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A SIMPLIFIED RAT MODEL FOR STUDYING NASAL DRUG ABSORPTION

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ABSTRACT

A simple and rapid rat model for studying nasal drug absorption was developed. In this model, a solution of the test drug, propranolol hydrochloride, was gradually deposited into the nasal cavity of an anesthetized rat through a PE-20 polyethylene catheter connected to a tuberculin syringe via a 30 gauge needle. The extent of drug bioavailability was assessed by measuring propranolol blood levels and the changes in heart rate. For comparative purposes, identical experiments were repeated using the intravenous route of administration, an established rat model requiring surgery, and the proposed model after tracheal cannulation and esophageal ligation. Although the pharmacokinetic parameters for the various models tested indicated bioavailabilities that were quite similar to that obtained by the intravenous route of administration, the drop in heart rates appeared to be more pronounced with the proposed model than with any of the other two models. In addition to its simplicity, the proposed rat model represents a less stressful and more physiological means of delivering a drug by the nasal route.

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INTRODUCTION

The nasal route is considered an ideal alternative to parenteral drug administration because of the rich vascularity, extensive surface area and relative metabolic inertness of the nasal membrane, and because of the ease of an intranasal administration[1,2]. In addition to representing a convenient and effective route for administering drugs which exhibit poor intestinal absorption, undergo extensive hepatic first-pass elimination, are susceptible to extensive degradation in GI fluids or undergo significant gut wall metabolism[2], it can provide drug blood levels that are comparable to those attained by using the intravenous route[4-8].

In view of the favorable attributes and known reliability of the nasal route, several rat models have been proposed for studying the nasal absorption of a variety of drugs[1,5,7,10]. One of the most widely utilized rat models is the one first reported by Hirai *et al.*[9] and later demonstrated by Hussain *et al.*[4-7]. Although the validity of this model, or a suitable modification, has been verified by several investigators[1,11,12], it necessitates the use of surgery and the sealing of the nasopalatine tract with an adhesive agent.

The purpose of this study was to develop a rat model for testing the nasal absorption of drugs that

would circumvent the surgical requirements of previous *in vivo* models. The validity of the proposed model was demonstrated by comparing both pharmacokinetic parameters and physiological responses to a dose of the adrenoceptor ß-blocker propranolol hydrochloride with those obtained using the rat model of Hirai *et al.*[9].

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (Taconic Farms, Germantown, NY), weighing about 275 g, were fasted overnight. Prior to the administration of the drug, the rats were anesthetized with urethane, 1 g/5 mL saline/kg body weight, intraperitoneally, and then divided into groups of 6 animals each.

Drug Administration

One hundred µL of a solution of propranolol hydrochloride (Sigma Chemical Co., St. Louis, MO), containing 10 mg/mL in saline was administered as follows: intravenously through the jugular vein (Model 1); directly into the nasal cavity through the nostrils of a rat surgically prepared as described by Hirai *et al.*[9] (Model 2); directly into the nasal cavity by means of a catheter (constructed from a 15 cm piece of PE-20 polyethylene tube, blunted over a flame, and attached to a 1 mL tuberculin syringe via a 30 gauge needle) inserted to a

depth of 20 mm into the nostril of a rat whose trachea had been previously cannulated and its esophagus previously ligated (Model 3); and directly into the nasal cavity through the nostril as for Model 3, but without the preliminary tracheal cannulation and esophageal ligation (Model 4).

Analytical Method

At various time intervals a 0.1 to 0.3 mL sample of blood was collected from the femoral artery of each rat into an EDTA disodium-containing test tube, and assayed for propranolol content by the fluorometric method of Susuki et al.[13].

Physiological Responses

Heart rates were assessed from tachograms obtained after connecting the ECG leads of a 4-channel Model 79E polygraph with Model 7DAG DC driver amplifier and Model 7P4H EKG tachograph preamplifier (Grass Instruments, Quincy, MA) to the anesthetized rats.

