Drug Development and Industrial Pharmacy, 22(11), 1167-1171 (1996)

Delivery of Renin Inhibitor Through Mouth Mucosa

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ABSTRACT

The aim of this work was to investigate the efficiency of transporting the orally inactive renin inhibitor A-64662 through oral mucosa—floor of mouth, cheek, or gum—using the dog as an animal model. It has been demonstrated that A-64662, can be effectively delivered to the bloodstream through mouth mucosa with various dosage forms. Compared to buccal adsorption, a relatively fast onset was observed after sublingual administration of an aqueous solution. A slightly higher bioavailability but lower C_{max} and extended plasma drug levels were observed after sublingual administrationof a slow-release gel formulation. This work has also shown that mucoadhesive patch application can provide sustained and controlled release of A-64662 by either buccal or gum administration. The absorption through the gum is slower than the cheek.

INTRODUCTION

Renin is the enzyme that catalyzes the first and rate-limiting step in the formation of angiotensin II, and is selective for a single naturally occurring substrate, angiotensinogen (1). Renin inhibitors provide target specificity in treating various cardiovascular disorders. A potent renin inhibitor, A-64662, was synthesized by the scientists at Abbott Laboratories (2). It is a dipeptide with a molecular weight of 657 and the chemical structure [*N*-(3-amino-3-methyl-1-oxobutyl)-4-methoxy-L-phenyl-alanyl]-*N*-[1*S*,2*R*,3*S*)-1-(cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]-L-histidinamide. The compound is orally inactive in various animal species such as monkey, dog, and rat. The transdermal delivery of A-64662 was attempted and it demonstrated a low feasibility due to the poor skin permeability (3). The permeability differences among oral mucosal regions reflect differences in the nature of the intercellular barrier material and the thickness, which have been investigated by numerous workers (4-7). Drug absorption via the mucosal epithelium of the oral cavity is an established route of drug delivery, which is especially useful if peroral absorption is incomplete or ineffective, for example, with drugs undergoing strong first-pass effects after ingestion, and with peptide drugs being digested upon gastrointestinal transit. The pharmacokinetic profiles of A-64662 through various dosage forms—solution, gel, and bilayer mucoadhesive patches—were examined.

EXPERIMENTAL METHODS

Formulations

Aqueous Solution

The aqueous solution contained 0.3 M acetic acid and 0.5% ethanol to obtain adequate solubility of A-64662. The pH was around 6 and the drug concentration was 167 mg/ml.

Sustained-Release Gel

A clear gel was made with 3% hydroxypropyl cellulose (Klucel EF, from Hercules) in a mixed solvent of 50% geraniol oil, 45% ethanol, and 5% water. The drug was completely dissolved in the solvent first, and final drug concentration in the gel was 168 mg/ml.

Mucoadhesive Patch

The patch was prepared with an adhesive film on the top of a backing layer. The adhesive film contained drug, castor oil as plasticizer, and the hydrophilic polymer hydroxypropyl cellulose (Klucel LF, from Hercules). The backing layer was made from the hydrophobic polymer ethylene vinyl acetate (EVA). The patch was made as a rectangular shape with a constant area of adhesive film, 3×1 cm^2. The adhesive layer was prepared by dissolving adequate amounts of drug, plasticizer, and polymer in ethanol, and then uniformly castered on a Teflon plate. The backing layer was prepared by dissolving 3% EVA in a mixed solvent containing 90% methylene chloride and 10% methanol, and then castered on a Teflon plate. Two layers were adhered together by spreading 25 μl of ethanol on the surface and air drying.

In Vivo Studies

Beagle dogs weighing 9–11 kg were used for the present work. Dogs were first anesthetized by IV injection which kept dogs immobilized for 8–12 hr. Dogs were then placed in a dorsal recumbent position on a table and kept warm by blanket. The formulation was administered around the dosing area, floor of mouth or cheek. Blood samples were collected after dosing via the saphenous vein on the rear leg. The concentration of A-64662 in plasma was determined by a high-performance liquid chromatographic (HPLC) method. An intravenous injection was performed in the same group of dogs to serve as a control.

