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Report

Bioavailability of Propranolol After Oral, Sublingual, and Intranasal Administration

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The bioavailability of propranolol was compared after oral, sublingual, and intranasal administration in eight healthy male volunteers. Relative to the bioavailability after intranasal (in) administration, which was previously shown to be nearly complete ($F_{rel_{in}}$ = 100%), the sublingual (sl) administration of a standard 10-mg tablet gave a bioavailability of $F_{rel_{sl}}$ = 63 ± 22%, while the oral (or) administration yielded only $F_{rel_{or}}$ = 25 ± 8%. The serum concentration–time curves of propranolol after sublingual administration resembled those of a sustained-release preparation. This sustained-release phenomenon after the sublingual route is reflected in the mean residence times (MRTs) of propranolol in the body (MRT_{or} = 5.7 ± 1.3 hr, MRT_{sl} = 6.4 ± 1.3 hr, MRT_{in} = 4.6 ± 1.0 hr; mean ± SD; N = 8). MRTs after sublingual administration were significantly longer than after the oral and the intranasal doses ($P < 0.05$ and $P < 0.002$, respectively).

KEY WORDS: propranolol; intranasal; sublingual; absorption; bioavailability; pharmacokinetics.

INTRODUCTION

Propranolol, a nonselective β-adrenoceptor antagonist, is widely used in the treatment of several cardiovascular diseases. The pharmacodynamic and pharmacokinetic properties of propranolol and its congeners are reviewed by Frishman (1) and Regårdh (2).

Propranolol is a high-clearance drug with a short elimination half-life of 2 to 4 hr and a very low and variable bioavailability. Serum levels of propranolol show a great inter- and intraindividual variation. Up to 24-fold differences between minimum and maximum concentrations within persons receiving 40 mg three times a day are reported (3). The first-pass effect of the drug decreases with the intake of food (4).

Several attempts have been made to design propranolol formulations that achieve a more constant plasma level or avoid the extensive first-pass metabolism. The nasal, buccal, and rectal routes of administration have been studied by several authors (5–9). The rectal bioavailability after administration as an osmotic delivery system was found to be 33%. First-pass elimination after rectal infusion cannot be completely avoided (9). The intranasal route of administration, which avoids the first-pass effect of propranolol, shows a very rapid absorption and a high bioavailability, approximately 100% (5).

The nasal mucosa has a relatively large surface with a very high blood flow (10). The obtained plasma concentration curves in volunteers are virtually identical to the curves after an iv injection. However, the intranasal application of propranolol is not suitable for chronic treatment, because propranolol has a devastating influence on the ciliated epithelium of the nose. In an *in vitro* model, Van de Donk and Merkus demonstrated a rapid and irreversible decrease in the ciliary activity of human and chicken ciliated tissue at a propranolol concentration 50 times less than the concentration of the nasal formulation as used by Hussain *et al.* (11). Ciliary activity is the most important factor in the mucociliary clearance of the nose (12,13), and it should not be impaired. Kates studied the buccal absorption of propranolol in a 10-ml solution retained in the mouth of volunteers. He found the extent of absorption to range from 40 to 60%, after a 5-min contact time followed by rinsing with 100 ml water (8). Absorption may be greater after a longer contact time without rinsing.

In this study we investigated the sublingual absorption of propranolol administered as a normal tablet in comparison with intranasal and oral administration.

MATERIALS AND METHODS

Subjects

Eight healthy male volunteers participated in the study after medical approval. They all gave written informed consent. The average age of the volunteers was 26.6 years, with a range from 20 to 40 years. The mean body weight was 69.4 kg, with a range from 62 to 75 kg.

Study Design

The volunteers received in random order the following three propranolol HCl formulations:

40 mg, oral tablet with 100 ml water

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(Inderal, ICI, Lot No. 82K19/1);
10 mg, sublingual (standard oral 10-mg tablet, Inderal, ICI, Lot No. 83C18); and
5 mg, intranasal.

Each study day started at 9:00 AM; a 2-week washout period was taken between the study days. The oral tablet was administered after an overnight fast. The 5-mg intranasal dose was administered as a solution of propranolol HCl in 0.2 ml 2% methylcellulose gel, ±400 mPa · sec, pH 7.4.

The viscous solution was administered with a 1-ml syringe in the nostril which was, at the start of the study day, the most patent.