RESULTS AND DISCUSSION

Propranolol is a drug well suited for nasal administration inasmuch as it is inefficiently and variably absorbed from oral dosage forms[4], and it exhibits wide variability in plasma levels and low and unpredictable bioavailability when administered orally[3,14]. Indeed,

previous work in the rat model of nasal absorption has indicated that this ß-blocker is rapidly absorbed from the nasal mucosa, and that the blood drug levels after intravenous and nasal administrations of 1 mg doses were identical and considerably higher than those obtained by the oral route[5].

The rat model for studying the nasal delivery of drugs reported by Hirai *et al.*[9] (Model 2) requires the surgical preparation of the anesthetized rat, i.e., the incision of the neck area in order to cannulate the trachea with a polyethylene tube and the incision of the esophagus to insert another polyethylene tube toward the posterior part of the nasal cavity. Prior to the delivery of the drug solution to the nasal cavity with a syringe, either through the esophageal cannula or the nostril, the nasopalatine tract leading from the nasal cavity to the oral cavity is sealed with an adhesive agent to prevent the drainage of drug solution from the nasal cavity into the mouth[5,9]. In contrast, the proposed model (Model 4) utilizes an anesthetized rat which is not subjected to any surgical or invasive manipulation. However, to validate its results against the established *in vivo* model, in a separate rat the trachea was cannulated and the esophagus ligated prior to the deposition of the drug solution in the nasal cavity (Model 3).

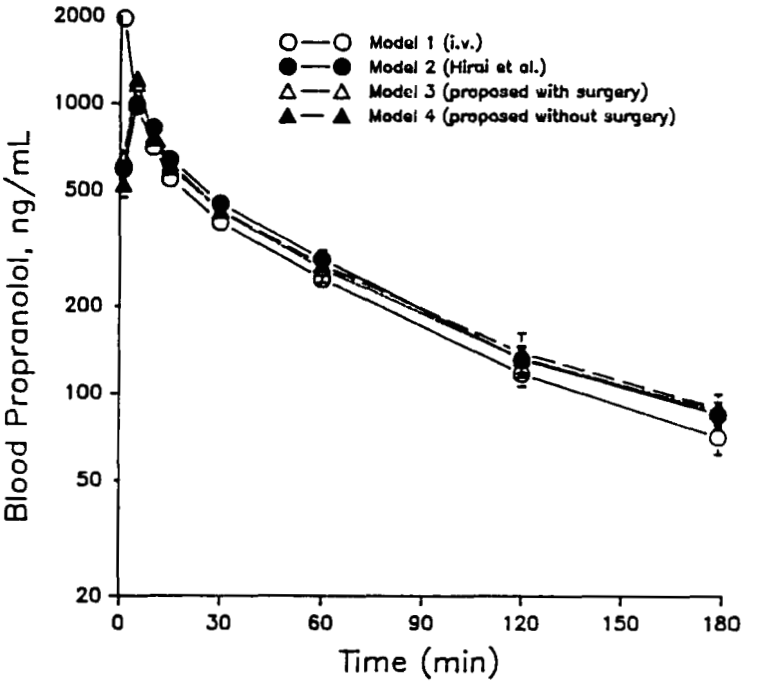

Figure 1

Time courses of the blood propranolol levels of rats receiving 1 mg/0.1 mL of propranolol hydrochloride intravenously and by using three rat models of nasal administration. Points represent mean ± SEM (n = 6).

As seen from the blood values shown in Figure 1 and the summary of the blood pharmacokinetic data presented in Table 1, all of the rat models evaluated yielded AUC (area under the blood concentration-time curve) and $t_{\frac{1}{2}}$ values that were approximately equivalent to that of the intravenous injection, with the $t_{\frac{1}{2}}$ values agreeing well with those reported in the literature[15]. On the other hand, whereas the time to peak (t_{max}) values and relative bioavailabilities (%) were quite similar among the

TABLE 1

Pharmacokinetic parameters for propranolol administered intravenously and by the intranasal route using three rat models (n = 6)

