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Pharmacodynamic Comparison of a Nasal Formulation of Verapamil and Intravenous and Oral Dosage Forms

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ABSTRACT

The nasal route has been shown to be effective for the administration of numerous drugs in order to improve drug bioavailability. A nasal gel of verapamil hydrochloride was formulated and evaluated pharmacodynamically in humans, using electrocardiographic results, with comparison to oral and IV routes. Seven volunteers were involved in the study and the pharmacodynamic parameters were evaluated statistically. Experimental nasal gel showed similar pharmacodynamic results with the intravenous route, which is a hint to the reduction in verapamil-induced first-pass metabolism. However, oral route of administration showed a tendency of less efficacy. No reasonable effect of verapamil could be obtained with the placebo group.

INTRODUCTION

In recent years, the possibility that the intranasal administration route might be useful for many compounds whose oral bioavailability is low has received a great deal of attention. This route is of great interest for the drugs whose hepatic inactivation is important because venous blood passes directly from nasal mucosa (which has a large epithelial surface area) to systemic circulation (1). Among the drugs investigated to enhance their bioavailability from intranasal route are luteinizing-hormone releasing hormone (2), antidiabetic agents insulin (3) and glibenclamide (4), beta-blocker propranolol (5), contraceptive agent progesterone (6), male sex hormone testosterone (7), and antiarrhythmic compound clofilium tosylate (8). These compounds undergo extensive degradation due to the first-pass hepatic metabolism, which can be minimized after nasal administration (9,10). The

nasal route offers not only the advantages of rapid absorption and avoidance of the first-pass effect, but also offers a means to avoid the degradation of pharmaceuticals in the gastrointestinal tract.

Several polymeric materials including cellulose derivatives (4), Carbopol 934 and 941 (11), albumin (1), and DEAE-Sephadex (Diethylaminoethyl-Sephadex) (9) have been used as drug carriers for a continuous application of drugs, and the nasal absorption of drugs was enhanced by the addition of surfactants and mainly nonionic surfactants with an HLB (hydrophilic-lipophilic balance) value of 8–14 (11). Other surfactants studied were bile salts (12,13) and Laureth 9 (12).

Verapamil hydrochloride with a molecular weight of 491.08, a papaverine derivative, is a calcium channel blocker belonging to the phenylalkylamine class. This compound has vasodilatory as well as antiarrhythmic properties and is effective in the treatment of angina, hypertension, and supraventricular tachyarrhythmias (14,15).

The approximate amount of verapamil absorbed after oral administration is 90% (16). However, orally administered verapamil is subject to extensive first-pass hepatic elimination (17,18). Because of the high rate of first-pass metabolism, the effects observed after oral administration of verapamil differ from those observed after intravenous administration.

A significant correlation has been found between the prolongation of the PR interval and verapamil plasma levels by several investigators (18–22). Cardiac electrophysiological alterations in humans include a decrease in the heart rate (22,23) besides the prolongation of the PR interval on the surface electrocardiogram due to a delay in atrioventricular conduction.

This paper describes the nasal absorption of verapamil in comparison to oral and intravenous routes by evaluating the prolongation of PR time intervals on electrocardiograms of healthy volunteers.

EXPERIMENT

Subjects

The subjects enrolled in the study were 7 healthy volunteers (4 females, 3 males) aged 20–25 years (mean 22.5 ± 2.5) with body weights of 47–75 kg (mean 61 ± 14). Each volunteer was informed about the characteristics of the drug. Routine hematological and biochemical tests were obtained for each subject prior to drug administration. All the results were within the normal range.

On the day of drug administration, subjects had breakfast 1 hr before the application of the dose. Drug administration was performed according to an open randomized crossover design with a minimum period of 1 week between administration periods.

Nasal Formulation and Administration

Methyl cellulose (5%) (Aldrich Chemical Company, Gilingham, United Kingdom) was chosen as the carrier and Polysorbate 80 (Henkel, Istanbul, Türkiye) with an HLB value of 15.0 was used as a surfactant, to increase the absorption of verapamil. Verapamil hydrochloride used in formulating the nasal gel was obtained from Knoll, Istanbul, Türkiye.

