

Sublingual epinephrine tablets versus intramuscular injection of epinephrine: Dose equivalence for potential treatment of anaphylaxis

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Background: Epinephrine autoinjectors are underused in the emergency treatment of anaphylaxis in the community, perhaps in part because of fear of needles.

Objectives: To determine the sublingual epinephrine dose from a novel fast-disintegrating tablet required to achieve epinephrine plasma concentrations (EPPCs) similar to those obtained after epinephrine 0.3 mg intramuscular injection.

Methods: In a prospective 5-way crossover study, sublingual tablets containing epinephrine 0, 10, 20, and 40 mg, and epinephrine 0.3 mg intramuscular in the thigh (EpiPen) were compared in a validated rabbit model. Blood samples were collected before dosing and 5, 10, 15, 20, 30, 40, 60, 90, 120, 150, and 180 minutes afterward. EPPCs were measured by using high-performance liquid chromatography–electrochemical detection. Pharmacokinetic parameters were calculated by using WinNonlin.

Results: The area under the curve (AUC), maximum concentration (C_{max}), and time at which C_{max} was achieved (T_{max}) did not differ significantly ($P > .05$) after epinephrine 40 mg (AUC = 1861 ± 537 ng/mL/min, $C_{max} = 31.0 \pm 13.1$ ng/mL, and $T_{max} = 9 \pm 2$ minutes) and epinephrine 0.3 mg intramuscular (AUC = 2431 ± 386 ng/mL/min, $C_{max} = 50.3 \pm 17.1$ ng/mL, and $T_{max} = 21 \pm 5$ minutes). The AUC after tablets containing epinephrine 0 mg (AUC = 472 ± 126 ng/mL/min), epinephrine 10 mg (AUC = 335 ± 152 ng/mL/min), and epinephrine 20 mg (AUC = 801 ± 160 ng/mL/min) did not differ significantly from each other, but were significantly lower ($P < .05$) than the AUC after epinephrine 0.3 mg intramuscularly. **Conclusion:** Sublingual administration of epinephrine 40 mg from this tablet formulation resulted in EPPCs similar to those obtained after epinephrine 0.3 mg intramuscular injection in the thigh.

Clinical implications: For treatment of anaphylaxis in the community, self-injectable epinephrine is underused. This

novel, fast-disintegrating epinephrine tablet formulation for sublingual administration is a feasible alternative that warrants further development. (J Allergy Clin Immunol 2006;117:398-403.)

Key words: Epinephrine, adrenaline, sublingual tablet, sublingual absorption, EpiPen, anaphylaxis, systemic allergic reaction

There is universal agreement that prompt epinephrine injection is the drug of choice for the treatment of anaphylaxis.¹⁻⁴ The recommended epinephrine dose for the treatment of anaphylaxis is 0.3 to 0.5 mg in adults and 0.01 mg/kg, to a maximum of 0.3 mg, in children, given by intramuscular injection.¹⁻⁴ These recommendations are based on clinical experience and/or studies in healthy volunteers,⁵ rather than on randomized, double-blind, placebo-controlled dose-ranging studies in patients experiencing anaphylaxis, which are impossible to perform from an ethical standpoint.³

Most anaphylactic reactions occur unexpectedly in the community as a result of foods, insect stings, medications, natural rubber latex, and other triggers.¹⁻³ For out-of-hospital emergency treatment of anaphylaxis, epinephrine autoinjectors such as EpiPen (Dey LP, Nappa, Calif), EpiPen Jr, Twinject 0.3 mg, and Twinject 0.15 mg (Verus Pharmaceuticals Inc., San Diego, Calif) are prescribed; however, self-injectable epinephrine is underused when anaphylaxis occurs.^{6,7} The drawbacks of epinephrine autoinjectors include high cost, which limits affordability and availability worldwide⁸; perceived large size and bulkiness; limitations on repeat dosing (if required)⁹; fear and anxiety associated with the use of needles³; and dosing errors caused by incorrect technique of administration.^{7,10} In addition, it is impossible to give an accurate dose to infants and to many children using currently available autoinjectors, which provide only 2 different premeasured, fixed epinephrine doses, 0.15 mg and 0.3 mg.³ Alternatives to an epinephrine autoinjector, such as an epinephrine ampule/syringe/needle or an epinephrine metered-dose inhaler, are impractical with regard to rapid and accurate dosing.^{3,11,12}

