PERCUTANEOUS ABSORPTION OF DISOPYRAMIDE, LIDOCAINE AND TRIMECAINE

Jan Příborský[a,b,*], Katsuya Kikuchi[c], Kozo Takayama[c], Tsuneji Nagai[c]

[a] *Glaxo Wellcome s.r.o., K Žižkovu 4, 190 00 Prague, Czech Republic*
[b] *Institute of Pharmacology, Faculty of Medicine, Palacký University, Hněvotínská 3, 77 515 Olomouc, Czech Republic*
[c] *Department of Pharmaceutics, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142,Japan*

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Promoting effect of cyclic monoterpenes on percutaneous absorption of antiarrhytmic drugs disopyramide, lidocaine and trimecaine was investigated in the rats. Laurocapram (Azone) was used as a standard comparator of penetration enhancement. The absorption of trimecaine was significantly enhanced by addition of limonene, trans-p-menthane and Azone in 1% concentration. Lidocaine and disopyramide penetrated across the skin only when 1% of limonene was used. Other cyclic monoterpenes showed no effect on percutaneous absorption of examined drugs.

INTRODUCTION

Previous studies performed in our laboratory proved that several antirheumatics are suitable candidates for percutaneous drug formulations[1,2]. Percutaneous absorption of drugs can be enhanced by means of cyclohexanone derivatives[1], cyclic monoterpenes [2] and other penetration enhancers like Azone, DMSO, pyrrolidones[3] or dioxolanes[4]. This study was carried out to screen possible candidates for percutaneous drug formulations from the group of antiarrythmic drugs using cyclic monoterpenes limonene and cineole as penetration enhancers. Limonene proved an excellent absorption promoting ability compared with other cyclic monoterpenes[2], cineole was reported as a good penetration enhancer in the formulations containing propylene glycol[5,6]. Azone was used in the study as a standard absorption promotor. Great advantage of limonene is its low toxicity. This substance has GRAS status by FEMA since 1965[7] and is approved by FDA for food use. The Council of Europe included d-limonene with a technological limit, except for chewing gum, in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health in 1974[8]. More recent information dealing with physicochemical properties of limonene are summarised by Thomas and Bessiere[9]. The experiments were conducted in the rats in vivo using carboxyvinyl polymer gel in which the ethanolic solution of drug and enhancer was formulated.

MATERIALS AND METHODS

Materials

Following antiarrythmics were examined: disopyramide purchased from Sigma Chemical Company (St. Louis, Mo, USA), lidocaine from Wako, Pure Chemical Industries Ltd. (Tokyo, Japan) and trimecaine hydrochloride which was generous gift from Sanitas (Říčany u Prahy, Czech Republic). Following cyclic monoterpenes were used: hydrocarbons – limonene and trans-p-menthane, alcohols – menthol, ketones – menthone and ethers – cineole, all by Tokyo Chemical Industries Co., Ltd. (Tokyo, Japan). Laurocapram (Azone) was supplied by Sumisho-Nelson Co., Ltd. (Osaka Japan). Carboxyvinyl polymer, marketed as „hiviswako 105" was supplied from Wako Pure Chemical Industries Ltd. (Tokyo, Japan). Other chemicals were of reagent or HPLC grade.

Formulations

The preparation of gel ointments including penetration enhancers was described previously (2). The concentration of antiarrythmics was in all gel ointments 2 % (Table 1). Trimecaine in 2% concentration and with 1% limonene was also formulated into the propylene glycol.

Table 1. General pattern of antiarrhytmic ointment with cyclic monoterpenes and Azone as penetration enhancer.

