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Buccal transport of flecainide and sotalol: effect of a bile salt and ionization state

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Abstract

Patients with infrequent attacks of supraventricular arrhythmia may benefit from self administration of antiarrhythmic drugs on an 'as required' basis. The oral cavity is easily accessible and the potential for rapid absorption exists. The effects of ionization state and sodium glycocholate on the ex vivo transport of sotalol and flecainide across porcine buccal mucosa were studied. The permeated amounts at 3 h (Q) and fluxes (J) of sotalol in an aqueous solution at pH 7.4 and 9.0 were similar. At pH 7.4, in contrast to pH 9.0, the addition of 1.0% (w/v) sodium glycocholate decreased Q and J four and five fold. Flecainide base in propylene glycol resulted in a nine and 12 fold higher Q and J as compared with an aqueous solution of flecainide acetate at pH 5.8. The presence of sodium glycocholate reduced the transport rate of the flecainide base. However, Q and J were increased 110 and 75 fold by adding 1.0% (w/v) sodium glycocholate to a solution of flecainide acetate at pH 5.8. Sodium glycocholate seems to be an effective penetration enhancer for the buccal absorption of the more polar ionized form of flecainide in an aqueous solution. Sodium glycocholate does not seem to improve the transport of sotalol.

Keywords: Ex vivo buccal absorption model; Porcine buccal mucosa; Penetration enhancer; Sodium glycocholate; Sotalol; Flecainide

1. Introduction

The on demand self administration of antiarrhythmic drugs at the onset of supraventricular arrhythmia could overcome the problems

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associated with chronic prophylactic antiarrhythmic treatment such as side effects and non-compliance (Margolis et al., 1980; Lie-A-Huen et al., 1990; Lie-A-Huen, 1991; Alboni et al., 2001; Squire et al., 1984). Sotalol and flecainide are drugs with proven efficacy in terminating supraventricular tachycardia (Sung et al., 1995) or atrial fibrillation (Suttorp et al., 1989, 1990). For on demand self administration, dosage forms with a fast absorption profile are needed. After oral administration of flecainide and sotalol it takes 2–4 h to reach peak serum levels (Le Coz et al., 1992; Williams et al., 1988).

Buccal administration of flecainide and sotalol may be useful in episodic treatment, because of its convenience of administration and the potential for rapid absorption exists (Veuillez et al., 2001). To enhance buccal absorption, bile salts have been proven, both ex vivo and in vivo to be effective (Senel et al., 1994; Hoogstraate et al., 1996a,b; Gandhi and Robinson, 1985). The ex vivo buccal transport of beta-blockers like propranolol seems highly pH dependent. With increasing pH and thus higher fraction of the more lipophilic unionized molecule the permeation of propranolol improved (Kai et al., 1992).

The aim of the present study was to investigate the permeation of sotalol and flecainide across porcine buccal mucosa ex vivo, the effects of the ionization state of these molecules and the effects of the presence of sodium glycocholate. Porcine buccal tissue was chosen, because its non-keratinized morphology is quite similar to human buccal epithelium (Wertz and Squier, 1991).

2. Materials and methods

2.1. Materials

Analytical or pharmaceutical grade chemicals were used. Hepes and sodium glycocholate were purchased from Sigma Chemical Co., St Louis, USA. Phosphoric acid 85%, perchloric acid 70%, dichloromethane, methanol, Tris–HCl, tetrahydrofuran, ammonium carbamate, acetic acid 100%, acetonitrile and KH_2PO_4 were obtained from Merck, Darmstadt, Germany. Flecainide acetate was a gift from 3M Pharma, Zoetermeer, The Netherlands. Sotalol HCl, KCl, Na_2CO_3, NaCl, $NaH_2PO_4{\cdot}2H_2O$, $CaCl_2{\cdot}2H_2O$, $MgSO_4{\cdot}7H_2O$ and glucose$\cdot 1H_2O$ were purchased from Bufa BV, Uitgeest, The Netherlands. Triethylamine and sodium heptanesulfonic acid were obtained from Fluka, Neu-Ulm, Germany. Krebs buffer was prepared by dissolving 6.75 g/l NaCl, 0.31 g/l KCl, 0.37 g/l $CaCl_2{\cdot}2H_2O$, 0.25 g/l $NaH_2PO_4{\cdot}2H_2O$, 0.20 g/l $MgSO_4{\cdot}7H_2O$, 0.95 g/l Hepes, 1.83 g/l Na_2CO_3 and 2.2 g/l glucose$\cdot 1H_2O$ in distilled water. With phosphoric acid 85% pH was adjusted to 7.4. Tris buffer had the following composition: 5.5 g/l NaCl, 0.30 g/l KCl, 0.037 g/l $CaCl_2{\cdot}2H_2O$, 0.25 g/l $NaH_2PO_4{\cdot}2H_2O$, 0.164 g/l $MgSO_4{\cdot}7H_2O$, 6.0 g/l Tris, 1.83 g/l Na_2CO_3 and 2.2 g/l glucose$\cdot 1H_2O$. With phosphoric acid 85% pH was adjusted to 9. Phosphate buffer 0.01 M pH 3.2 was prepared by dissolving 1.69 g/l $Na_2PO_4{\cdot}2H_2O$ and 0.068 g/l KH_2PO_4. By adding phosphoric acid 85% pH was adjusted to 3.2.