The sublingual route of administration is a promising alternative route for epinephrine administration. Drugs

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Abbreviations used

AUC: Area under the plasma epinephrine concentration versus time curve

C_{baseline} : Baseline plasma concentration (endogenous epinephrine)

C_{max} : Maximum plasma epinephrine concentration

T_{max} : Time of maximum plasma epinephrine concentration

that are absorbed sublingually bypass potential metabolic conversion in the gastrointestinal tract and hepatic first-pass metabolism, and reach the systemic circulation in a pharmacologically active form.¹³⁻¹⁶ Lipophilic drugs with a low molecular weight such as epinephrine are likely absorbed across the sublingual mucosa into the venous circulation by transcellular diffusion,¹⁷ a mechanism driven by the concentration gradient (Fig 1).¹⁸

The aims of this study were to confirm the feasibility of epinephrine absorption from a novel sublingual tablet formulation, to ascertain if absorption was dose-dependent, and to determine the sublingual dose required to achieve plasma epinephrine concentrations similar to those obtained after the intramuscular injection of 0.3 mg epinephrine.

METHODS

The research was conducted according to current guidelines published by the Canadian Council on Animal Care¹⁹ and was approved by the University of Manitoba Protocol Management and Review Committee.

Novel rapidly disintegrating tablets containing 0 mg (placebo), 10 mg, 20 mg, and 40 mg epinephrine were formulated in the manufacturing laboratory of the Faculty of Pharmacy at the University of Manitoba. They contained no lactose and met United States Pharmacopeia standards for tablet weight variation, content uniformity, and friability. They disintegrated in less than 15 seconds, as assessed by using a novel *in vitro* disintegration test developed to simulate the sublingual environment.^{20,21}

In a prospective, controlled, 5-way crossover study, 5 New Zealand white rabbits (mean weight, 4.8 ± 0.2 kg) were investigated on 5 different study days at least 4 weeks apart, using a protocol described previously.²² Each rabbit received epinephrine 10 mg, 20 mg, and 40 mg as sublingual tablets, a placebo sublingual tablet (epinephrine 0 mg) as a negative control, and epinephrine 0.3 mg by intramuscular injection in the right thigh from an EpiPen as a positive control.

For sublingual epinephrine tablet administration, the rabbit's mouth was opened, and a wooden rod was inserted between the jaws. The tongue was elevated by using flat forceps, and the tablet was placed underneath by using another pair of forceps. The mouth was gently but firmly held shut for 5 minutes with the wooden rod in place to prevent chewing or swallowing the tablet. Water 0.3 to 0.5 mL was administered immediately after dosing to facilitate tablet disintegration. An additional 0.7 to 0.5 mL water was administered at the end of the 5-minute immobilization time to remove any remaining epinephrine from under the tongue.

Epinephrine 0.3 mg was injected intramuscularly in the thigh by using an EpiPen, after which the solution remaining in the EpiPen was evacuated into a polystyrene test tube and frozen at -20°C , to be analyzed for epinephrine content using a reverse-phase HPLC system (Waters Corp, Milford, Mass) with UV detection.²³

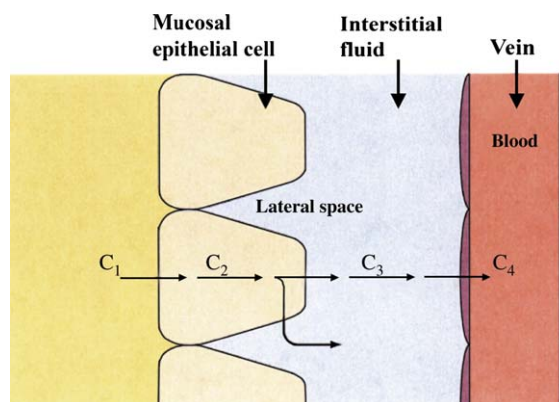


FIG 1. Transcellular absorption of epinephrine from the sublingual cavity into the sublingual venous circulation. C_1 epinephrine concentration, which depends on the epinephrine dose and the volume of saliva available; C_2 epinephrine concentration within the mucosal epithelial cells; C_3 epinephrine concentration in the interstitial fluid; C_4 plasma epinephrine concentration. From Bundle: Human Physiology: From Cells to Systems (with CD-ROM and InfoTrac), 5th + Photo Atlas for Biology 5th edition by Sherwood.¹⁸ © 2004. Adapted and reprinted with permission of Brooks/Cole, a division of Thomson Learning: www.thomsonrights.com.

