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Nasal absorption of alprenolol and metoprolol

G.S.M.J.E. Duchateau [1], J. Zuidema [1], W.M. Albers [1] and F.W.H.M. Merkus [1,2]

[1] *Department of Biopharmaceutics, University of Amsterdam, Amsterdam (The Netherlands)* and [2] *Center for Bio-Pharmaceutical Sciences, Leiden University, Leiden (The Netherlands)*

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Summary

In order to determine the importance of hydrophobicity in nasal drug absorption, we studied the bioavailability of the β-adrenoceptor blocking drugs, alprenolol and metoprolol, in volunteers, after nasal administration. The results were related to the oral and sublingual administration. The intranasal bioavailability, T_{max}-, MRT- and MAT_{corr}-values of the hydrophilic metoprolol after intranasal administration did not differ significantly from the oral and sublingual administration ($n = 4$). Metoprolol is probably swallowed after intranasal and sublingual administration and absorbed in the gastrointestinal tract. In contrast, great differences were found in the intranasal bioavailability, T_{max}-, MRT-, and MAT_{corr}-values of the hydrophobic alprenolol, related to the oral dose ($n = 5$). Nasal absorption of alprenolol was fast and showed a high bioavailability ($T_{max} = 0.45 \pm 0.11$ h). MRT-values after intranasal administration were significantly different from the other two administrations ($MRT_{in} = 3.0 \pm 0.5$ h, $MRT_{sl} = 3.9 \pm 0.9$ h, $MRT_{or} = 3.5 \pm 0.6$, $P = 0.047$ and $P = 0.022$, respectively). The results of this study indicate that hydrophobicity may be an important factor in nasal membrane passage.

tants on the ciliated epithelium and the covering mucus layer may result in a reduced ciliary activity and a reduced mucociliary clearance. Surfactants reduce the ciliary activity and reduce the visco-elastic properties of the mucus layer (Duchateau et al., 1986a; Martin et al., 1978).

The aim of this study was to investigate the influence of hydrophobicity of the drug on intranasal absorption. In the absorption studies we used two β-adrenoceptor blocking drugs (β-blockers), alprenolol and metoprolol.

These drugs differ greatly in their hydrophobicity (apparent octanol/buffer partition coefficient by the shake flask method, $K_{sf} = 9.5$ and $K_{sf} = 0.5$, respectively, apparent partition coefficient by reversed phase HPLC, $K_{HPLC} = 12.4$ and $K_{HPLC} = 1.45$, respectively (Hinderling et al., 1984)), but not in other physical properties such as pK_a and molecular size. Both β-blockers are very soluble in water. For comparison, the sublingual and oral bioavailability of both drugs was also studied in the same volunteers. Comparison is possible because the dosage regimen in both experiments resulted in approximately the same AUCs, so that deviations due to non-linear pharmacokinetics can be excluded.

The results are discussed in relation to earlier investigations with oral, sublingual and intranasal propanolol (Duchateau et al., 1986b).

Metoprolol experiment:

50 mg oral (Selokeen, Astra, lot no. 84K16-15 720)

50 mg sublingual, the same tablet as orally administered

20 mg intranasal as a solution of metoprolol-tartrate dissolved in 0.2 ml methylcellulose gel (≈ 400 mPa · s, pH = 7.4).

Alprenolol experiment:

100 mg oral (2 × 50 mg Aptine, Astra, lot no. 85C14-1 893)

50 mg sublingual, the same tablet as orally administered

10 mg intranasal as a solution of alprenolol HCl dissolved in 0.2 ml methylcellulose gel (≈ 400 mPa · s, pH = 7.4).

Each study day started at 09.00 h: a 2-week wash-out period separated the different study days. The oral tablets were administered after an overnight fast, and swallowed with 100 ml water. The intranasal doses were administered with a small syringe in one nostril of the volunteer. The β-blockers were dissolved in a gel to prevent leakage of the solution out of the nostril after administration.