Flecainide base was obtained by dissolving 1 g of flecainide acetate in 100 ml distilled water and adding 20 ml of 4 M NaOH. The aqueous suspension was extracted twice with 250 ml of dichloromethane. The dichloromethane layer was separated and after the addition of sodium sulphate the organic layer was filtrated and evaporated to dryness. The residue was dried in a vacuum excicator.

2.2. Tissue preparation

Porcine buccal tissue provided by a local slaughterhouse, was freshly obtained, stored in Krebs buffer pH 7.4 and immediately transported to the experimental set-up. From experiments it appeared that buccal mucosa could be considered viable for up to 8 h after removal (Hoogstraate and Boddé, 1993). Therefore, experiments were organized in such a way that they were completed within 8 h after tissue removal. After removal of the submucosal tissue, the buccal mucosa was dermatomed at a thickness of approximately 400 μm. The basal lamina connects the epithelium to the connective tissue layer. The permeability of the epithelium and connective tissue are not similar. The basal lamina is strongly undulated (Wertz and Squier, 1991). A tissue thickness of 400 μm was chosen in stead of removing the entire epithe-

lium since the latter would result in tissue samples with highly variable amounts of connective tissue.

2.3. Transbuccal permeation studies

Dermatomed buccal mucosa was mounted in Ussing diffusion chambers with a diffusion area of 1.13 cm^2 and compartment volumes of 7 ml. During the experiments the temperature within the donor and acceptor compartment was maintained at 34 °C by a water jacket, which also protected the diffusion cells from light. Since, the temperature at the apical side of the buccal epithelium is 34 °C (Lesch et al., 1989), the studies were performed at this temperature. Carbogen (a mixture of 95% O_2 and 5% CO_2) was circulated through both compartments for stirring and to maintain tissue viability. After a 0.5 h equilibrium period with Krebs buffer in both compartments, the acceptor side was filled with 6 ml of Krebs buffer and the donor side with 6 ml of the drug solution. Samples of 0.6 ml were taken from the acceptor side at 10, 20, 30, 40, 50, 60, 80, 100 min, 2, 2.5 and 3 h and replaced with the same amount of fresh Krebs buffer. Experiments were performed in at least quadruple.

2.4. Drug assays

The concentration of sotalol was determined by a reversed phase HPLC method with ultraviolet detection at 226 nm (Waters 996 PDA detector, Waters, Etten-Leur, The Netherlands). The HPLC system consisted of a Waters 600 MS pump, a Waters 717 plus autosampler and MILLENNIUM software (Waters) for data acquisition and integration. A mixture of methanol, acetonitrile, phosphate buffer pH 3.2 (2.5:17.5:80 v/v) in which sodium heptanesulfonic acid was dissolved at a concentration of 1 g/l was eluded through a Lichrospher 100-RP-18 (5 μm) Lichrocart 125-4 column (Merck) at a flow of 1 ml/min. An aliquot (20 μl) of the sample taken from the acceptor side of the diffusion chamber was injected into the HPLC system. Concentrations of samples were calculated by using calibration curves obtained by linear regression analysis of peak heights and concentrations of standards.

The concentration of flecainide was determined by a reversed phase HPLC method with fluorescence detection (FP-920, Yasco Benelux BV, Maarssen, The Netherlands). The excitation wavelength was set at 300 nm and the emission wavelength at 375 nm. The mobile phase consisted of a mixture of methanol, distilled water, ammonium carbamate 25%, triethylamine, tetrahydrofuran (55:45:0.4:0.25:1 v/v) and was run through the same type of column as used in the sotalol assay at a rate of 1 ml/min. An aliquot (50 μl) of the sample taken from the acceptor side of the diffusion chamber was injected into the HPLC system. Concentrations of samples were calculated by using calibration curves obtained by linear regression analysis of peak areas and concentrations of standards.

