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The effect of different oils on the absorption of probucol in the rat

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The effect of oily vehicles on the gastrointestinal absorption of the hypocholesterolaemic agent probucol has been investigated in the rat. The plasma concentration was determined following its administration in arachis oil (peanut oil), Miglyol 812 (fractionated coconut oil) and liquid paraffin. The total absorption of the drug, calculated as the area under the plasma concentration time curve, was significantly greater for the arachis oil formulation than with the other vehicles. The drug was selectively absorbed via the lymphatic system, lymph drug concentrations being highest following co-administration of arachis oil.

Probucol is a hypocholesterolaemic drug structurally unrelated to other lipid depleting agents. It is virtually insoluble in water and strongly lipophilic, the predicted octanol : water coefficient using Hansch analysis being of the order of 10^{11}. Oral absorption is limited and variable (Martz 1979), though improved by the presence of food. Administration of a single oral dose to man gives peak plasma concentrations after 24 h and elimination is biphasic with half-lives of approximately 1 and 23 days (Heeg & Tachizawa 1980). During chronic administration, the plasma concentration of probucol gradually rises reaching a stready state after 2–4 months. After discontinuance of the drug, elimination is slow with 60% of the original plasma concentration remaining after 6 weeks (Martz 1979). This characteristic slow rise and fall in plasma values is due to the storage of the drug within body adipose tissue (Heel et al 1978). The major route of excretion of probucol is via the bile, resulting in high faecal clearance and negligible renal clearance (Murphy 1977).

In all these properties, probucol resembles the insecticide DDT. Our previous studies have shown that the oral absorption of DDT is enhanced by co-administration of arachis oil and that absorption occurs primarily via the lymphatic route (Palin et al 1982). It follows that probucol may be selectively absorbed via the lymph, and that co-administration with oil enhances this absorption. If this occurs, re-formulation of the drug into an oily vehicle may promote uptake, resulting in elevated and more uniform absorption and more rapid achievement of steady-state plasma values.

We have set out to determine whether the bioavailability of probucol is affected by co-administration of different oily vehicles in the rat and secondly whether the drug is selectively absorbed into the lymph from the gastrointestinal tract.

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Materials and methods

Male Wistar rats (190–210 g) were used. Probucol and its analogue, 2-pentanone bis(3,5-di-t-butyl-4-hydroxyphenyl)mercaptol, (internal standard) were supplied by Dow Chemical Co., USA. The oils investigated were arachis oil BP (Evans Ltd., Liverpool), Miglyol 812 (a fractionated coconut oil) (Dynamit Nobel, Slough, Berks) and liquid paraffin BP (Shell Ltd, London). Tween 80 was obtained from Sigma (London) Chemical Co. Ltd, (Poole, Dorset) and Dulbecco's solution (A + B) was obtained from Oxoid Ltd (Basingstoke, Herts). All other reagents were Analar grade and were used without further purification.

Animal procedures. Male Wistar rats were starved overnight but had free access to water. Each animal was orally dosed, as described by Palin et al (1982), with probucol (100 mg kg^{-1}) in solution in 0·5 ml volumes of arachis oil, Miglyol 812 or liquid paraffin. Blood samples were taken from the tail tip at intervals over 33 h and the plasma was collected and stored at −20 °C before analysis.

Lymphatic absorption of the drug, administered in solution in the three oils or as an aqueous suspension in 6% Tween 80, was measured by cannulation of the thoracic duct as described by Palin et al (1982). Lymph was collected continuously from the thoracic duct for 4 h and samples taken for analysis. Blood samples were taken from the tail tip at half-hourly intervals and plasma collected and analysed.

Probucol analysis. The samples were analysed with an adaptation of an unpublished hplc procedure provided by the Dow Chemical Company. Plasma and lymph samples (50 µl) in 0·9% NaCl (saline) (450 µl) were 'spiked' with a solution of a probucol analogue (2-pentanone-bis(3,5-di-t-butyl-4-hydroxyphenyl)-mercaptol), 7·5 µg in 100 µl methanol) and were then treated with 2·5 ml methanol–acetone (3 : 2 w/v). After centrifugation (10 min 3000*g*), the upper layer was decanted into fresh tubes containing 1 ml hexane. The samples were then extracted and centrifuged for 5 min, and the hexane layer removed and evaporated to dryness in 1 ml vials. The residue was redissolved in 50 µl methanol and 20 µl samples applied to a Hypersil ODS 5 µm hplc column. A fixed wavelength detector (Applied Chromatography Model 750) was used to

monitor the eluate at 240 nm. The mobile phase was acetonitrile, hexane, 0·1 M ammonium acetate (90 : 8 : 2 v/v/v) at a flow rate of 0·9 ml min^{-1}. Retention times for the probucol and internal standard were 4·0 and 6·0 min respectively. Probucol standards in plasma in the concentration range from 0·25 to 100 μg ml^{-1} were extracted. The detection limit of the assay was found to be 0·15 μg ml^{-1}.

Results

The plasma concentration-time curves after administration of probucol in different oily vehicles to conscious animals exhibited significant differences between the formulations (Fig. 1). For each curve the maximum plasma concentration (Cp_{max}), the time to the Cp_{max} (T_{max}) and the total drug absorbed calculated as the area under the cruve between 0 and 16 h ($AUC_{0-16\,h}$) using the trapezoidal method, were determined (Table 1). The plasma concentration of probucol from the liquid paraffin solution remained below the limits of detection of the assay (<0·15 μg ml^{-1}) and the pharmacokinetic parameters could not be calculated. Co-administration of arachis oil significantly increased the peak plasma value and total drug absorption of probucol compared with co-administration of Miglyol 812 ($P < 0·05$ for Cp_{max} and $AUC_{0-16\,h}$ unpaired Student's *t*-test).