Determination method

Blood samples were taken by venipuncture at regular times (0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 6, 9 and 12 h). After clotting

sil-ODS (5 μm) as the stationary phase and a Schoeffel FS 970 fluorometer. Alprenolol and metoprolol were eluted with a mixture of acetonitrile/water/triethylamine, 25 : 75 : 1 (v/v/v) for alprenolol and 15 : 85 : 1 (v/v/v) for metoprolol. The pH of both eluents was adjusted with phosphoric acid to pH = 5.0. Flow rate was set to 1 ml/min. The maximal excitation wavelength was for alprenolol 200 nm and for metoprolol 220 nm. A 300 nm cut-off filter was placed in the emission beam. Chromatograms were recorded on a 10 mV flat-bed recorder. Unknown drug concentrations were estimated from a calibration curve. The detector response was linear to at least 400 ng/ml serum concentration. The limit of detection for both β-blockers was 0.3 ng/ml serum concentration.

All chemicals used in the serum analysis were of HPLC or analytical grade and obtained from Merck (Darmstadt, F.R.G.) and Rathburn (Walkerburn, U.K.).

Calculations and statistics

Elimination rate constants (k_{el}) for each volunteer and dose were calculated with a log-linear regression analysis in the terminating part of the curves. The area under the curve (AUC) and the area under the moment curve (AUMC) were calculated by the linear trapezoidal rule. Bioavailabilities (F) of the sublingual (sl) and intranasal (in) dose were related to the oral (or) administration. Mean residence times (MRTs) and mean absorption times (MATs) were calculated according to the method of Riegelman and Collier (1980). MATs were corrected for the disintegration time of the tablets (MAT_{corr}'s). Differences between the formulations in F-, MRT-, MAT_{corr}-values and times to maximal concentration (T_{max}'s) were statistically tested with one-way analysis of variance (ANOVAR). If the null-hypothesis could be rejected, the results were further tested with the Student's *t*-test for paired results.

Results

Metoprolol study

The differences in F of metoprolol, administered orally, sublingually and intranasally are presented in the bar graph of Fig. 1. The mean F-values (± S.D.) are also shown in Fig. 1. Representative examples of the three metoprolol concentration–time curves in one volunteer are presented in Fig. 2. No significant difference in F-values exists, corrected for the dose and k_{el}, after sublingual or intranasal administration, compared with the oral route. Also, T_{max}-, MAT_{corr}- and MRT-values, are not significantly different between the three administration forms. The individual parameters calculated from the obtained serum concentration time curves are presented in Table 1. No side-effects after intranasal, sublingual or oral metoprolol administration were reported. Sublingual metoprolol was tasteless.

Alprenolol study

In contrast to the results obtained in the metoprolol study, great differences exist in F of alprenolol administered intranasally, sublingually or orally. The individual parameters as calculated from the serum concentration–time curves are presented in Table 1. The differences in F are presented in the bar graph of Fig. 3. Representative serum concentration–time curves are shown in Fig. 4. Alprenolol shows a very rapid absorption after intranasal administration. This is clearly expressed in the T_{max} values which, after intranasal administration for all the volunteers, are 30 min or less, 1–2 h after the sublingual dose, and 1–1.5 h after the oral administration. This difference is significant (ANOVAR, $P = 0.0031$), and the

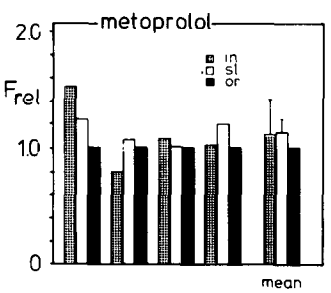

Fig. 1. Bar graph of the individual bioavailabilities, corrected for the dose, of metoprolol ($n = 4$) after intranasal (in) and sublingual (sl) administration, related to the oral (or) administration ($F_{or} = 1$). Mean values ± S.D. are also indicated.

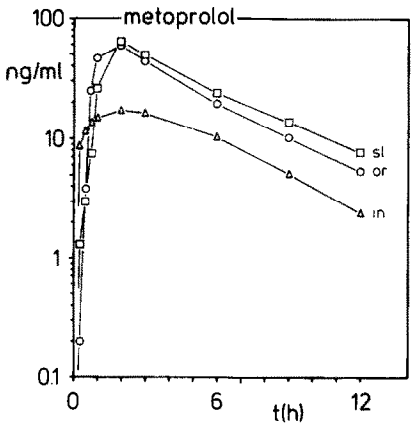

Fig. 2. Representative serum concentration time curves of metoprolol in subject no. 3, after intranasal (in), sublingual (sl) and oral (or) administration.

