravenous administration. Thus, the penclomedine is released from the emulsion rather quickly and the emulsion dosage form should not interfere with the pharmacokinetics of the intravenous dosing.

Anesthetized rats weighing approx. 300 g were dosed with the emulsions via intraduodenal infusion at a rate of 0.85 ml/h. Administration of the different penclomedine formulations enabled the absolute and relative bioavailabilities to be calculated, assuming linear kinetics, and identification of the best dosage form. These experiments also showed the effects of various oil vehicles on the absolute bioavailability of the drug.

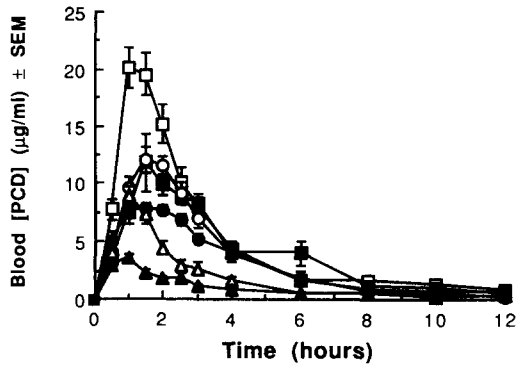

Fig. 3. A plot of the average whole blood concentration (with standard error bars) vs time obtained following intraduodenal administration of 5 mg penclomedine (PCD) in all emulsion and aqueous suspension formulations (10 mg/g) to rats. Trioctanoin ($n = 8$), □; soybean oil ($n = 6$), ■; triolein ($n = 8$), ○; mineral oil ($n = 8$), ●; tributyrin ($n = 11$), △; and aqueous suspension ($n = 6$), ▲.

The results for all of the penclomedine formulations from an intraduodenal administration are shown in Fig. 3 as a plot of mean penclomedine concentrations in whole blood vs time. The points shown are the average of several evaluations with standard error bars. Table 2 gives some relevant

TABLE 2

Mean pharmacokinetic parameters for penclomedine (5 mg, 16.7 mg/kg) determined after i.v. adminstration in a 10% o/w soybean oil emulsion and intraduodenal administration in various 10% o/w emulsions and an aqueous suspension to rats

Formulation (n, number of rats)	t_{max} [a] (h) ±SE [e]	C_{max} [b] (μg/ml) ±SE	AUC [c] (μg h ml^{-1}) ±SE	F [d]
Intravenous				
Soybean oil (7)			82.3 ± 4.5	1.00
Oral				
Trioctanoin (8)	1.2 ± 0.1	20.9 ± 1.8	57.6 ± 6.6	0.70
Soybean oil (6)	1.8 ± 0.2	12.5 ± 2.1	45.8 ± 3.3	0.56
Triolein (8)	1.6 ± 0.2	12.9 ± 1.0	38.9 ± 2.9	0.47
Mineral oil (8)	1.5 ± 0.1	8.4 ± 0.4	35.6 ± 3.2	0.43
Tributyrin (11)	1.1 ± 0.1	9.5 ± 0.7	21.4 ± 2.2	0.26
Suspension (6)	1.1 ± 0.3	4.0 ± 0.3	10.9 ± 1.3	0.13

[a] Time of maximum blood concentration.
[b] Maximum blood concentration.
[c] Area under the curve from time 0 to 12 h.
[d] Absolute bioavailability assuming linear kinetics.
[e] Standard error of the mean.

parameters for the intraduodenal formulations including the area under the curve data calculated by the trapezoidal method from 0 to 12 h for each of the formulations, as well as the intravenous soybean oil emulsion An extrapolated area under the curve from 0 to ∞ was not used because after 12 h, the blood level for all formulations was very close to zero. Therefore, little difference would be seen between the area under the curve between 0–12 h and 0–∞. The absolute fractional bioavailability, F in Table 2, is defined as the area under the curve of an intraduodenal formulation divided by that of the intravenous formulation. This assumes that penclomedine in this dose range follows linear kinetics.

Is the apparent incomplete bioavailability of penclomedine due to presystemic clearance or incomplete absorption from the gastrointestinal tract? Assuming that penclomedine is metabolically cleared by liver metabolism via linear kinetics, it is possible to calculate the expected first-pass effect of penclomedine, F_H, from the intravenous data. Assuming the hepatic blood flow to be approx. 780 ml/h (Birnie and Grayson, 1952), the expected fraction of penclomedine surviving liver first-pass metabolism can be calculated to be 0.92 based on Eqn. 2:

$$F_H = 1 - \frac{D}{AUC_{i.v.} Q_H} \quad (2)$$

where F_H is the fraction of the dose reaching the general circulation (assuming complete absorption), D is the administered dose, $AUC_{i.v.}$ is the area under the curve from the intravenous administration, and Q_H is the hepatic blood flow. This calculation tends to indicate, within the limits of the assumption used to derive this equation, that there was no major first-pass effect for penclomedine. However, about 8% of the incomplete bioavailability might be accounted for by a possible first-pass effect.