Measurement of plasma epinephrine concentrations

An indwelling catheter (OPTIVA* 22G 1", Johnson & Johnson Medical, Arlington, Tex) was inserted into an ear artery 30 minutes before dosing. A 2-mL blood sample was obtained immediately before dosing and at 5, 10, 15, 20, 30, 40, 60, 90, 120, 150, and 180 minutes afterward.

Blood samples were refrigerated within 1 hour of sampling and centrifuged at 4°C . Plasma was frozen at -20°C . Before analysis, plasma was thawed at room temperature, and epinephrine was extracted by a solid-liquid extraction process, with an efficiency of 70% to 80%. Epinephrine concentrations were measured by using HPLC system (Waters Corp) with electrochemical detection (EC).²⁴⁻²⁶ Two calibration curves with 2 different epinephrine concentration ranges were prepared. The low-range calibration curve was linear over the range of 0.1 to 1.0 ng/mL with a coefficient of variation of 0.8% at 0.1 ng/mL and 1.4% at 1.0 ng/mL. The high-range calibration curve was linear over the range of 1.0 to 10.0 ng/mL with a coefficient of variation of 4.8% at 1.0 ng/mL and 1.1% at 10.0 ng/mL.

Data analysis

Mean ($\pm$ SEM) maximum plasma epinephrine concentrations (C_{max}), the times at which C_{max} were achieved (T_{max}), and the area under the plasma concentration versus time curves (AUC) were calculated from the plasma epinephrine concentration versus time plot of each individual rabbit using WinNonlin 5.0 (Pharsight, Mountain View, Calif). The AUC, C_{max} , and T_{max} values for each rabbit were compared by using repeated-measures ANOVA, Tukey-Kramer tests, and paired Student *t* test using NCSS Statistical Analysis Software (NCSS, Kaysville, Utah). Differences were considered to be significant at $P < .05$.

RESULTS

The mean ($\pm$ SEM) epinephrine dose injected using EpiPen autoinjectors was 0.34 ± 0.002 mg as calculated

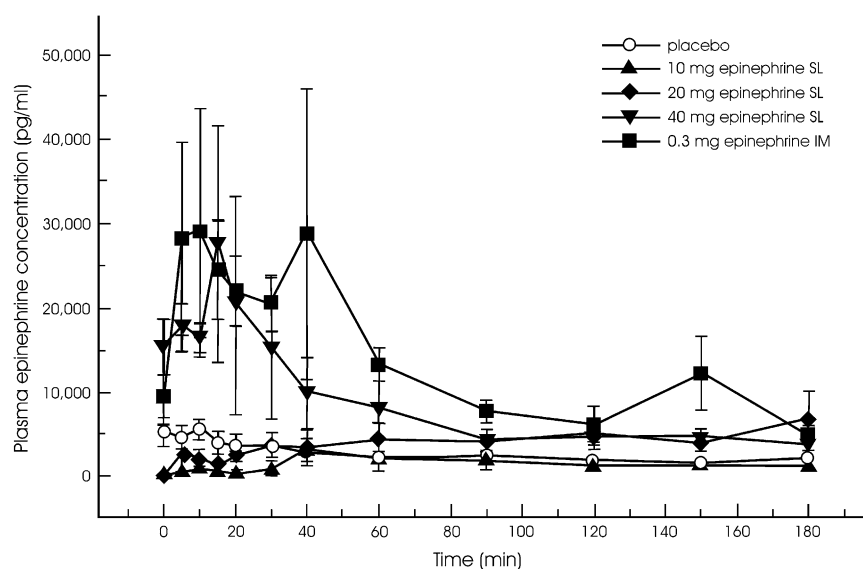


FIG 2. Plasma epinephrine concentration versus time plots after administration of epinephrine or placebo sublingually (SL) and after epinephrine intramuscular injection (IM). Mean ($\pm$ SEM) AUC, C_{max} , and T_{max} after administration of 40 mg epinephrine sublingual tablets and epinephrine intramuscular injections were not significantly different ($P > .05$).