Pharmacokinetic Data Analysis

The AUC, area under plasma concentration versus time curve, was determined by the trapezoidal rule. C_{max}, the maximum plasma concentration; and T_{max}, the time elapsed to C_{max}, were directly obtained from the data. $F\%$, bioavailability, was calculated by comparing total AUC of sublingual or buccal administration to intravenous injection. One-sample, two-sided t tests were employed to test the hypothesis of no difference between treatments. A t test was declared significant if the associated p value was less than or equal to 0.05.

RESULTS AND DISCUSSION

Bioavailability: Sublingual Versus Buccal

The aqueous solution and gel formulation were administered to the floor of mouth and cheek in 3 dogs for bioavailability evaluation. The study was designed for a period of 3 consective weeks; in the first week, the aqueous solution was administered for sublingual absorption, in the second week the aqueous solution was administered for buccal absorption, and in the third week the gel formulation was administered for sublingual absorption. The pharmacokinetic results from each study are shown in Table 1. Figures 1 and 2 plot the plasma drug concentrations following the time after sublingual or buccal administration. It is not surprising that a fast onset was observed after sublingual administration of an aqueous solution. Figure 1 shows that at 15 min, the plasma concentration of drug reached 1030 ng/ml after administration of the aqueous solution sublingually. After buccal administration, the plasma drug concentrations were delayed, but equivalent bioavailability was achieved as compared to sublingual administration. However, sublingual administration of a gel formulation resulted in a relatively higher bioavailability but lower C_{max} and extended plasma drug levels as compared to an aqueous solution.

Mucoadhesive Patch Compositions Versus Absorption

The mucoadhesive patches prepared with various compositions were evaluated in dogs for buccal absorption. Each composition was tested in 3 dogs and the and the results are shown in Table 2. The patch was well

Table 1

Bioavailability of A-64662 in Dogs Following Sublingual and Buccal Administration of Aqueous Solution vs. Gel Formation: Dose 10 mg/kg

	Site	C_{max} (ng/ml)	T_{max} (hr)	AUC (0–8 hr)	F(%)
Aqueous	(A) Buccal	704 (322)	0.50	1680 (439)	28.0 (7.3)
Aqueous	(B) Sublingual	1036 (285)	0.50	1466 (504)	28.6 (9.8)
Gel	(C) Sublingual	433 (101)	1.00	2670 (634)	33.9 (11.0)
Significance[a]		B > A > C		A = B = C	

[a] p value ≤ 0.05.

adhered to the cheek area for 6 hr during the entire study period. It was found that the amount of drug compound A-64662 absorbed into the bloodstream from patch 4 was more than from the other preparations. The patch 4 preparation contained a fairly small amount of polymer, but it was able to keep the patches in decent shape when they were removed from the cheek area. Based on this study, it is concluded that the release rate of A-64662 can be controlled by the methods used for patch preparation. And a desirable release pattern may be achieved by an adequate patch design, as previously reported (8).

Table 2

Composition of Mucoadhesive Patch: Comparison of Buccal Absorption in Dogs

	Patch No.			
	1	2	3	4
Klucel, mg	80	80	25	8
Caster oil, mg	10	10	3	1
Drug (mg)	20	40	50	50
AUC (0–8 hr), (hr × ng/ml)	87.1	321.8	546.3	1005.8
Drug absorbed (mg) in 8 hr	1.2	4.5	7.3	13.4

