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Effect of egg yolk lecithin on transdermal delivery of bunazosin hydrochloride

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Transdermal delivery of bunazosin HCl and the enhancing effect of egg yolk lecithin were examined using an in-vitro hairless mouse skin preparation and rabbits for in-vivo systemic absorption. The delivery of bunazosin in-vitro was small, but it was significantly enhanced when lecithin was incorporated into the same vehicle. This enhancing effect was confirmed with other drugs in-vitro. The enhancing ability was also seen in-vivo. Very little bunazosin was delivered from a propylene glycol suspension, but levels of 100–200 ng mL^{-1} were achieved by the incorporation of the lecithin.

Bunazosin HCl (4-amino-2-(4-butanoylhexahydro-1*H*-1,4-diazepin-1-yl]-6,7-dimethoxyquinazoline hydrochloride) is a newly synthesized α_1-adrenoceptor-blocking drug, that reduces peripheral resistance, has a therapeutic effect on essential hypertension, and is active by mouth (Igarashi et 1976; Kawasaki et al 1981). Prolonged antihypertensive action would be of therapeutic value, and as this may be achieved by various approaches, transdermal delivery and the effects of egg yolk lecithin on this have been examined.

Materials and methods

Egg yolk lecithin was a gift from Asahi Kasei Co, Ltd. Bunazosin was from Eisai Co, Ltd. Other chemicals were of reagent grade.

The details of the diffusion procedure were described by Lotfson & Bodor (1981) and Mukai et al (1985). Male hairless mice (8–10 weeks) were killed by cervical dislocation, and immediately the dorsal skin was removed with all layers intact and used within 30 min. Each skin was mounted in a diffusion cell containing, as receptor fluid, 50 mL of isotonic phosphate buffer solution previously adjusted to pH 7·4 with 0·17 M $NaHCO_3$ and 0·17 M K_2HPO_4. The cell was left in a controlled 37 °C incubator throughout the experiment. The area used for diffusion was 8·04 cm^2. The vehicle used in the in-vitro study was propylene glycol in which bunazosin, theophylline and isosorbide dinitrate were suspended at 37 °C (50, 50 and 100 mg g^{-1} solvent, respectively). The lecithin at 1% w/w was also dissolved in this vehicle. After vehicle, 0·5 mL, had been applied to each skin, samples of receptor fluid, 1 mL, were withdrawn periodically and replaced with the same volume of buffer solution.

The solubility of bunazosin in propylene glycol was determined by addition of excess propylene glycol with shaking at 37 °C for 48 h. After equilibration, the sample was filtered through a fluorinert filter (type FA, Millipore) preheated at 37 °C in an incubator. The filtrate was adequately diluted with water and analysed by HPLC.

The amounts of drugs were determined by an HPLC system equipped with a variable wavelength UV-detector (UVIDEC 100-II, Jasco). The stationary phase was Nucleosil $_5C_{18}$ packed in a column (4·6 × 150 mm). Mixtures of acetonitrile–water were used as the mobile phase with a flow rate of 1·0 mL min^{-1}. The details of the mobile phase constituents are summarized in Table 1. The standard solutions were chromatographed and calibration lines constructed on the basis of peak-height measurements.

For the in-vivo absorption study, male rabbits (2·5 kg) were used. The dorsal hair was removed 24 h before the experiment. The vehicle used was again propylene glycol, in which bunazosin was dissolved and to which lecithin 3% w/w was added as required. Vehicle, or suspensions, was applied by covering the clipped area of 25 cm^2 (5 × 5 cm) with absorbant cotton containing 5 g of the vehicle alone or with drug, 250 mg per rabbit. This area was then wrapped with a polyvinylidene chloride sheet and secured with tape. During the absorption, rabbits were restrained. Blood (3 mL) was collected from the ear vein and plasma was obtained by centrifugation (3000 rev min^{-1} × 5 min). The drug was extracted with toluene from plasma mixed with a small amount of 0·5 M NaOH, and re-extracted with 0·2 M acetate solution. The concentration of drug in this solution was determined by measuring the fluorescence (excitation 330 nm/emission 390 nm).

Results

Topical delivery of bunazosin was small, but was enhanced by a small amount of lecithin (Fig. 1) with the effect of increasing the amount of drug in the receptor fluid 24 h after application by about 55-fold (7·3 mg/0·13 mg).