Propranolol Assay in Serum

Blood samples, 5 ml, were taken by venipuncture at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, and 12 hr. Exactly 1 hr after the blood sample was taken, the tube was centrifuged and the serum layer was transferred to a glass tube. The blood samples were all centrifuged exactly after 1 hr to avoid differences in concentration as a result of the shift of propranolol from the erythrocytes to the plasma because of hemolysis. Contact with plastics was avoided to prevent absorption and changes in plasma binding by the plasticizers (14). All serum samples were stored at −24°C and assayed within 2 weeks.

Five-tenths milliliter of the sample was pipetted in a clean centrifuge tube. To the serum 0.5 ml of a phosphate buffer, pH 11 (0.05 *M*), was added. The samples were vortexed with 2.0 ml hexane–isoamylalcohol (96 + 4) for 30 sec and centrifuged. An aliquot of the organic layer was transferred to a clean tube, and the propranolol was back-extracted with 200 μl of acetic acid (10%) by vortexing for 30 sec. After centrifugation 100 μl of the acid layer was injected into the high-performance liquid chromatography (HPLC) system.

Propranolol was determined in the serum samples with a HPLC system with fluorimetric detection. The system consisted of a Waters Model 6000A pump, a Kontron MSI 660 autosampler with a 100-μl injection loop, a 4 × 100-mm column with Hypersil-ODS (5 μm) as the stationary phase, and a Schoeffel FS 970 fluorometer.

The mobile phase was a mixture of 2-propanol (35%) and a 0.1 *M* ammonium acetate buffer (65%), with 0.05% sodium dodecyl sulfate (SDS). The pH of the eluent was adjusted with glacial acetic acid to 4.5. The flow rate was 0.8 ml/min. The exitation wavelength of the fluorometer was set at 217 nm. A 300-nm cutoff filter was placed in the emission beam. The time constant was 3 sec, and the amplifier range varied between 0.05 and 0.2 μA, depending on the amount of propranolol in the samples.

A standard solution of propranolol (10 mg/100 ml, calculated as the base) was prepared in methanol and stored at −24°C. From this solution a working standard solution was prepared frequently by 1000-fold diluting with distilled water. This aqueous standard was stored between analyses at 4°C. With this aqueous standard human blank serum samples (0.5 ml) were spiked with increasing amounts of propranolol. The response of the detector was linear from zero to at least a 400 ng/ml serum concentration (propranolol base).

Unknown drug concentrations were estimated from the calibration curve. The calculated limit of detection of the whole assay was 0.5 ng/ml serum concentration. The recovery of known amounts of propranolol added to serum was 95.2 ± 6.5% (N = 5).

All chemicals were of analytical or HPLC grade and supplied by Merck (Darmstadt, FRG). Propranolol HCl was a gift of ICI (The Netherlands).

Calculations and Statistics

Elimination rate constants (k_{el}) for each volunteer and dose were calculated with a log-linear regression analysis in the terminal part of the curve. A one-compartment model was assumed. The area under the curve (AUC) and the area under the moment curve (AUMC) were calculated by the trapezoidal rule. The mean residence time (MRT) and the mean absorption time, corrected for the lag time (MAT_{corr}) were calculated according to the method of Riegelman and Collier (15).

Outliers in the data sets were tested with the method of Doornbos and Prins (16). Differences were tested with the Student t test for paired results.

RESULTS AND DISCUSSION

The calculated pharmacokinetic parameters for all the volunteers are presented in Table I. A representative example of the serum concentration time curves for one volunteer is given in Fig. 1.

Absorption of propranolol after intranasal administration is very fast. In four of the eight volunteers a maximum serum concentration was reached at 15 min or less, three within 1 hr, and one volunteer reached a peak concentration at 2 hr. The short absorption phase is also expressed in the MATs. The curves obtained after the sublingual 10-mg dose show a relatively slow absorption. The maximum serum concentrations after the sublingual dose were found at 2–4 hr. The slow absorption is even more clearly expressed in the MRTs, which vary between 4.4 and 8.0 hr (mean ± SD, 6.4 ± 1.3 hr). The parameters of the oral dose take an intermediate place between those of the intranasal and those of the sublingual administrations. Maximum concentration is reached between 1.5 and 2 hr after the administration for all the volunteers except one, who reached a maximum level at 4 hr (MRT = 8.1 hr). MRTs for the eight volunteers varied from 4.3 to 8.1 hr, with a mean of 5.7 ± 1.3 hr. The MRT for the oral dose for volunteer 4 was 8.1 hr. This value was found to be an outlier ($P < 0.05$, df = 6). Removal of this value yielded a mean MRT of 5.3 ± 0.9 hr. Differences between the MRTs, found after the nasal, sublingual, and oral administration, were statistically analyzed with the Student t test for paired results. The P values are listed below; values in parentheses are calculated without removal of the outlier 8.1 hr for volunteer 4 [df = 6 (7)].

