Intranasal Delivery of RS-93522, a Dihydropyridine-Type Calcium-Channel Antagonist

Roger Cherng-Chi Fu,[1,2] John L. Whatley,[1] and Jeffrey S. Fleitman[1]

Received January 23, 1990; accepted July 3, 1990
KEY WORDS: nasal absorption; nasal drug delivery; calcium-channel antagonist.

INTRODUCTION

RS-93522, (2-[4-(2,3-dihydroxypropoxy)phenyl]ethyl-methyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate; Fig. 1), a dihydropyridine-type calcium-channel antagonist, has been investigated for treating congestive heart failure and hypertension. Preliminary bioavailability studies in animals showed that the drug is insufficiently and variably absorbed from solid powder via oral administration. The variation as well as low bioavailability may be attributed to the following factors: low aqueous solubility (0.012 mg/ml), slow intrinsic aqueous dissolution rate (1), extensive drug metabolism in the GI tract, and first-pass hepatic metabolism. Other alternative routes of administration were explored to improve bioavailability.

The intranasal administration route has been useful for many compounds which are poorly absorbed by the oral route. Drugs such as propranolol (2–4), progesterone (5), clofilium tosylate (6), and enkephalins (7) have been reported to be absorbed effectively via the nasal route with bioavailabilities comparable to the intravenous route of administration. The nasal delivery route is attractive for several reasons, including low proteolytic activity in the nasal mucosa (8), elimination of first-pass hepatic metabolism, and rapid absorption into the systemic circulation.

This paper reports the nasal absorption of RS-93522 in rats after its administration in a solution. For comparison, the results on intravenous administration of the identical drug solution to the rats are also presented.

MATERIALS AND METHODS

Chemicals

RS-93522 was synthesized by and received from the Institute of Organic Chemistry, Syntex Research. Polyoxyethylated vegetable oil (Emulphor EL-719) was obtained from GAF, New York.

Animal Protocols

Male Sprague–Dawley rats weighing 350–500 g were obtained from Bantam Kingman (Hayward, CA).

Composition of Formulation

The formulation used for nasal administration in the rats consisted of 1.0% RS-93522, 7% polyoxyethylated vegetable oil, 5% sorbitol, 0.304% sodium phosphate monobasic monohydrate, 0.043% sodium phosphate dibasic anhydrous, and water for injection q.s. to a volume. The solution pH was approximately 6.0. Because of the low aqueous solubility of RS-93522, polyoxyethylated vegetable oil was employed as a solubilizer. For intravenous administration, a solution of 0.2% RS-93522 in an identical vehicle was used.

Animal Studies

Male Sprague–Dawley rats were anesthetized with a 50-mg/kg intraperitoneal injection of sodium pentobarbital (Abbott Laboratories, Chicago) and kept under a heat lamp during the course of the experiments. Blood was collected from a heparinized cannula implanted in the carotid artery. For nasal administration, an approximate dose of 35–50 μl solution was instilled into the nasal cavity through the nostrils using a micropipet. For the intravenous administration, the drug was injected through the tail vein and the injection volume was between 175 and 250 μl. In all studies, the delivered dose was 1.0 mg/kg. The animals were maintained in a supine position and heads were tilted downward during the course of the study to prevent the drainage or loss of solution from nasopalatine tract or nostrils.

Analytical Procedure

Plasma levels of RS-93522 were assayed by HPLC.

HPLC. The chromatographic equipment included an isocratic pump (Model LC/9521, IBM), an autosampler (Model 728, Micromeritics, Norcross, GA), a variable wavelength detector (Model LC/9523, IBM), and an integrator (Model SP 4270, Spectra Physics, San Jose, CA). The column used was an Alltech Spherisorb ODS 5 μm × 25-cm column. The mobile phase consisted of acetonitrile:water:phosphoric acid (30:60:1). The injection volume was 50 μl; the flow rate was 1.0 ml/min. An ether extraction method (8) was used to recover RS-93522 from rat plasma. An internal standard, RS-71645 (an analogue of RS-93522), was included to ensure accurate and reliable quantitation.

Sample Preparation. A 0.5-ml plasma aliquot was spiked with internal standard. The samples were extracted twice with 4.0 ml of anhydrous ether. The ether extract was dried under nitrogen. After ether evaporation, the dry residue was reconstituted with 0.5 ml of mobile phase.

RESULTS AND DISCUSSION

Figure 2 shows the mean plasma level of RS-93522 in rats following nasal and intravenous administrations of a 1 mg/kg dose. The pharmacokinetic parameters of the intranasal and intravenous administrations are presented in Table I. The average maximum concentration in plasma after intra-

[1] Institute of Pharmaceutical Science, Syntex Research, Palo Alto, California 94304.
[2] To whom correspondence should be addressed.