Parameter	Rat model[a]			
	1	2	3	4
$AUC_{0-\infty}$, ng min/mL	49242 ±234.2	49797 ±294.5	48703 ±274.9	49187 ±324.6
C_{max}, ng/mL	-	990 ±55.0	1162 ±39.6[b]	1202 ±45.2[b]
t_{max}, min	-	5	5	5
$t_{\frac{1}{2}}$, hr	2.89	2.82	2.96	3.12
Bioavailability, %[c]	-	101.0	98.9	99.9

[a]Rat models are described under Materials and Methods.
[b]Comparison vs. Model 2 ($p<0.001$).
[c]Calculated from $AUC_{nasal}/AUC_{iv} \times 100$.

various in vivo models used, the proposed model (Model 4) and proposed model with surgery (Model 3) yielded peak blood levels (C_{max}) that were significantly higher ($p<0.001$) than that seen with the established rat model (Model 2).

In terms of the reductions in heart rates (Figure 2), use of the intravenous route resulted in a maximum change of 68.1% of the initial value at about 1 min postadministration; by the established model, it was 68.2% of initial at 10 min postadministration; and by

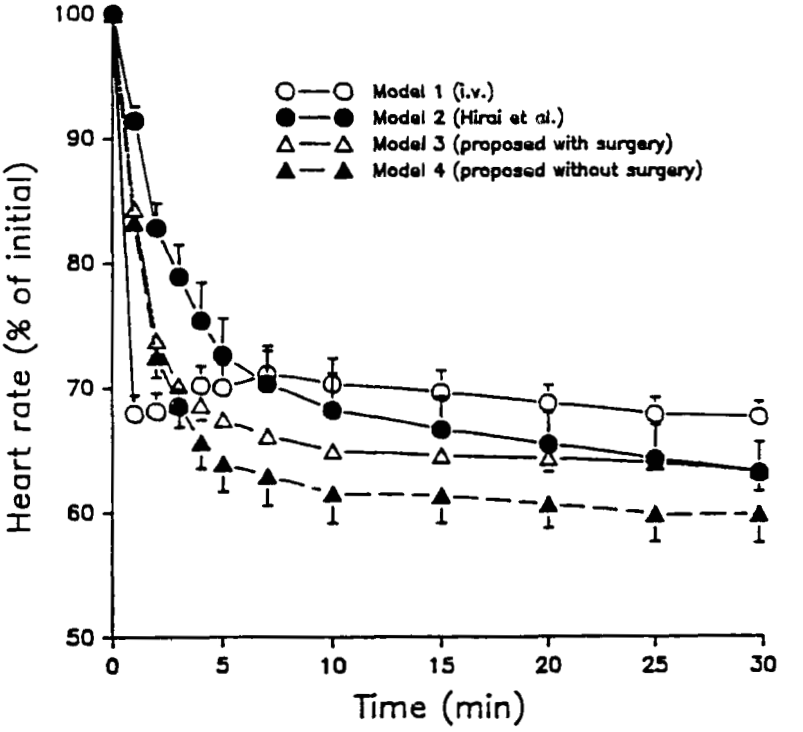

Figure 2

Changes in the heart rates of rats receiving 1 mg/0.1 mL of propranolol hydrochloride intravenously and by using three rat models of nasal administration. Points represent mean ± SEM (n = 6).

the proposed method with and without surgical intervention it was 64.9 and 61.4% of initial, respectively, at 10 min postadministration. After 30 min, the above values were 67.3, 63.0, 63.1 and 59.8% of initial, respectively. The intravenous route initially produced a very marked drop in the heart rates, but the values started to rise after 1 min and they remained fairly constant thereafter. Among the various models used, the proposed

method without surgery (Model 4) yielded the lowest heart rate values.

CONCLUSIONS

The present study demonstrates that the use of a catheter to deliver a drug into the nasal cavity of the rat can lead to pharmacokinetic results that are comparable to those achieved by the intravenous route of administration. Moreover, since there is no need for surgery and/or the mechanical sealing of the nasopalatine tract, it represents a more natural means of studying nasal drug absorption than with a previously reported *in vivo* model.

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