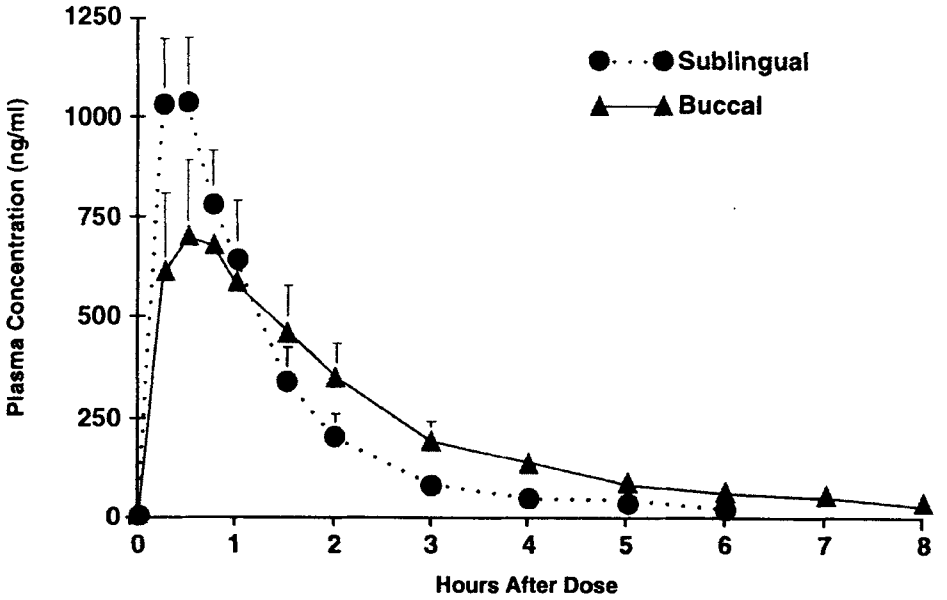

Figure 1. Bioavailability comparison of A-64662 in dogs following administration of aqueous solution, 10mg/kg dose.

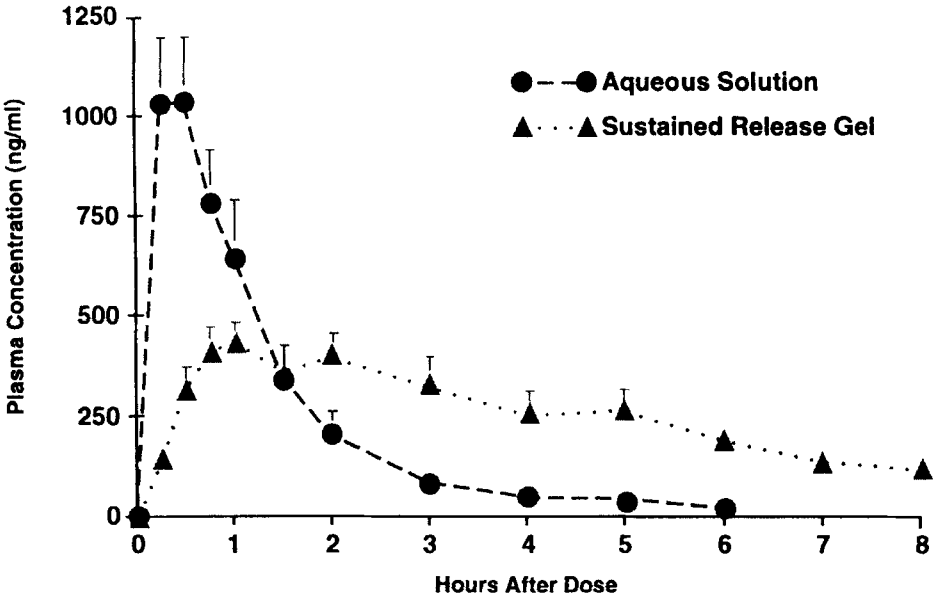

Figure 2. Bioavailability comparison of A-64662 in dogs following sublingual administration (10mg/kg).

Buccal Versus Gum Absorption

The absorption of A-64662 through buccal and gum mucosa was evaluated in dogs with patch 4, mentioned previously. Figures 3 and 4 plot the plasma drug concentrations following buccal and gum administration in 3 individual dogs. It is shown that the absorption through gum mucosa was slower than through buccal mucosa, but both routes of administration provided extended and prolonged drug levels. A sustained and con-