5 mg intranasal vs 10 mg sublingual	$P = 0.0014$	($P = 0.0014$)
5 mg intranasal vs 40 mg oral	$P = 0.017$	($P = 0.015$)
10 mg sublingual vs 40 mg oral	$P = 0.046$	($P = 0.053$)

Table I. The Pharmacokinetic Parameters, Obtained with a One-Compartment Model (Values in Parentheses Are Calculated Without the Outliers)

	AUC [(ng × hr)/ml]			AUMC (ng × hr²/ml)			MRT (hr)			MAT_{corr} (hr)			F_{rel} (%)	
Subject no.	5 mg	10 mg	40 mg	5 mg	10 mg	40 mg	5 mg	10 mg	40 mg	5 mg	10 mg	40 mg	10 mg	40 mg
1	82	83	93	352	412	478	4.3	5.0	5.1	0.2	0.6	0.4	51	14
2	47	84	59	210	589	274	4.5	7.0	4.7	0.1	1.4	0.2	91	16
3	83	117	232	284	634	1094	3.4	5.4	4.7	0.0	0.6	0.6	70	35
4	58	104	115	304	839	929	5.2	8.0	8.1*	0.6	1.2	1.9**	90	25
5	79	81	173	267	352	742	3.4	4.4	4.3	0.1	1.1	0.4	55	27
6	106	162	202	472	1221	1160	4.4	7.5	5.7	0.2	1.4	0.8	76	24
7	74	54	212	471	369	1294	6.4	6.8	6.1	0.7	1.2	0.9	37	36
8	86	60	109	446	424	736	5.2	7.2	6.7	0.7	1.0	1.0	35	23
Mean	77	93	149	351	605	838	4.6	6.4	5.7 (5.3)	0.3	1.1	0.8 (0.6)	63	25
SD	18	35	64	101	299	349	1.0	1.3	1.3 (0.9)	0.3	0.3	0.5 (0.3)	22	8

* Outlier, $P < 0.05$.
** Outlier, $P < 0.0001$.

For comparison of the relative bioavailability (F_{rel}), the intranasal administration was taken as a standard because absorption of propranolol after intranasal administration is essentially complete (5). It was found that the F_{rel}, compared with the intranasal formulation, of the sublingual administration was rather high, with the F_{rel} varying between 35 and 91%. In contrast, the F_{rel} after the oral dose was much lower (range, 14–36%). This difference in relative bioavailability was significant ($P = 0.0037$, paired t test).

The results of this study confirm the very rapid absorption of propranolol after intranasal administration as described by Hussain *et al.* (5). In this study we also found a relatively high absorption efficiency for the sublingual administration of propranolol. Comparison of the bioavailabilities is possible because the chosen dosage regimen resulted in approximately the same serum concentrations, so that deviations that are due to nonlinear pharmacokinetics can be excluded.

Absorption after intranasal administration is very fast, but the dosage form is not well tolerated. All volunteers noticed a stinging sensation in the nose, immediately after installation of the gel in the nostril. This adverse effect lasted for approximatley 30 min. We could not explain this effect, as propranolol has also a membrane stabilizing effect, i.e., a local anesthetic effect. The local anesthetic effect was in fact noticed for 20 to 25 min during the sublingual administration, but it was not experienced as burdensome by the volunteers. The sublingual administration showed a slow absorption, resulting in a high MRT value, ranging from 4.4 to 8.0 hr. The serum concentration–time curves look similar to those obtained after a sustained-release preparation of propranolol (17–19). This sustained-release effect can be explained by assuming a "depot function" of the mucosa.

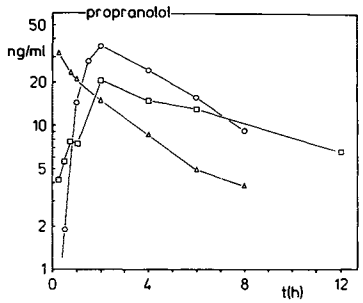

Fig. 1. Representative serum concentration–time curves (subject 6). (○) Oral tablet, 40 mg; (□) sublingual tablet, 10 mg; (△) intranasal gel, 5 mg.

This phenomenon has been described in the kinetic model of the buccal absorption by Beckett *et al.* and Schürmann and Turner (20,21). This depot function of mucosal tissue is also seen in the intravaginal administration of propranolol and in the transdermal application of drugs such as nitroglycerin (22–25).