The composition of the nasal preparation contained 0.25% verapamil hydrochloride, 5% methyl cellulose (5%), and 1% Polysorbate 80 in saline solution. Methyl cellulose gel was prepared by mixing methyl cellulose and one-third of the water, which was heated to 80–90°C. After about an hour, the remaining amount of water was added at room temperature to form a slurry and dissolved by stirring. A specified amount of verapamil hydrochloride and Polysorbate 80 was dispersed in the gel. Serum physiologique was added by stirring slowly to avoid the air bubble formation.

The volunteers received 2.5 mg verapamil hydrochloride applied into the nose on both sides as a single dose. The nostrils were then closed with an adhesive agent. The same formulation excluding the active ingredient was prepared for the placebo administration and applied the same way as the nasal formulation.

ORAL AND INTRAVENOUS ADMINISTRATION

Commercially available (Knoll, Istanbul, Türkiye) verapamil preparations were used for oral and intravenous administration. Oral dosage was applied as a solution containing 2.5 mg verapamil hydrochloride in 1 ml of distilled water. For intravenous administration, 2.5 mg/1 ml dose of verapamil hydrochloride was injected through the anticubital vein.

Pharmacodynamic Data Analysis

After each verapamil dose, two pharmacodynamic parameters—electrocardiographic PR interval and heart rate—were determined at each time interval. All subjects were kept in the supine position to avoid posture-in-

duced alterations. The mean PR interval was determined on 6 PQRST complexes (lead II). Electrocardiographic PR interval was measured for six successive cardiac cycles, and the mean was used for that individual data point. Pharmacodynamic parameters were evaluated statistically using analysis of variance.

RESULTS AND DISCUSSION

Table 1 shows verapamil-induced prolongation of electrocardiographic PR intervals and heart rates after intravenous, oral, and nasal administration of a single dose and the placebo. As can be predicted, the oral route of administration shows a tendency of less efficacy than the intravenous and nasal administration. The equivocal results may be due to the low dose of drug applied. Since we are looking for hints to the reduction in the verapamil-induced first-pass metabolism through the intranasal route, the results seem to be satisfactory. In a comparison of PR intervals after intravenous and oral verapamil, others (19) have attributed the lower efficacy of oral doses to a stereospecific metabolism of the more active L-isomer during first pass through the liver and an increase in the proportion of the less active D-isomer in serum. Another possible explanation is that the large amounts of metabolites formed after oral doses compete with verapamil at the receptor (16). Whatever is the explanation, it is apparent that nasal application resembles the intravenous application and the first-pass effect seems to be reduced through those two routes.

One-factor ANOVA has been used to investigate the variance between the three routes of administration. When the F value, which has been determined to be 5.97, was compared to table F value, it was decided that there is a significant variance between the three routes at the significance level of 0.01 ($p < 0.01$). To determine the origin of this significant variance, variance between each of the two routes of administration was investigated. It was found that there is a significant variance between intravenous and oral routes ($p < 0.01$) whereas there is no variance between the intravenous and nasal routes ($p > 0.05$), and the variance between oral and nasal routes is not that significant ($p < 0.05$).

Table 1 also shows the decrease in pulse frequencies. Mean heart rate has decreased from 94 beats/min to 71 beats/min after intravenous dosing. The high heart rate just before intravenous administration is probably due to the effect of the fear of injection. A similar pattern of decrease is seen after nasal application beginning with 82 beats/min and 75 beats/min at the end of the run-in period as can be followed in the table. After the oral dosing, a rapid decrease is seen at the beginning and especially at the 15th minute.