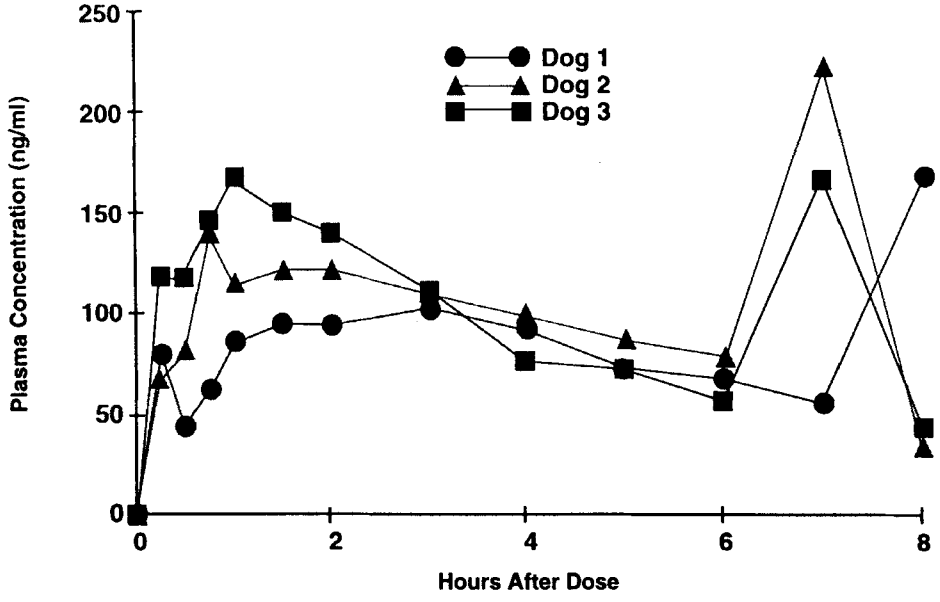

Figure 3. Plasma concentrations of A-64662 in dogs following administration of adhesive patch to cheek.

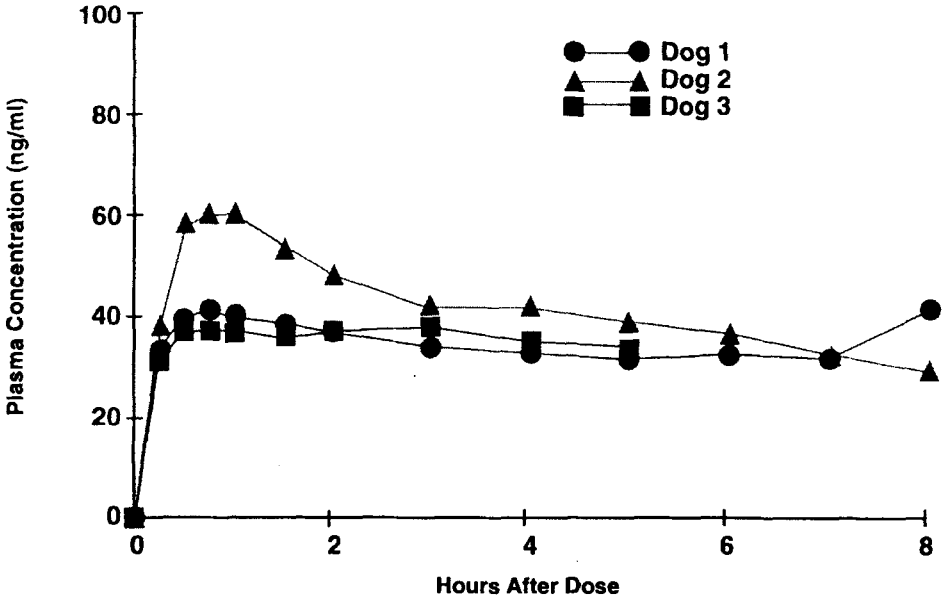

Figure 4. Plasma concentrations of A-64662 in dogs following administration of adhesive patch to gum.

trolled delivery of A-64662 is apparently feasible by either buccal or gum administration.

CONCLUSION

The renin inhibitor A-64662 can be effectively delivered to the bloodstream through mouth mucosa, by sublingual, buccal, or gum administration, based on the present work performed in dogs. This work has shown that the pharmacokinetic profile of A-64662 in dogs is affected by the dosage form and formulation. For therapeutic benefits, sustained delivery of A-64662 with a controlled release rate may be achieved by mucoadhesive patch application. The patch can be applied to the cheek or gum area.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Kennan Marsh for her help in HPLC analysis of all plasma samples, and Mr. Edward Johnson for the animal work performed by his group.

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