With respect to the observed bioavailability and pharmacokinetic behavior after intraduodenal drug administration, a significantly lower ($p < 0.05$) area under the curve was seen with the suspension dosage form compared to all other dosage forms except for the tributyrin emulsion. Upon ingestion of a suspension, dissolution of the solid must occur in order to achieve significant absorption from the gastrointestinal lumen (Watson and Rijnberk, 1987). Since penclomedine has such a low aqueous solubility, the low bioavailability from the suspension is probably due to the inability of the drug to dissolve in the gastrointestinal tract. Although an increase in the solubility of a poorly water soluble molecule in the presence of bile salts, lecithin and other lipid digestion products has been noted by Serajuddin et al. (1988), the expected increase in the solubility of penclomedine in the intestinal fluid was evidently not sufficient to solubilize the drug.

The tributyrin emulsion had the next lowest area under the curve. Tributyrin is a short-chain triglyceride with significant water solubility. Tributyrin is rapidly metabolized to its corresponding monoglyceride and fatty acids which are themselves water soluble. When this occurs, tributyrin and its metabolic products may dissipate quickly leaving the drug to precipitate. Such a phenomenon was observed by Alvarez and Stella (1989) in their study of series of phenytoin prodrugs dissolved in tributyrin which are subjected to pancreatic lipase. This may account for the poor performance of penclomedine in the tributyrin vehicle, i.e., once the drug has precipitated, dissolution may become a problem. The area under the curve for penclomedine from tributyrin was significantly different ($p < 0.05$) from all formulations except for the mineral oil emulsion and the aqueous suspension.

The mineral oil emulsion resulted in higher blood levels than initially expected. Since mineral oil is not metabolized or absorbed from the gastrointestinal tract, the only way for the drug to be released for absorption is by diffusing from the oil into the micellar phase of the intestinal contents. The relatively high bioavailability of penclomedine from the mineral oil emulsion compared to that of the aqueous suspension shows the importance of drug dispersion in the intestinal tract. That is, even dissolving the drug in a high surface area non-absorbable oil is favorable compared to the suspended drug in this case. Since the mineral oil is neither hydrolyzed nor absorbed, it remains in the lumen carrying the

portion of the drug still dissolved in the oil phase to the colon and feces (Volpenhein et al., 1980; Rozman et al., 1983). The area under the curve of the mineral oil emulsion was significantly different ($p < 0.05$) from only the trioctanoin emulsion and the suspension dosage forms.

The soybean oil and triolein emulsions are made with long-chain triglycerides which are metabolized quite slowly (Alvarez and Stella, 1989). In the present study, penclomedine absorption from the emulsion was less than ideal (relatively and absolutely). Since the vehicle may be metabolized relatively slowly, the major component of the release of the drug from these emulsions is probably due to the diffusion of the drug from the oil. Several researchers have found that release from the administered oil due to digestion of the vehicle was important for absorption (Muranishi et al., 1971; Yamahira et al., 1979; Vetter et al., 1985). Since these vehicles are hydrolyzed to some extent, there may also be some release due to the degradation of the vehicle, Since the rats in the present study were anesthetized during the entire experimental procedure, gastrointestinal motility and other intestinal functions may be altered compared to an unanesthetized animal. This may affect the overall processing and intestinal transit time of the emulsion.

There was no significant difference between the area under the curve for the soybean oil and triolein emulsions. This is expected since the oils are both long-chain triglycerides and similar in fatty acid composition. Both of the emulsions were significantly different ($p < 0.05$) from the tributyrin emulsion and the aqueous suspension. The area under the curve of the triolein emulsion was also significantly different from that of the trioctanoin emulsion.

The trioctanoin emulsion gave significantly higher ($p < 0.05$) blood levels and area under the curve than all the other formulations except for the soybean oil emulsion. The trioctanoin is metabolized rather quickly (Greenberger et al., 1966; Yamahira et al., 1979b; Alvarez and Stella, 1989). The drug may be released from the oil by a combination of diffusion and metabolism. However, the metabolism may not be so fast that the drug precipitates, as occurred with the tributyrin emulsion. As the trioctanoin is hydrolyzed, the penclomedine may distribute between the oil and micellar phases that are enriched by the oil metabolic products, the monoglyceride and the formed free fatty acids (Rautureau and Rambaud, 1981). After the drug has moved into the micellar phase, the diffusion of these compounds to the surface of the intestinal mucosal cell can occur although in all likelihood, it is the free drug that is transported across the intestinal mucosa. Another factor that may help the absorption of penclomedine from the trioctanoin emulsion is that the products from the metabolism of trioctanoin help solubilize the drug, and therefore, contribute to the micellar phase of the luminal contents (Rosoff and Serajuddin, 1980; Reynier et al., 1981). The favorable results from the trioctanoin emulsion may be due to a combination of these effects.