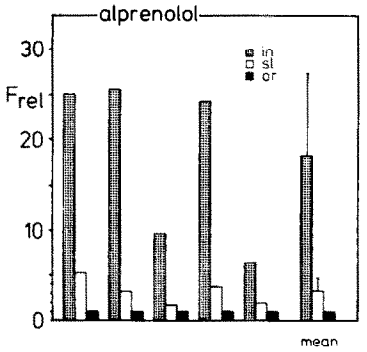

Fig. 3. Bar graph of the individual bioavailabilities, corrected for the dose, of alprenolol ($n = 5$) after intranasal (in) and sublingual (sl) administration, related to the oral (or) administration ($F_{or} = 1$). Mean values ± S.D. are also indicated.

T_{max}-values after intranasal administration are shorter than after sublingual and oral administration ($P = 0.017$, respectively, $P = 0.003$). The short T_{max}-values after intranasal administration indicate that the drug is absorbed intranasally, before it is cleared by the mucociliary clearance system.

The MRT values after intranasal administration range from 2.5 to 3.7 h, with a mean (± S.D.) of 3.0 ± 0.5 h, and are significantly shorter than

TABLE 1

INDIVIDUAL PHARMACOKINETIC PARAMETERS OBTAINED IN 4 VOLUNTEERS RECEIVING METOPROLOL INTRANASALLY (i.n.) (20 mg), SUBLINGUALLY (s.l.) (50 mg) AND ORALLY (or.) (100 mg), AND ALPRENOLOL INTRANASALLY (10 mg), SUBLINGUALLY (50 mg) AND ORALLY (100 mg)

Subject no.	F_{rel}		MRT (h)			MAT_{corr} (h)			T_{max} (h)		
	i.n.	s.l.	i.n.	s.l.	or.	i.n.	s.l.	or.	i.n.	s.l.	or.
Metoprolol											
1	1.52	1.24	4.6	4.2	3.6	0.4	0.5	0.5	2.0	2.0	1.5
2	0.80	1.07	5.4	5.2	4.4	0.7	0.6	0.6	2.0	3.0	1.0
3	1.08	1.01	5.3	5.8	5.0	1.1	0.8	0.5	2.0	2.0	2.0
4	1.02	1.20	7.2	7.9	7.5	0.8	1.3	1.2	3.0	3.0	3.0
Mean	1.11	1.13	5.6	5.8	5.1	0.75	0.8	0.7	2.25	2.5	1.9
S.D.	0.30	0.11	1.1	1.6	1.7	0.08	0.13	0.11	0.25	0.33	0.7
ANOVAR n.s. = $F_{2,9} < 1$	n.s.		n.s.			n.s.			n.s.		
Alprenolol											
1	25.01	5.07	2.7	3.7	3.3	0.1	0.5	0.1	0.5	2.0	1.0
2	25.54	3.02	3.1	4.9	3.8	0.3	0.2	0.3	0.5	1.0	1.5
3	9.73	1.76	3.7	4.8	4.1	0	0.2	0.3	0.5	1.0	1.0
4	24.23	3.94	3.2	3.3	3.7	0.1	0.6	0.2	0.25	1.0	1.0
5	6.47	2.00	2.5	2.8	2.5	0	0.7	0.4	0.5	1.0	1.5
Mean	18.20	3.26	3.0	3.9	3.5	0.1	0.4	0.3	0.45	1.2	1.25
S.D.	9.30	1.38	0.5	0.9	0.6	0.12	0.2	0.1	0.11	0.45	0.27
ANOVAR	$P = 0.00056$		$P = 0.194$			$P = 0.022$			$P = 0.0031$		

TABLE 2

PHARMACOKINETIC AND PHYSICOCHEMICAL PARAMETERS OF METOPROLOL, ALPRENOLOL AND PROPRANOLOL

F = oral bioavailability related to i.v. administration; MRT = MRT after oral administration; K_{sf} = apparent partition coefficient determined by the shake flask method; K_{HPLC} = capacity factor in an reversed-phase HPLC system. Data from Hinderling et al. (1984) and Johnsson and Regardh, (1976)

	% abs.	F (%)	MRT (min)	pK_a	K_{SF}	K_{HPLC}
Metoprolol	> 95	≈ 50	281	9.7	0.5	1.45
Alprenolol	> 90	≈ 10	170	9.7	9.5	12.4
Propranolol	> 90	≈ 30	195	9.45	13.5	19.0

after sublingual or oral administration (ANOVAR: $P = 0.194$, paired t-test: $P = 0.047$ and $P = 0.022$, respectively).