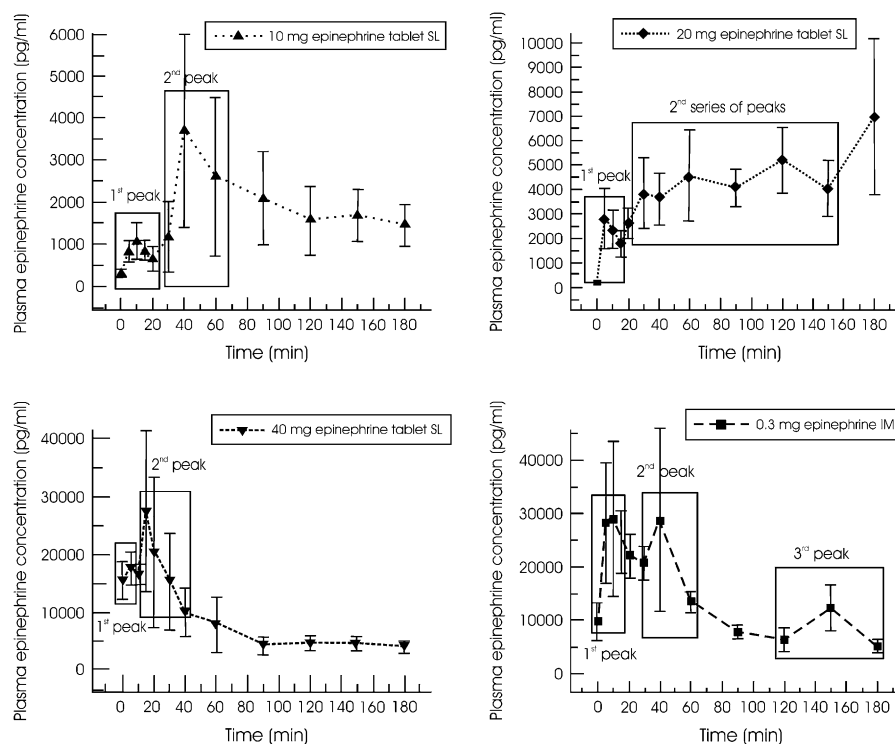


FIG 3. Plasma epinephrine concentration versus time plots after administration of epinephrine or placebo sublingually (SL) and after epinephrine intramuscular injection (IM). Mean ($\pm$ SEM) AUC, C_{max} , and T_{max} after administration of 40 mg epinephrine sublingual tablets and epinephrine intramuscular injections were not significantly different ($P > .05$).

by multiplying the epinephrine concentration measured in the solution remaining in the EpiPens after injection by the stated injected volume (0.3 mL).

Mean ($\pm$ SEM) plasma epinephrine concentration versus time plots after the administration of epinephrine 0 mg (placebo), epinephrine 10 mg, epinephrine 20 mg, and

TABLE I. Epinephrine bioavailability after sublingual administration of different epinephrine doses and epinephrine intramuscular injection in the thigh

Mean $\pm$ SEM*	Sublingual tablets				EpiPen
Epinephrine dose (mg)	0	10	20	40	0.3
AUC (ng/mL/min)	472 $\pm$ 126	335 $\pm$ 152	801 $\pm$ 160	1861 $\pm$ 537†	2431 $\pm$ 386†
C _{baseline} (ng/mL)	5.5 $\pm$ 1.6	0.3 $\pm$ 0.1	0.2 $\pm$ 0.1	15.4 $\pm$ 3.2	9.6 $\pm$ 3.5
C _{max} (ng/mL)	6.5 $\pm$ 1.3	5.2 $\pm$ 2.3	6.6 $\pm$ 1.4	31.0 $\pm$ 13.1†	50.3 $\pm$ 17.1†
T _{max} (min)	—	37 $\pm$ 11	31 $\pm$ 9	9 $\pm$ 2	21 $\pm$ 5

*n = 5.

†P < .05.

epinephrine 40 mg sublingual tablets and epinephrine 0.3 mg intramuscularly are shown in Figs 2 and 3. Mean ($\pm$ SEM) AUC, C_{baseline} (endogenous), C_{max}, and T_{max} values, after the administration of placebo, epinephrine 10 mg, epinephrine 20 mg, and epinephrine 40 mg sublingual tablets and epinephrine 0.3 mg intramuscularly, are shown in Table I.