To address the question of the role of oil particle size and the importance of surface area, an experiment was performed where either intraduodenal administration of an emulsion or straight oil (followed by a lecithin suspension) was infused at a rate of 0.85 ml/h. For the straight oil experiments, 50 μl of oil was infused followed by 450 μl of the lecithin aqueous suspension used in the emulsion formation. This procedure was followed in an effort to mimic the emulsion composition without actually administering an emulsion. Since the straight oil was not emulsified, the oil particle size should be much larger than with the emulsion. The particle size for the straight oil would probably even be larger in our methodology for two reasons, gastric emptying is bypassed and the use of anesthetized animals decreases intestinal motility, resulting in a smaller oil-to-water interfacial area, causing a slower rate of metabolism of the vehicle and rate of diffusional release of drug from the oil.

The results from the administration of penclomedine dissolved in straight oil vs emulsion administration for trioctanoin and mineral oil are shown in Figs 4 and 5. These plots show that the trioctanoin emulsions gave significantly higher ($p < 0.05$) blood levels compared to the administration of drug dissolved in the corresponding

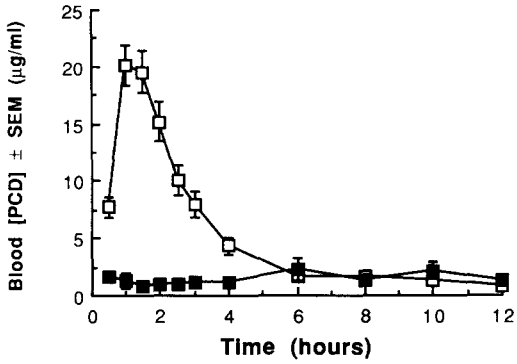

Fig. 4. A plot of the average whole blood concentration (with standard error bars) vs time obtained following intraduodenal administration of 5 mg penclomedine (PCD) in either 0.5 g of a 10% o/w trioctanoin emulsion (10 mg/g), □ ($n = 8$); or 50 μl trioctanoin oil (10 mg/g), ■ ($n = 3$) to rats.

straight oil. Because of the small number of animals used in this experiment ($n = 3$), the mineral oil emulsion did not show significantly higher levels at the 95% confidence limits compared to the oil, however, qualitatively, drug absorption from the oil was lower than from the emulsion. These results indicate that dispersed oil droplets (emulsion) compared to a non-dispersed oil (straight oil) do affect the absorption of the drug, however, a more thorough study employing a more gradual change in particular size would provide more conclusive evidence on the importance of particle size.

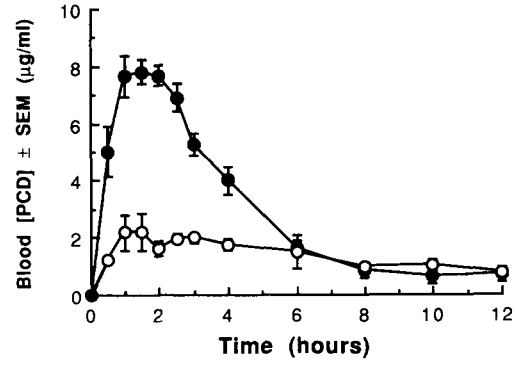

Fig. 5. A plot of the average whole blood concentration (with standard error bars) vs time obtained following intraduodenal administration of 5 mg penclomedine (PCD) in either 0.5 g of a 10% o/w mineral oil emulsion (10 mg/g), ● ($n = 3$); or 50 μl mineral oil, ○ ($n = 3$) to rats.

In summary, the objective of this work was to evaluate the role of emulsion dosage forms in enhancing the bioavailability of the lipophilic, poorly water-soluble compound, penclomedine. The emulsion dosage form was chosen as a possible solution to the problem of low bioavailability. Most of the emulsions studied showed a significantly higher bioavailability when compared to the aqueous suspension (solid drug). The trioctanoin emulsion resulted in the highest bioavailability. This was explained by a balancing of the diffusion from the oil and the metabolism of the vehicle resulting in the efficient release of drug. Other oils either released the drug too slowly, resulting in incomplete absorption, or too rapidly, probably resulting in possible precipitation of the released drug in the intestinal contents and slow subsequent dissolution as demonstrated by the incomplete absorption from the suspension.

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