0724-8741/91/0100-0134$06.50/0 © 1991 Plenum Publishing Corporation

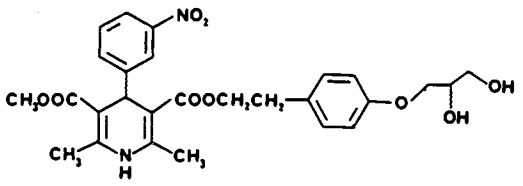

Fig. 1. RS-93522.

nasal administration was achieved in about 30 min. The plasma drug levels increased rapidly after nasal administration, with significant blood levels attained within 15 min. The pharmacokinetic parameters—including apparent volume of distribution and systemic clearance rate—are approximately equivalent for both administration routes. The areas under the plasma level–time curves (0–infinity) calculated for nasal and intravenous administration were 233 and 254 (ng/ml) · (hr), respectively. The relative nasal bioavailability calculated from the ratio of the area under the curves (nasal/intravenous) was found to be 92%.

CONCLUSION

In summary, the nasal route for RS-93522 appears to be as effective as the intravenous route. The onset of absorption was rapid and the drug plasma levels after nasal administration were similar to those following intravenous administration. Excellent nasal bioavailability and rapid absorption were observed. Therefore, therapeutic treatment with this compound via nasal administration is a viable approach and offers an alternative to oral administration where ineffective and variable absorption is a problem.

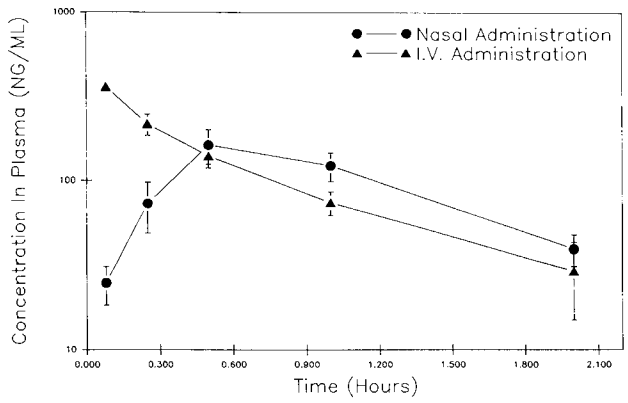

Fig. 2. Plasma levels of RS-93522 after nasal and iv administration.

Table I. Pharmacokinetic Parameters for RS-93522[a]

Parameter	Route of administration	
	iv	Nasal
Half-life (hr)	0.72	0.74
Apparent volume of distribution (V_{dB}, liters/kg)	4.09	4.58
Systemic clearance (CL_s, liters/hr/kg)	3.94	4.29
$AUC_{0-\infty}$ (ng/ml) (hr)[b]	254 ± 30	233 ± 34
C_{max} (ng/ml)	355	162
T_{max} (hr)	—	0.5

[a] A total of six rats was used in this study. Three rats were given solution intranasally, and three rats received solution by intravenous administration.

[b] The AUC from 0 to 2 hr following iv and nasal administration was 221 and 190 (ng/ml) (hr), respectively.

REFERENCES

1. L. Gu. Personal communication, Syntex Research.
2. A. Hussain, S. Hirai, and R. Bawarshi. Nasal absorption of propanolol in rats. *J. Pharm. Sci.* **68**:1196 (1979).
3. A. Hussain, T. Foster, S. Hirai, T. Kashihara, R. Batenhorst, and M. Jones. Nasal absorption of propanolol in humans. *J. Pharm. Sci.* **69**:1240 (1980).
4. A. Hussain, S. Hirai, and R. Bawarshi. Nasal absorption of propanolol from different dosage forms by rats and dogs. *J. Pharm. Sci.* **69**:1411–1413 (1980).
5. G. F. X. David, C. P. Puri, and T. C. Anand Kumar. Bioavailability of progesterone enhanced by intranasal spraying. *Experientia* 37:533–534 (1981).
6. K. S. E. Su, K. M. Campanale, and C. L. Gries. Nasal drug delivery system of a quaternary ammonium compound: Clofilium tosylate. *J. Pharm. Sci.* 73:1251–1254 (1984).
7. K. S. E. Su, K. M. Campanale, L. G. Mendelsohn, G. A. Kerchner, and C. L. Gries. Nasal delivery of polypeptides. I. Nasal absorption of enkephalins in rats. *J. Pharm. Sci.* 74:394–398 (1985).
8. A. T. Wu, J. Thompson, and I. J. Massey. Specific determination of RS-93522 and its pyridine metabolite in plasma by HPLC method employing mixed mode separation. *Pharm. Res.* 3:5S (1986).