Mean ($\pm$ SEM) AUC after the administration of epinephrine 40 mg sublingual tablets (1861 $\pm$ 537 ng/mL/min) and epinephrine 0.3 mg intramuscularly (2431 $\pm$ 386 ng/mL/min) did not differ significantly. Mean AUC after the administration of epinephrine 10 mg (335 $\pm$ 152 ng/mL/min) and epinephrine 20 mg (801 $\pm$ 160 ng/mL/min) sublingual tablets were significantly lower than after epinephrine 0.3 mg intramuscularly (2431 $\pm$ 386 ng/mL/min), and not significantly higher than after placebo sublingual tablets (472 $\pm$ 126 ng/mL/min). The bioavailability of sublingual epinephrine, as assessed by using AUC, increased linearly with a linear increase in dose (Fig 4).

Mean ($\pm$ SEM) C_{max} values after epinephrine 40 mg sublingual tablets (31.0 $\pm$ 13.1 ng/mL) and epinephrine 0.3 mg intramuscularly (50.3 $\pm$ 17.1 ng/mL) did not differ significantly. Mean C_{max} values after epinephrine 10 mg (5.2 $\pm$ 2.3 ng/mL) and epinephrine 20 mg (6.6 $\pm$ 1.4 ng/mL) sublingual tablets were significantly lower than after epinephrine 0.3 mg intramuscularly (50.3 $\pm$ 17.1 ng/mL), and not significantly higher than after placebo sublingual tablets (6.5 $\pm$ 1.3 ng/mL).

Mean ($\pm$ SEM) T_{max} after the administration of epinephrine 10 mg (37 $\pm$ 11 minutes), epinephrine 20 mg (31 $\pm$ 9 minutes), and epinephrine 40 mg (9 $\pm$ 2 minutes) sublingual tablets and epinephrine 0.3 mg intramuscularly (21 $\pm$ 5 minutes) did not differ significantly.

No adverse effects were observed.

DISCUSSION

The readily accessible, convenient sublingual route of administration has long been used to administer medications such as nitroglycerine. The high vascularity of the sublingual mucosa facilitates rapid drug absorption directly into the venous circulation through the sublingual and frenular veins, bypassing the gastrointestinal tract, the hepatic portal circulation, and hepatic first-pass metabolism.¹³⁻¹⁶ Further drug absorption can be terminated if necessary by

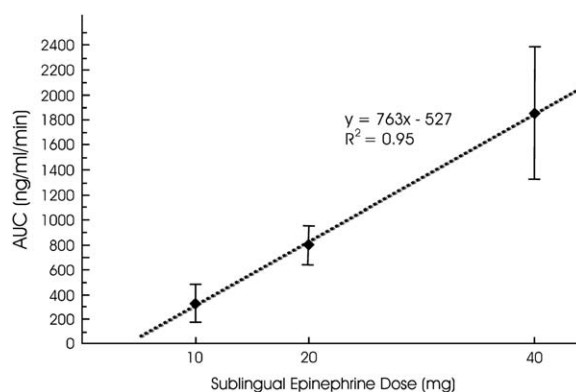


FIG 4. Correlation between epinephrine sublingual dose and the bioavailability of epinephrine. The linear increase in the epinephrine dose administered resulted in a linear increase ($R^2 = 0.95$) in epinephrine bioavailability (AUC). Each data point is expressed as the mean $\pm$ SEM of individual AUC values.

removing the tablet from the sublingual space. Sublingual epinephrine tablets should be less expensive to produce than the currently available autoinjectors are. They are unobtrusive to carry and to self-administer, and repeat dosing is practical. They can be formulated in a range of epinephrine doses to provide accurate dosing for individuals with a wide range of body weights.

The most important rationale for using a rabbit model for epinephrine pharmacokinetic studies was that this epinephrine-tolerant species does not develop any apparent adverse effects after high doses of epinephrine on a milligram per kilogram basis relative to human doses; epinephrine 0.3 mg intramuscularly from an autoinjector was well tolerated in this study and in a previous study.²⁷

In this model, we have demonstrated for the first time that the bioavailability of sublingual epinephrine increased linearly with a linear increase in the dose, indicating that the absorption follows first-order kinetics. We have also determined for the first time that a 40-mg sublingual epinephrine dose from a novel, rapidly disintegrating tablet formulation resulted in AUC, C_{max}, and T_{max} values that did not differ significantly from those achieved with a mean dose of 0.34 mg epinephrine intramuscularly. Similar mean ($\pm$ SEM) AUC (1420 $\pm$ 340 ng/mL/min) and C_{max} (26.2 $\pm$ 6.9 ng/mL) results were reported previously after epinephrine intramuscular

injection in the thigh using this rabbit model and similar study conditions.²⁷ Rapid epinephrine absorption is critical for achieving high plasma epinephrine concentrations and fast onset of action by decreasing the release of inflammatory mediators from mast cells and basophils and relieving the symptoms of anaphylaxis.³ In addition, we have confirmed that sublingual epinephrine tablets produced mean T_{max} results similar to those achieved after epinephrine injected intramuscularly, as reported in preliminary studies with an early sublingual epinephrine formulation.²⁸