Component	Content
Antiarrythmic drug	2.0 g
Carboxyvinyl polymer	2.0 g
Triethanolamine	2.5 g
Ethanol	50.0 g
Penetration enhancer	1.0 g
Distilled water	ad 100.0 g

Animal procedure

Male Wistar rats weighing 170–190 g were used. After anaesthetisation with urethane saline solution (25%, 3.0 ml/kg i.p.) the rats were fixed on their back and the hair on the abdominal site of the body was removed with

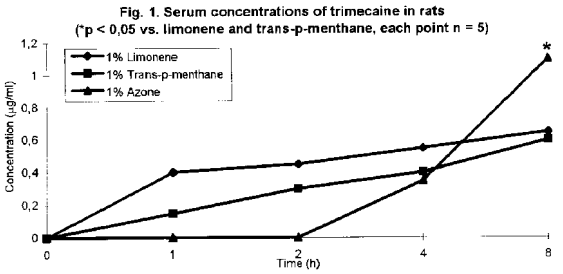
an electric animal clipper. Modified Franz glass cells (16,0 mm inner diameter, 10 mm height) containing the gel ointment under test (1,5 g) were attached to the shaved skin with cyanoacrylate type adhesives. Blood samples (250 ml) were collected via the jugular vein at 1, 2, 4 and 8 hours after administration.

Determination of antiarrythmics

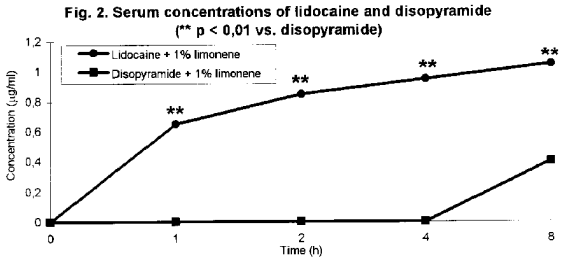
Determination of antiarrythmics was based on modified reversed phase HPLC procedure published by Proelss and Townsend[10]. Trimecaine, which is not described in this study, was estimated using similar approach as in the case of lidocaine. After centrifugation 100 ml of plasma samples were taken and mixed with 100 ml of internal standard. In the case of lidocaine and trimecaine 30.0 mg/ml of disopyramide was employed as standard and in the case of disopyramide estimation 30.0 mg/ml of trimecaine was used as internal standard. Hydrochloric acid (0.1 mol/l) was used as a solvent for internal standards. To this mixture 100 ml of 0.005 mol/l Na_2CO_3 was added and mixed for 15 s using Vortexer (Scientific Industries, Inc., Bohemia, NY, USA). The samples were shaken for 30 min and centrifuged (1.5 min) after addition of 500 ml of methylene chloride. The aqueous layer was removed and the organic phase was filtered using Acro LC 8S disposable filter unit (Gelmann Sciences, Ann Arbor, MI, USA). The samples were evaporated under nitrogen atmosphere at 45 °C. Before estimation, the samples were dissolved in 150 ml of mobile phase (acetonitrile: methanol: phosphate buffer – 60:33:7). The phosphate buffer was prepared using 1.5 g KH_2PO_4 dissolved in 1000 ml of water deionised using Mili Q Labo, Nihon Millipore Kogyo, KK (Yonezawa, Japan). The pH was adjusted by means of triethylamine (75 ml) to 5.7. After mixing with acetonitrile and methanol the final pH was between 6.7–7.1. Ultraviolet detection at 205 nm was used, the column (4,6 mm x 250 mm) was packed with Spherisorb 5 CN Senshu Pak, Senshu Science Co., Ltd. (Tokyo, Japan), elution was at room temperature, flow rate 2.0 ml/min, pressure 200 kg/m^2.