2.5. Preparation of drug solutions

Sotalol HCl was dissolved in Krebs-buffer pH 7.4 and Tris–buffer pH 9 at a concentration of 80 mg/ml (259 mmol/l). The permeability of sotalol was also studied in the presence of sodium glycocholate at a concentration of 10 mg/ml (1.0%, w/v). The NaCl concentration of the buffers were adjusted to the concentration of sotalol HCl and sodium glycocholate. First the compounds were dissolved in the buffers and subsequently pH was adjusted with 4 M NaOH.

Flecainide acetate was dissolved in distilled water at a concentration of 10 mg/ml (21 mmol/l) and pH was adjusted to 5.8 with 4 M acetic acid. The solution was made isotonic with NaCl. The effect of the addition of sodium glycocholate at a concentration of 10 mg/ml (1.0%, w/v) was also studied. Solutions of flecainide base in propylene glycol at a concentration of 10 mg/ml (24 mmol/l) were prepared with and without sodium glycocholate.

2.6. Analysis of permeation data

The flux, J, is defined as the slope of the linear, i.e. steady state, part of the line obtained by plotting the cumulative amount of the permeated drug per unit surface area versus time (Senel et al., 1994). Visual inspection of the curves of the

individual permeation studies showed that a steady state situation was not reached in all cases. It was decided that calculation of J was based on the slope of the cumulative curve between 150 and 180 min. If slopes were calculated over a longer time period, fluxes would have been underestimated in non steady state situations.

2.7. Statistical analysis

All statistical calculations were performed by using SPSS (version 10, SPSS Inc., Chicago, USA). Data are expressed as medians (ranges). Differences in cumulative amount of permeated drug (Q) and J were examined by ANOVA with the tested solution as fixed factor. To meet the assumption of normal distribution $\log_{10}$-transformed data were used. The least significant difference method was used to study differences between tested solutions. A P value of less than 0.05 was considered statistically significant.

3. Results

Buccal epithelium slices which were prepared for use in the flux studies, had a mean thickness of 418 ± 38 μm, with a range of 310–435 nm ($n = 44$).

The cumulative amounts of permeated sotalol and flecainide are shown in Figs. 1 and 2. Q and J are tabulated in Tables 1 and 2, in which statistically significant differences between solutions are indicated. Significant differences among the tested sotalol solutions for Q ($P = 0.005$) were found. Permeation of sotalol was smallest at pH 7.4 in the presence of sodium glycocholate. Comparisons between solutions showed that Q of this solution was significantly smaller than Q of the other sotalol solutions (Table 1). The addition of sodium glycocholate at pH 7.4 reduced median Q 3.9 fold from 55.1 (14.5–138.7) to 14.2 (1.2–18.3) μg ($P = 0.002$). Highest permeation was observed at pH 9.0 in the presence of sodium glycocholate with a median Q of 64.0 (20.1–258.1) μg, equivalent to 235 (73–948) nmol sotalol. At pH 9.0 Q was increased 1.7 fold by sodium glycocholate, however, differences did not reach statistical significance. Similar to Q, the composition of the sotalol solution was a significant factor for J ($P = 0.002$). J at pH 7.4 in the presence of sodium glycocholate was smallest and significantly smaller as compared with the other tested solutions (Table 1). Sodium glycocholate decreased J 4.9 fold from 27.7 (7.6–43.6) to 5.7 (0.5–9.4) μg/cm^2 per h ($P = 0.002$). The highest median J, being 34.4 (11.6–134.3) μg/cm^2 per h, was obtained with an aqueous solution of sotalol at pH 9.0 also containing sodium glycocholate in the donor compartment.