From the experiments by Kates (8) we know that propranolol is rapidly absorbed by the mucosa of the mouth, but the appearance in the central compartment is much slower. He found a very rapid input of propranolol ($t_{1/2} \cong 8$ min) as determined from the oral contents, but the $t_{1/2}$ of the absorption as determined from the blood levels was much longer ($t_{1/2} = 23.4$ min). This slow appearance in the bloodstream is in accordance with our results. The MRTs for the sublingual dose are significantly longer than the MRTs for the oral and intranasal doses ($P = 0.046$ and $P = 0.0014$, respectively).

The results of this study show that propranolol is rapidly absorbed from the nasal cavity. The intranasal administration appears, however, less suitable for chronic treatment because of the local side effects on the nasal epithelium and possibly an effect of propranolol on ciliary epithelial function (11). The intranasal administration of propranolol may be an alternative for intravenous administration, as a rapid onset of action is desirable.

Absorption after sublingual administration is slow but

the absorption efficiency is high compared with that of the oral route. With sublingual administration it is possible to avoid partly the first-pass metabolism and to achieve a more constant serum concentration.

REFERENCES

1. W. Frishman. *Am. Heart J.* 97:663–670 (1979).
2. C. G. Regårdh. *Acta Med. Scand. Suppl.* 665:49–60 (1982).
3. E. Vervloet, B. F. M. Pluym, J. Cilissen, K. Köhlen, and F. W. H. M. Merkus. *Clin. Pharmacol. Ther.* 22:853–857 (1977).
4. A. J. McLean, C. Isbister, A. Bobik, and F. J. Dudley. *Clin. Pharmacol. Ther.* 30:31–34 (1981).
5. A. Hussain, T. Foster, S. Hirai, T. Kashihara, R. Batenhorst, and M. Jones. *J. Pharm. Sci.* 69:1240 (1980).
6. D. C. Hicks. *Br. J. Pharmacol.* 47:680P–681P (1973).
7. J. A. Henry, K. Ohashi, J. Wadsworth, and P. Turner. *Br. J. Clin. Pharmacol.* 10:61–65 (1980).
8. R. E. Kates. *J. Med.* 8:393–402 (1977).
9. L. G. J. de Leede, C. G. Hug, S. de Lange, A. G. de Boer, and D. D. Breimer. *Clin. Pharmacol. Ther.* 35:148–155 (1984).
10. M. Bende, K. Flisberg, I. Larsson, P. Omlin, and P. Olson. *Acta Otolaryngol.* 96:277–285 (1983).
11. H. J. M. van de Donk and F. W. H. M. Merkus. *J. Pharm. Sci.* 71:595–596 (1982).
12. W. J. Warwick. *Eur. J. Resp. Dis.* 64 (Suppl. 127):162–167 (1983).
13. G. S. M. J. E. Duchateau, K. Graamans, J. Zuidema, and F. W. H. M. Merkus. *Laryngoscope* 95:854–859 (1985).
14. R. H. Cotham and D. Shand. *Clin. Pharmacol. Ther.* 18:535–538 (1975).
15. S. Riegelman and P. Collier. *J. Pharmacokin. Biopharm.* 8:509–535 (1980).
16. R. Doornbos and H. J. Prins. *Indag. Math.* 20:38–55, 438–447 (1958).
17. D. Dvornik, M. Kraml, J. Dubuc, J. Coelho, L. A. Novello, J. D. Arnold, and J. F. Mullane. *Curr. Ther. Res.* 34:595–605 (1983).
18. E. Perucca, R. Grimaldi, G. Gatti, M. Caravaggi, F. Crema, S. Lecchini, and G. M. Frigo. *Br. J. Clin. Pharmacol.* 18:37–43 (1984).
19. K. Ohashi, A. Ebihara, K. Kondo, and M. Usami. *Arzneim.-Forsch./Drug Res.* 34(I):507–512 (1984).
20. A. H. Beckett, R. N. Boyes, and E. J. Triggs. *J. Pharm. Pharmacol.* 20:92–97 (1968).
21. W. Schürmann and P. Turner. *J. Pharm. Pharmacol.* 30:137–147 (1978).
22. L. G. Patel, S. J. Warrington, and R. M. Pearson. *Br. Med. J.* 287:1247–1248 (1983).
23. R. M. Pearson, E. J. Ridgway, A. Johnston, and J. Vadukul. *Lancet* II:1480 (1984).
24. H. P. Blumenthal, Ho-Leung Fung, E. F. McNiff, and S. K. Yap. *Br. J. Clin. Pharmacol.* 4:241–242 (1977).
25. H. Maier-Lenz, L. Ringwelski, and A. Windorfer. *Arzneim.-Forsch./Drug Res.* 30(I):320–324 (1980).