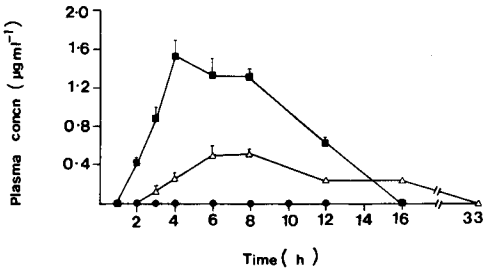

FIG. 1. Plasma concentration–time profile of probucol in rats after oral administration of 100 mg kg^{-1} in different oil vehicles (0·5 ml); arachis oil (■), Miglyol 812 (△) and liquid paraffin (●). Each point represents the mean result (+ s.e.m.) of 4 experiments.

Table 1. Pharmacokinetic data following oral administration to rats of probucol (100 mg kg^{-1}) in solution in different oily vehicles (0·5 ml volumes) (means ± s.d. n = 4 per group).

Vehicle	Cp_{max} μg ml^{-1}	T_{max} h	$AUC_{0-16\,h}$ μg ml^{-1} h^{-1}
Arachis oil	1·73 ±0·18	5·00 ±2·00	11·74 ±1·55
Miglyol 812	0·54 ±0·08	7·00 ±2·00	4·57 ±0·93
Liquid paraffin	ND	ND	ND

The lymph concentration of probucol, determined in thoracic lymph samples, was significantly higher for the arachis oil formulation than for the other vehicles (Table 2). The plasma drug concentration in these rats was near the limit of detection of the assay (0·15 μg ml^{-1}).

Table 2. Lymph concentration of probucol (μg h^{-1}) in anaesthetized rats, following oral administration of probucol (100 mg kg^{-1}) in different vehicles (0·5 ml volumes). (Mean ± s.d. n = 4 per group.)

Vehicle	Time after dosing 1·5 h	2·5 h	3·5 h
Arachis oil	4·26 ±4·96	5·71 ±3·02	7·05 ±3·56
Liquid paraffin	<0·15	0·17 ±0·17	0·17 ±0·03
6% Tween 80 in water	<0·15	0·20 ±0·16	0·32 ±0·22
Miglyol 812	*	*	*

* All animals died with 1 h of dosing.

After the administration of probucol in Miglyol 812 to anaesthetized rats, each animal died within 1 h of dosing. A similar phenomenon has been observed in anaesthetized animals dosed with DDT in Miglyol 812. Administration of the oil to conscious animals caused no deaths.

Discussion

The oral absorption of probucol in conscious rats is thus dependent on the lipid vehicle in which it is administered; arachis oil yielded higher plasma drug concentrations than Miglyol 812 or liquid paraffin. The same rank order for the effect of the different oils on drug absorption was found when DDT was given orally to rats (Palin et al 1982).

From the results it appears that probucol is selectively absorbed via the lymphatic pathway from both aqueous suspensions and oil solutions. The drug was not detected in plasma samples from the thoracic duct, but was detectable in the lymph samples. The higher concentrations of probucol in the lymph after administration in arachis oil suggest that digestion and absorption of this oil facilitates the intestinal absorption of the drug. The water-insoluble long chain fatty acids released during arachis oil digestion are incorporated into mixed bile salt micelles in the intestinal lumen (Hofmann 1966) and into chylomicrons within the enterocytes before transport into mesenteric lymph (Caselli et al 1979). In contrast, the products of digestion of Miglyol 812, medium chain fatty acids, are water soluble and are absorbed into portal blood. Liquid paraffin does not undergo appreciable digestion, being poorly absorbed from the gastrointestinal tract.

Pentobarbitone is known to reduce gastrointestinal

motility and blood flow (Lee 1965; Green 1979) so results obtained from anaesthetized rats must be interpreted with caution. However, the same rank order for the effects of the oils on plasma and lymph concentrations of the drug, strongly suggests that the mechanism of absorption is unaltered, although the extent is reduced by anaesthesia. Previous experiments (Palin 1981) have shown that pentobarbitone reduces the plasma concentrations of DDT delivered in the three oils, but the enhancing effect of arachis oil is still seen.

It is concluded that probucol absorption in rats can be enhanced by co-administration with arachis oil. It may be possible to achieve a similar effect in man by reformulation of the drug, although the ratio of oil volume administered : body weight would have to be greatly reduced. It has been reported that at low rates of infusion into in-situ rat intestinal loops, a significant proportion of unsaturated long chain fatty acids is absorbed via the portal route (McDonald et al 1980). Only at higher rates of infusion are these fatty acids directed into the lymphatic system.

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Letters to the Editor

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Recent IUPAC Nomenclature Recommendations

Listed below are the titles of chemical nomenclature recommendations published by IUPAC during recent months. Comments on the proposals (addressed to the originating IUPAC Commission) would be welcomed.

1. Glossary of terms used in physical organic chemistry (Pure Appl. Chem. 1983, 55: 1281).
2. Extension of rules concerning numerical terms used in organic chemical literature (Pure Appl. Chem. 1983, 55: 1463).
3. Nomenclature and symbolism for amino acids and peptides (Pure Appl. Chem. 1984, 56: 595).
5. Nomenclature, symbols and units recommended for in situ microanalysis (Pure Appl. Chem. 1983 55: 2023).
5. Nomenclature, symbols, units and their usage in analysis by molecular luminescence spectroscopy (Pure Appl. Chem. 1984, 56: 231).

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Joint Royal Society/Royal Society of Chemistry, Panel on Chemical Nomenclature