MAT_{corr}-values range from 0 to 0.3 h after intranasal administration and these MAT_{corr} values are slightly significantly shorter than after sublingual and oral administration (ANOVAR: $P = 0.022$, paired t-test; $P = 0.067$ and $P = 0.12$, respectively).

Alprenolol, administered intranasally caused a stinging sensation in the nose for a few minutes, sublingual alprenolol tasted bitter and the local anaesthetic properties were noticed as a deafening of the sublingual mucosa for approximately 20 min.

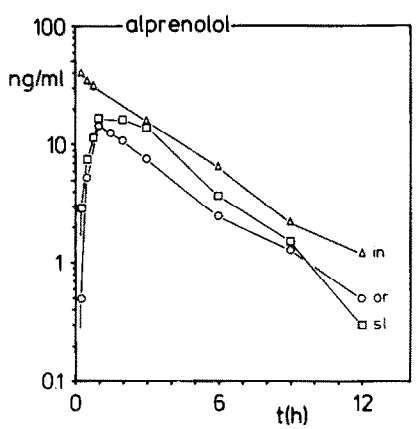

Fig. 4. Representative serum concentration time curves of alprenolol in subject no. 5, after intranasal (in), sublingual (sl) and oral (or) administration.

Discussion

As already stated, metoprolol and alprenolol are drugs showing a high first-pass effect and a large difference in hydrophobicity.

No significant improvement in the bioavailability of the hydrophylic metoprolol after intranasal or sublingual administration, related to the oral dose, could be found. It is therefore obvious that metoprolol is hardly absorbed by the nasal or sublingual mucosa but mainly absorbed in the gastrointestinal tract. After intranasal administration the metoprolol–methylcellulose gel is transported by the mucociliary clearance system in approximately 20 min or less towards the pharyngeal cavity where it is swallowed without being noticed.

The hydrophilic drug alprenolol, in contrast, shows a large improvement in bioavailability after intranasal administration, suggesting that alprenolol is completely absorbed after intranasal administration. The absorption is very fast and clearly not influenced by the mucociliary clearance system. Bioavailability after oral administration is very low, approximately 10%, due to the extensive first-pass metabolism (Alvàn et al., 1977). The high bioavailability of intranasal alprenolol indicates the circumvention of the first-pass effect.

Also the hydrophobic drug propranolol is absorbed almost completely via the intranasal route (Hussain et al., 1980; Duchateau et al., 1986b). After sublingual administration the first-pass effect could partly be avoided. Furthermore, for buccal and sublingual propranolol absorption a depot function of the mucosa exists (Kates, 1977;

Duchateau et al., 1986b). The most important parameters of these three β-blockers are listed in Table 2.

The high bioavailability of intranasal and sublingual alprenolol and propranolol, and the low bioavailability of intranasal and sublingual metoprolol compared with the oral administrations, indicate that hydrophobicity may be an important factor in mucosal membrane passage.

In a study of the buccal absorption of β-blockers a similar relation between hydrophobicity and absorption was found (Hicks, 1973). At physiologic pH the β-blockers, propranolol and Ro-3-3528, both hydrophobic, were absorbed through the buccal mucosa for 30–40%; pindolol and practolol, both hydrophilic, were absorbed for only 15–20%. The same effect of the hydrophobicity on the buccal absorption was found for propranolol and atenolol (Schürmann and Turner, 1978). Propranolol is absorbed through or onto the buccal mucosa, whereas atenolol is not.

The MRT values after the sublingual administration of metoprolol are longer than after the oral administration (Table 1). This longer MRT can be explained by the dissolution time of the tablet. We used no specially formulated tablets for sublingual administration, but commercially available tablets for oral administration, with a relatively long disintegration time in the small amount of saliva. This is in agreement with the observation of the volunteers who all noticed the metoprolol tablet for at least 20 min in the sublingual cavity. Tablet residues were visual until that time after inspection of the sublingual cavity. The dissolved metoprolol is swallowed and absorbed in the gastrointestinal tract.

In conclusion, the hydrophobic drugs, alprenolol and propranolol, are well absorbed from the nasal mucosa in contrast to the hydrophilic metoprolol.

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