In case of the flecainide experiments the tested solution also appeared to be a significant factor for both Q and J (Fig. 2 and Table 2). Q of flecainide base, being 40.5 (17.7–60.9) μg, was respectively, nine and seven fold higher as compared with Q of flecainide acetate ($P = 0.001$) and Q of flecainide base in the presence of sodium glycocholate ($P = 0.003$). Flecainide acetate in the presence of sodium glycocholate with a Q of 510.2 (39.0–733.2) μg, equivalent to 1231 (94–1769) nmol, and a J of 151.7 (50.0–368.9) μg/cm^2 per h

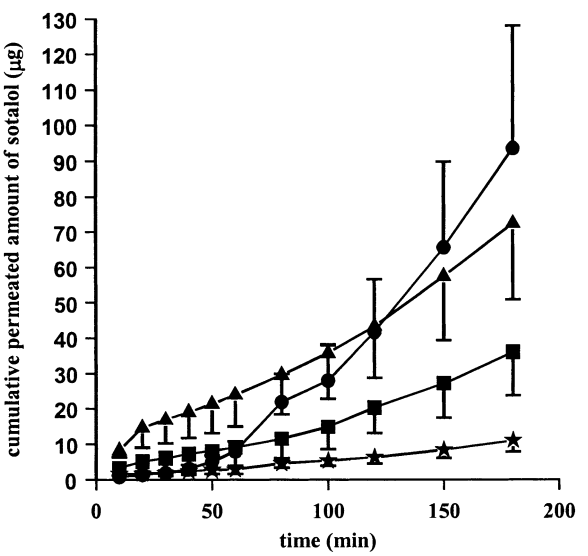

Fig. 1. Cumulative amount (mean ± S.E.M.) of permeated sotalol across porcine buccal mucosa; (▲) 80 mg/ml sotalol HCl pH 7.4, (■) 80 mg/ml sotalol HCl pH 9.0, (★) 80 mg/ml sotalol HCl pH 7.4 + 1% (w/v) sodium glycocholate 10 mg/ml, (●) 80 mg/ml sotalol HCl pH 9.0 + 1% (w/v) sodium glycocholate 10 mg/ml.

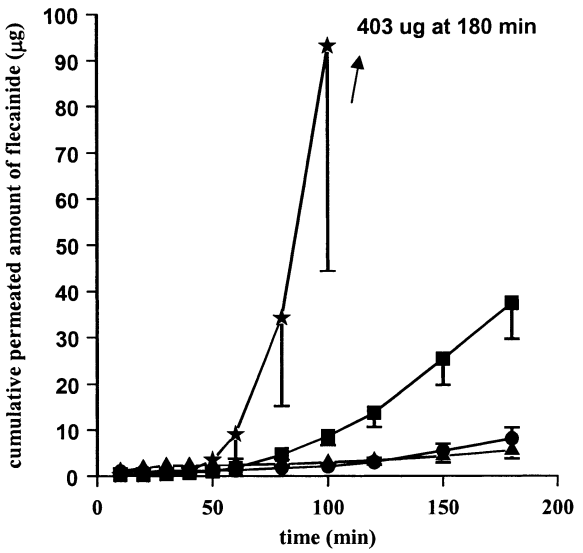

Fig. 2. Cumulative amount (mean ± SEM) of permeated flecainide across porcine buccal mucosa; (▲) 10 mg/ml flecainide acetate pH 5.8 as aqueous solution, (★) 10 mg/ml flecainide acetate pH 5.8 as aqueous solution + 1% (w/v) sodium glycocholate 10 mg/ml, (■) 10 mg/ml flecainide base in propylene glycol, (●) 10 mg/ml flecainide base in propylene glycol + 1% (w/v) sodium glycocholate 10 mg/ml.

had a significantly higher Q and J as compared with flecainide base, flecainide base in the presence of sodium glycocholate and flecainide acetate. The addition of sodium glycocholate to a solution of flecainide acetate increased Q and J of flecainide respectively 110 fold from 4.5 (1.4–14.3) to 510.2 (39.0–733.2) µg ($P < 0.0001$) and 75 fold from 2.0 (0.2–5.5) to 151.7 (50.0–368.9) µg/cm^2 per h ($P < 0.001$), respectively (Table 2).

4. Discussion

The permeation of sotalol across porcine buccal mucosa at pH 9.0 and pH 7.4 were similar. Drugs can permeate the buccal mucosa via the transcellular and paracellular routes (Wertz and Squier, 1991). The main pathway depends on the lipophilicity of the drug. Hydrophilic compounds mainly cross the buccal mucosa via the paracellular route between the cells. Lipophilic drugs penetrate cell membranes and the transcellular pathway is their main route. Sotalol is a small hydrophilic molecule with a molecular weight of 272 (Fig. 3). Therefore, the paracellular route is most likely the dominant pathway. The molecule consists of a sulfanilino group with a pK_a of 8.3 and a amine group with a pK_a of 9.8. For sotalol a maximum partition coefficient (chloroform/

Table 1
Effects of pH and sodium glycocholate on the cumulative amount of permeated sotalol (Q) and flux (J) through porcine buccal mucosa