Table 1. HPLC conditions for the assay of drugs.

Drug	Mobile phase	Ratio	Detect
Bunazosin	acetonitrile–0·017 M acetate, 0·005 M SLS	50:50	UV245
Theophylline	acetonitrile–0·017 M acetate	10:90	UV270
Isosorbide dinitrate	acetonitrile—water	40:60	UV220

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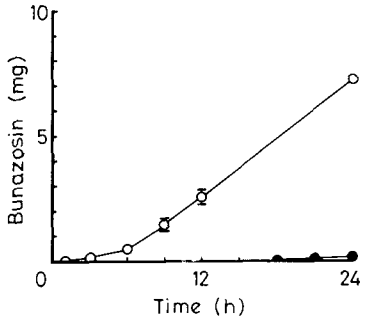

FIG. 1. Changes with time in amount of bunazosin in the receiving compartment (n = 6). Key: (●) suspension, (○) suspension + 1% lecithin. Bars represent standard deviation from the mean. Where no bar appears, the standard deviation is obliterated by the symbol.

The phase solubility diagram of the drug/lecithin system shows no significant change in drug solubility (Fig. 2).

The enhancing effect of the lecithin was also evaluated with theophylline and isosorbide dinitrate (Table 2) as lecithin has been shown to affect the skin transport of various drugs, although the degree of it differed.

To investigate the enhancing effect of lecithin in-vivo over 24 h, vehicles were painted onto the dorsal skin of rabbits. When the suspension of the drug was applied, no detectable drug appeared in the plasma, but when the suspension contained lecithin, levels of between 100

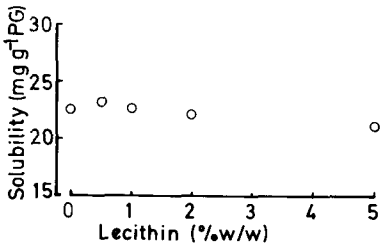

FIG. 2. Phase solubility diagram of the drug/lecithin system in propylene glycol at 37 °C.

and 200 ng mL^{-1} of bunazosin were found in the plasma 3 to 9 h after application (Fig. 3).

Discussion

Phospholipids are often used as additives, especially as liposome constituents. In our experiments, egg lecithin was dissolved in propylene glycol, and, in this state, improved the transdermal delivery of bunazosin and some other drugs.

Two possible reasons for this improvement of transdermal delivery were considered. One is a thermodynamic change of the penetrant in the vehicle that takes place as a result of the addition of lecithin, the other is a

Table 2. Amount of drugs in receiver compartment at 24 h.

Drug	Suspension (mg)	+ Lecithin (mg)
Bunazosin	0·13 ± 0·04	7·30 ± 0·02
Theophylline	0·97 ± 0·13	11·88 ± 1·31
Isosorbide dinitrate	4·02 ± 0·46	18·31 ± 3·20

Data represent mean ± s.d. of 3 experiments.

permeability change in the skin barrier resulting from the interaction of lecithin with components of the skin.

Phase solubility data of the drug/lecithin system (Fig. 2) indicate that addition of lecithin in amounts ranging from 0 to 5% w/w does not alter the solubility of the drug, and that there is no interaction between lecithin and bunazosin.

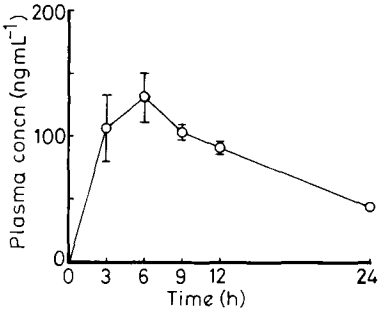

FIG. 3. Changes with time in plasma concentration of bunazosin after topical administration of bunazosin in a suspension containing 3% lecithin. No drug was detected when the suspension contained no lecithin (n = 3). Bars represent standard error from the mean. When no bars appear, the standard error is obliterated by the symbol.

Furthermore, all the suspensions used were saturated with drugs, so the thermodynamic activity could be considered constant.

Accordingly, the enhancing effect of the lecithin must be due to a change in the permeability of the skin barrier although the mechanism by which this occurs remains unclear.

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