Plotting the mean plasma epinephrine concentration versus time data of each administered sublingual epinephrine dose and the epinephrine intramuscular dose individually gives a clearer picture of the pattern of epinephrine absorption. After sublingual epinephrine administration, plasma epinephrine concentrations increase immediately (first small peak), followed by another rapid increase in the form of a second peak, or a series of intermittent peaks. This absorption pattern can be related to the strong vasoconstricting effect of epinephrine in the sublingual mucosa. Initially, epinephrine absorption is almost instantaneous. This is likely a result of rapid transport across the single epithelial cell layer of the mucosa into the interstitial fluid on the basolateral side of the epithelial cells and then into the venous circulation down the concentration gradient according to Fick's law. The initial rapid absorption of epinephrine induces local vasoconstriction, however, and is therefore followed by a temporary reduction in epinephrine absorption. Subsequent vasodilation is followed by a second and higher plasma epinephrine peak resulting from secondary absorption of the epinephrine that has accumulated in the interstitial fluid. The magnitude of this second peak, and the amount of epinephrine that reaches the systemic circulation, depend on the epinephrine dose and the concentration gradient created across the mucosal epithelial cell layer. Epinephrine absorption after intramuscular injection follows a similar pattern, except that the first peak is higher, perhaps indicating that larger amounts of epinephrine are absorbed before the initial vasoconstriction. The subsequent intermittent absorption of epinephrine in the form of small third or fourth peaks is also expected, because some epinephrine is still available at the site of injection.

Epinephrine appears to have a similar intermittent absorption pattern regardless of route of administration: after sublingual administration in a rabbit model,²⁸ intramuscular injection in a rabbit model^{22,27} and in humans,^{5,29,30} subcutaneous injection in a rabbit model²² and in humans,^{5,30} and inhalation in humans.¹² It has been suggested previously, on the basis of preliminary experiments with an early sublingual formulation, that the second peak occurring from 90 to 180 minutes after sublingual administration might be a result of "ongoing absorption from the sublingual mucosa,"²⁸ which can be only true for the epinephrine already transported into the mucosal epithelial cells or into the interstitial fluid in the basolateral space. Any epinephrine remaining in the sublingual cavity would be swallowed, and gastrointestinal

absorption would be minimal. After oral administration, epinephrine is rapidly metabolized by the catechol-O-methyltransferase in the gastrointestinal tract and by monoamine oxidase in the gastrointestinal tract and in the liver, and is excreted mainly as 3-methoxy-4-hydroxyphenylethyleneglycol and 3-methoxy-4-hydroxymandelic acid.³¹

The rate of epinephrine absorption as assessed by C_{max} and T_{max} , and the extent of epinephrine absorption as assessed by AUC, from the sublingual tablets was influenced by the magnitude of the epinephrine dose administered. High epinephrine saliva concentrations, the driving force of absorption, were associated with a high epinephrine concentration gradient across the mucosal epithelial cell layer. The increased absorption rate resulted in higher C_{max} at faster T_{max} , and ultimately in higher AUC values in each individual rabbit.

Administration of the 10-mg sublingual tablet may have resulted in epinephrine saliva concentrations that were too low to produce the concentration gradient necessary to achieve absorption across the sublingual mucosa into the venous circulation. The resulting C_{max} and AUC values achieved were not different from, and in some instances were even lower than, the endogenous epinephrine concentrations measured after administration of the placebo sublingual tablets. Although the rabbits were conditioned and handled in a consistent manner, considerable day-to-day variability in mean epinephrine $C_{baseline}$ was observed, as found in previous studies.^{22,27,28}

The sublingual administration of 40 mg epinephrine from a novel, rapidly disintegrating tablet resulted in plasma epinephrine concentrations similar to those obtained after epinephrine 0.34 mg intramuscular injection in the thigh. These tablets should be developed further for the potential emergency treatment of anaphylaxis in human beings.

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