It is useful at this stage to summarize the factors influencing the nasal absorption of drugs (9):

1. Drug (such as molecular weight, hydrophilic/lipophilic character, enzymatic degradation)
2. Nasal mucosa (such as rhinitis, local pathological changes, colds)
3. Delivery system (such as formulation, deposition, clearance)

It is well known that the nasal mucosa has many secretory glands and water transport through those secretory glands may occur. A preliminary study of Mor-

Table 1

PR Intervals (sec) and Heart Rates (beats/min) After Administration Through Intravenous, Oral, and Nasal Routes

Time (min)	Intravenous		Oral		Nasal		Placebo	
	PR Interval ±SD	Heart Rate ±SD	PR Interval ±SD	Heart Rate ±SD	PR Interval ±SD	Heart Rate ±SD	PR Interval ±SD	Heart Rate ±SD
0	0.179 ± 0.016	94 ± 26	0.181 ± 0.016	81 ± 19	0.182 ± 0.015	82 ± 20	0.171 ± 0.031	71 ± 11
5	0.189 ± 0.019	84 ± 17	0.179 ± 0.017	79 ± 16	0.190 ± 0.015	84 ± 21	0.171 ± 0.028	70 ± 13
10	0.195 ± 0.020	82 ± 17	0.179 ± 0.016	77 ± 14	0.192 ± 0.024	82 ± 19	0.170 ± 0.024	70 ± 15
15	0.198 ± 0.025	80 ± 19	0.177 ± 0.018	73 ± 15	0.194 ± 0.020	83 ± 18	0.168 ± 0.026	71 ± 15
30	0.196 ± 0.020	79 ± 17	0.183 ± 0.018	74 ± 11	0.197 ± 0.022	79 ± 15	0.170 ± 0.028	72 ± 16
60	0.194 ± 0.019	79 ± 17	0.185 ± 0.018	73 ± 12	0.187 ± 0.009	77 ± 17	0.165 ± 0.025	70 ± 14
90	0.192 ± 0.017	76 ± 17	0.186 ± 0.016	71 ± 12	0.185 ± 0.015	75 ± 16	0.165 ± 0.025	70 ± 14
120	0.189 ± 0.016	74 ± 10	0.184 ± 0.015	71 ± 6	0.180 ± 0.011	76 ± 21	0.168 ± 0.025	70 ± 13
150	0.184 ± 0.018	71 ± 13	0.184 ± 0.015	75 ± 11	0.181 ± 0.013	73 ± 14	0.165 ± 0.025	69 ± 12
180	0.184 ± 0.017	71 ± 12	0.186 ± 0.017	74 ± 10	0.181 ± 0.010	75 ± 19	0.165 ± 0.025	69 ± 13

imoto et al. (24), where polyacrylic acid gel was used, suggested that the water absorption promoted by this gel base most probably increased the absorption of insulin and calcitonin from nasal mucosa. In our case, methyl cellulose providing a hydrophilic matrix character carries a lipophilic drug, verapamil hydrochloride. Hydrophilic gel releases the lipophilic drug easily on the surface of nasal mucosa. The deposited verapamil is most possibly absorbed by the lipophilic nature of the drug and with an aid of the surfactant.

Generally, absorption enhancers (surfactants) seem to function by changing the permeability of the nasal membrane probably by altering membrane fluidity (25). Thus they are capable of increasing absorption of a variety of drugs through the nasal membrane quite effectively. It is believed that these enhancers do have an impact on the nasal membrane by disturbing the integrity of the membrane (25).

As a result of effective nasal absorption, the systemic effect of verapamil can be demonstrated by the prolongation of PR intervals and a decrease in heart rates.

CONCLUSION

Absorption from nasal mucosa seems to be similar to the intravenous route after administration of an equal single dose of verapamil hydrochloride since it has been reported that there is a relationship between electrocardiographic parameters and plasma concentration. As has been pointed out before, the first-pass effect is reduced but not eliminated through the nasal route and thus the pharmacodynamic results obtained with our experimental formulation show a tendency of better efficacy of verapamil hydrochloride than the oral route. The difference in the clinical effectiveness after oral and nasal routes may probably be explained by the difference in disposition patterns.

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