RESULTS

The aim of this study was to find out if cyclic monoterpenes are capable to promote transdermal absorption of antiarrythmics trimecaine, lidocaine and disopyramide. Trimecaine was assessed with 1% penetration promotors (limonene, trans-p-menthane, menthol, menthone and cineole). The only effective penetration enhancers were limonene and trans-p-menthane (Fig. 1). 1% Azone served as a control. 1% concentration of penetration enhancers used in the study was selected after our previous experience based on experiments in which 1% concentration was sufficient enough to promote percutaneous absorption[11]. Limonene and trans-p-menthane enhanced percutaneous absorption of trimecaine continuously from the very beginning of application. The increase was measurable from the first sampling (after 1 hour) and maintained linear pattern. The serum concentrations were 0.15, 0.30, 0.40 and 0.60 mg/ml after 1, 2, 4 and 8 hours respectively. Similar results were observed in case of limonene, where concentrations were 0.40, 0.45, 0.55, 0.65 mg/l after 1, 2, 4 and 8 hours respectively. There were no significant differences in penetration enhancing ability between limonene, trans-p-menthane and Azone up to 4th hour after start of the experiment. Penetration enhancing effect of Azone was delayed in the formulations containing trimecaine in comparison with cyclic monoterpenes. No detectable amount of trimecaine absorbed from ointment containing Azone was observed in first two hours. After 8 hours the amount of trimecaine in ointment containing 1% Azone was double in comparison with limonene and trans-p-menthane. The difference was statistically significant.



Lidocaine and disopyramide were examined only in ointment with 1% limonene and Azone. These two compounds were selected because they were found most efficient in the previous experiments with trimecaine. In our experiments with disopyramide and lidocaine only limonene promoted significantly transdermal absorption. Statistically significant enhancement of percutaneous absorption of lidocaine can be observed since 1st hour after application. Serum concentrations of lidocaine were 0.65, 0.85, 0.95 and 1.05 mg/ml after 1, 2, 4, and 8 hours respectively. Percutaneous absorption of disopyramide remained poor. The only measurable concentration (0.40 mg/ml) was observed 8 hours after application (Fig. 2).



DISCUSSION

Summarising our results, the ability of studied antiarrythmics to penetrate across the skin is variable. We used the same penetration enhancers as in the studies with antirheumatics where excellent effect was observed[2,3,4,5]. Carboxyvinyl polymer was found as a good matrix for antirheumatics[2]. All our results in this study were performed *in vivo*. Comparing with in vivo studies on antirheumatics[2,3] performed under the same experimental conditions the significant effect of limonene and trans-p-menthane can be seen. In comparison with the *in vitro* results on human skin conducted by Barry and Williams[4] with model penetrant, 5-fluorouracil, the results are contradictory. Limonene was found in our experiments repeatedly to be the most effective enhancer, while cineole was inefficient. When carboxyvinyl polymer gel was replaced by 100% propylene glycol, used by Barry and Williams, no penetration enhancing effect was observed. This difference may be elucidated by the diversity of physicochemical properties of used compounds as well as by the effect of formulation.

There are few data on percutaneous absorption of antiarrythmics and local anaesthetics in the literature. Novocaine, benzocaine and xylocaine (in the therapeutic group of local anaesthetics) and verapamil (antiarrhytmic), are mentioned in the patent published by Sarpotdar[12] as suitable active ingredients to their patented transdermal dosage form. Propylene glycol and glycerine were used in the ratio from 1:1 to about 1:5. Azone was probably used as penetration enhancer. There are no further comments on the efficacy of this transdermal dosage form. Das et al.[13] evaluated verapamil transdermal patch containing various concentrations of active ingredient in the dispersion of polyhydroxyethyl methacrylate and isopropyl myristate/propylene glycol as a penetration enhancer with good results. As far as lidocaine itself is concerned the penetration across the skin was achieved usually by means of iontophoresis[14], in this study human stratum corneum was employed. Sage and Riviere[15] used isolated porcine skin flap. There were no reports previously published on the trimecaine and disopyramide either employing iontophoresis of penetration enhancers[16].

Our results proved the possibility of percutaneous absorption of three antiarrythmic drugs. In the case of disopyramide the permeated amount is limited. Lidocaine and trimecaine permeated across the skin very well. The serum concentration increase was in the presence of 1% limonene very steep. 1% trans-p-menthane also promoted transdermal absorption of trimecaine. There are several possibilities of increasing plasma concentration: to increase efficient surface, or to increase the concentration of active ingredient, or to change the ethanol carboxyvinyl polymer content to some more beneficial ratio, or to change the concentration of penetration enhancers.

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