Solution	Composition	Q (µg)	J (µg/cm^2 per h)
1	pH 9.0	36.6 (21.2–58.7)[b]	11.9 (6.6–32.1)[b]
2	pH 9.0 + GC[a]	64.0 (20.1–258.1)[c]	34.4 (11.6–134.3)[d]
3	pH 7.4	55.1 (14.5–138.7)[c]	27.7 (7.6–43.6)[c]
4	pH 7.4 + GC[a]	14.2 (1.2–18.3)	5.7 (0.5–9.4)

Values are medians (ranges).
[a] GC: sodium glycocholate at a concentration of 1% (w/v) was added.
[b] Compared with solution 4, $P < 0.05$.
[c] Compared with solution 4, $P < 0.005$.
[d] Compared with solution 4, $P < 0.001$.

Table 2
Effects of ionization state and sodium glycocholate on the cumulative amount of permeated flecainide (Q) and flux (J) through porcine buccal mucosa

Solution	Composition	Q (µg)	J (µg/cm^2 per h)
1	base	40.5 (17.7–60.9)[b]	23.4 (11.3–30.4)[b]
2	base + GC[a]	5.6 (1.8–18.7)[c,d]	4.6 (1.0–12.1)[c,d]
3	acetate	4.5 (1.4–14.3)[c,d]	2.0 (0.2–5.5)[c,e]
4	acetate + GC[a]	510.2 (39.0–733.2)	151.7 (50.0–368.9)

Values are medians (ranges).
[a] GC: sodium glycocholate at a concentration of 1% (w/v) was added.
[b] Compared with solution 4, $P < 0.005$.
[c] Compared with solution 4, $P < 0.001$.
[d] Compared with solution 1, $P \leq 0.005$.
[e] Compared with solution 1, $P < 0.001$.

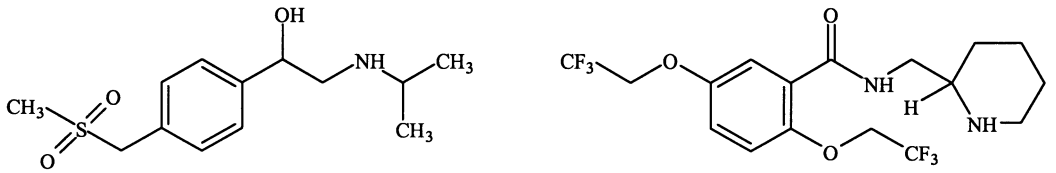

Fig. 3. Structural formula of sotalol (left) en flecainide (right).

buffer) of 0.08 was found at pH 9.0, while the partition coefficient at pH 7.4. was 0.03. At pH 9.0 the neutral form is in equilibrium with the zwitterion (Garrett and Schnelle, 1971). However, increased lipophilicity at pH 9.0 as compared with pH 7.4 did not result in a statistically significant increase in permeation across porcine buccal mucosa. Thus, the small increase in lipophilicity does not make the transcellular pathway to play a significant role in the permeation of sotalol. Increasing pH from 7.4 to 9.0 resulted in a much higher permeation through hamster cheek pouch of several beta-blocking agents with pK_a values varying between 9.2 and 9.4. Increasing pH resulted in a greater increase of lipophilicity of these agents as compared with sotalol. Furthermore, permeability was highest for the most lipohilic agent (Kai et al., 1992).

At pH 9.0 the presence of sodium glycocholate increased the fluxes and the cumulative amount of permeated sotalol. However, the difference between the sotalol test solutions with and without the bile salt did not reach statistical significance (Table 1). The permeability of porcine buccal mucosa to fluorescein isothiocyanate, as model compound, was increased 100–200 fold by the addition of bile salts. Morphological and ultrastructural changes were observed after the in vitro incubation with bile salts (Senel et al., 1994). Confocal laser scanning microscopy of the incubated tissue revealed that the intercellular penetration pathway of FITC across the buccal epithelium was enhanced (Hoogstraate et al., 1996a). As evident from the present studies, at pH 7.4 the transport of sotalol through buccal mucosa was significantly decreased by the addition of sodium glycocholate. This could be explained by a mechanism of ionpairing between the protonated amine group of sotalol and the anion of sodium glycocholate. The ionpairing prevents the bile salt from interacting with the mucosa. Furthermore, the larger molecular size of the ionpair might reduce the permeability.

The mean cumulative permeated amount of sotalol at pH 7.4 versus time, as shown in Fig. 1, suggests a rapid initial permeation. By checking the data of the individual experiments it appeared that this is caused by the results of only one of a total of six experiments. This might have been caused by a slight contamination of the acceptor side solution by the donor side solution.

Q and J of flecainide base was significantly higher as compared with flecainide acetate, being nine and 12 fold higher (Table 2). Flecainide has a molecular weight of 474.4 and a amine group with a pK_a of 9.3 (Fig. 3). The partition coefficient octanol/water at pH 7.4 is 11.4 (Lie-A-Huen, 1991). Based on ex vivo experiments with porcine buccal mucosa and buccal absorption studies in healthy subjects, the transcellular pathway has been considered to be the dominant route for propranolol permeation of buccal mucosa (Coutel-Egros et al., 1992; Schürmann et al., 1978). Propranolol with a pK_a of 9.5 and a partition coefficient octanol/buffer pH 7.4 of 14.6 has similar physicochemical properties as flecainide (Modamio et al., 2000). Both drugs most likely have the same transport mechanism across buccal mucosa. Similar to the observations with propranolol, unionized flecainide showed a higher rate of buccal permeation than the more hydrophilic ionized form (Fig. 2). These results are in agreement with a buccal absorption study with flecainide in a healthy subject. At pH 4 only 9% was absorbed while at pH 10 the absorption increased to 46% (Muhiddin and Johnston, 1981). In the present studies, sodium glycocholate appeared to decrease the transport of flecainide base across the buccal

mucosa. Since sodium glycocholate facilitates the permeation of compounds passing buccal mucosa by the paracellular route a higher transport rate was not expected in the presence of the bile salt (Hoogstraate et al., 1996a; Gandhi and Robinson, 1985).

Drug solubility in the vehicle influences buccal absorption. The distribution of a substance between a membrane and vehicle decreases with increasing solubility in the vehicle (Coutel-Egros et al., 1992). The bile salt might have increased the solubility by solubilization of flecainide in micelles. However, at pH 5.8 the permeability of porcine buccal mucosa to flecainide was increased more than 100 fold by the addition of 1.0% (w/v) sodium glycocholate. Therefore, it is very likely that, the bile salt enhances the paracellular transport of protonated flecainide and that this pathway becomes the dominant route.

There is an eight fold difference between the sotalol and flecainide concentrations of the drug solution used. Preliminary experiments showed that at the most favorable condition i.e. pH 9.0 and the presence of sodium glycocholate at a concentration of 1% (w/v), a ten fold increase of sotalol concentration resulted in an approximately ten fold increase of the cumulative amount of permeated sotalol. At concentrations of 0.8, 8 and 80 mg/l median cumulative amounts of permeated sotalol were 0.5, 6.8 and 64.0 μg, respectively. The difference between the cumulative permeated amounts of sotalol and flecainide would even be larger if solutions with equal concentrations were used.

The present results suggest that sodium glycocholate is a promising candidate as penetration enhancer for the in vivo buccal absorption of protonated flecainide. In vivo results show that in the presence of a bile salt the potential for rapid buccal absorption exists. Buccal delivery of FITC-dextran 4400 in pigs showed that co-administration of 0.45% (w/v) sodium glycodeoxycholate increased bioavailability seven fold and time to reach steady state plasma concentrations decreased from 95 to 58 min (Hoogstraate et al., 1996b). Episodic treatment with antiarrhythmic drugs is considered in patients with infrequent, i.e. a few times a year, attacks of supraventricular tachyarrhythmias. If in that case sodium glycocholate appears to damage human buccal mucosa to some extent, the time between two buccal administrations most likely is sufficient for repair of minor damages by re-epithelization. The absorbed amount could be further increased by applying the antiarrhythmic drug to a larger area of the buccal mucosa. A buccal spray, similar to nitroglycerin spray in angina pectoris, another cardiac disease, could be useful.

5. Conclusions

The ex vivo transbuccal permeation of flecainide at pH 5.8 was enhanced in the presence of 1.0% (w/v) sodium glycocholate. The permeability of porcine buccal mucosa for sotalol was not improved by the addition of sodium glycocholate. On the contrary, at pH 7.4 the transbuccal permeation of sotalol decreased in the presence of sodium glycocholate. A reduction in the permeated amount was also obtained by adding the bile salt to flecainide base. In these ex vivo experiments best results were obtained with flecainide. Flecainide, rather than sotalol, seems to be a candidate drug for the development of a buccal formulation. Sodium glycocholate seems to be an effective absorption enhancer and pH is critical.

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