

Letter to the Editor

Epinephrine (adrenaline) absorption from new-generation, taste-masked sublingual tablets: A preclinical study

To the Editor:

Prompt injection of epinephrine through an autoinjector in the mid-outer thigh is the recommended first-aid treatment of anaphylaxis in community settings. However, many patients at risk of anaphylaxis do not carry their epinephrine autoinjectors with them consistently because of bulky autoinjector size. Moreover, when anaphylaxis occurs, epinephrine autoinjectors are under-used, even by patients who have life-threatening respiratory or cardiovascular symptoms. Other reported issues with autoinjectors include incorrect injection technique, misfiring, unintentional injection with or without injury, availability of only a single dose in each device, and poor stability of the epinephrine solution in the autoinjector, which is associated with a short shelf-life.^{1,2}

Sublingual administration of epinephrine has the potential to overcome many of these perceived limitations; indeed, this accessible and convenient route has long been used for self-treatment in other medical emergencies, such as initial nitroglycerine treatment for angina.

In the sublingual area the mucosa is thin and the blood supply is abundant. This facilitates rapid absorption of medication across the epithelium into the interstitial fluid by means of passive diffusion according to Fick's law. A hydrophilic drug with a low molecular weight, such as epinephrine bitartrate, needs to be administered sublingually in a relatively high dose compared with the doses administered through other routes, to create the concentration gradient that drives its diffusion. Epinephrine is rapidly absorbed into the sublingual veins. It enters the systemic circulation in a pharmacologically active form, having bypassed the gastrointestinal tract and hepatic first-pass metabolism.³

In a proof-of-concept study in a validated animal model, administration of the first-generation sublingual epinephrine tablets that we developed resulted in plasma epinephrine concentrations that were similar to those measured after intramuscular injection of 0.3 mg of epinephrine from EpiPens (Dey Pharma LP, Napa, Calif).³ The limitations of the first-generation tablets included the intrinsic bitter taste of the epinephrine, a potential hindrance to patient acceptability, and the need to optimize epinephrine dissolution times from the tablets.

Subsequently, we have developed new-generation epinephrine sublingual tablets. Modification of the nonmedicinal ingredients by addition of citric acid led to efficient masking of the intrinsic bitter taste of epinephrine, as assessed by using an electronic tongue consisting of a multichannel array of liquid electrochemical sensors coated with an organic membrane (Alpha MOS, Toulouse, France). The electronic tongue is an established alternative to the human sensory analysis panels that are typically used to test pharmaceutical formulations after regulatory agency approval.⁴ Additionally, increasing tablet surface area and changing the relative proportions of the nonmedicinal ingredients (mannitol, microcrystalline cellulose, and low-substituted hydroxypropyl cellulose, a superdisintegrant) led to disintegration within 13 seconds and dissolution of the epinephrine within 60 seconds.⁵ These new-generation tablets are formulated by means of direct compression, without using heat or water, in the

latex-free manufacturing laboratory of the Faculty of Pharmacy at the University of Manitoba. They do not contain sodium metabisulfite or lactose. They meet *United States Pharmacopeia* standards for weight variation, content uniformity, and friability.⁵

Modification of the nonmedicinal ingredients in the tablets potentially affects the bioavailability of the active pharmaceutical ingredients.³ It was therefore necessary to study the rate and extent of epinephrine absorption from the new-generation sublingual tablets in the validated animal model.³ The research was conducted according to the Canadian Council on Animal Care guidelines and approved by the University of Manitoba Protocol Management and Review Committee.

We performed a randomized placebo-controlled study in New Zealand female white rabbits (an epinephrine-tolerant species) with a mean $\pm$ SD weight of 3.6 ± 0.1 kg by using the protocol previously described in detail.³ On study days at least 4 weeks apart, the animals received either a 40-mg epinephrine sublingual tablet, 0.3 mg of epinephrine administered by means of intramuscular injection in the thigh from an EpiPen (positive control), or a placebo sublingual tablet (negative control containing identical nonmedicinal ingredients to the sublingual epinephrine tablet, but no epinephrine). The technique of administering sublingual tablets was the same as previously reported,³ except that the sublingual residence time was decreased to 2 minutes.

In blood samples obtained at baseline, immediately before dosing, and 5, 10, 15, 20, 30, 40, and 60 minutes afterward, plasma epinephrine concentrations were measured by using HPLC (Waters Corp, Milford, Mass) with electrochemical detection. The maximum plasma epinephrine concentration ($C_{\max}$), the time at which $C_{\max}$ was achieved ($T_{\max}$), and the area under the plasma concentration versus time curve ($AUC_{0-1\text{ h}}$) were calculated from the plasma epinephrine concentration versus time plots by using WinNonlin 5.3 software (Pharsight, Mountain View, Calif) and analyzed by using 1-way analysis of covariance and Tukey-Kramer tests (NCSS Statistical Analysis Software, Kaysville, Utah).

Mean ($\pm$ SD) plasma epinephrine concentration versus time plots after administration of 40-mg epinephrine sublingual tablets, 0.3 mg of epinephrine administered by means of intramuscular injection, and placebo sublingual tablets are shown in Fig 1. Mean ($\pm$ SD) C_{baseline} , as well as $C_{\max}$, $T_{\max}$, and AUC values are shown in Table I.

The pharmacokinetic values $C_{\max}$, $T_{\max}$, and $AUC_{0-1\text{ h}}$ after administration of 40-mg epinephrine sublingual tablets did not differ significantly ($P > .05$) from $C_{\max}$, $T_{\max}$, and $AUC_{0-1\text{ h}}$ values after administration of 0.3 mg of epinephrine by means of intramuscular injection. However, $C_{\max}$ and $AUC_{0-1\text{ h}}$ values after administration of exogenous epinephrine through the sublingual or intramuscular routes differed significantly from $C_{\max}$ and $AUC_{0-1\text{ h}}$ values of endogenous epinephrine after administration of placebo sublingual tablets ($P \leq .05$, Table I).

Two peaks in plasma epinephrine concentrations were noted after administration of epinephrine sublingual tablets and also after intramuscular injection of epinephrine (Fig 1). This intermittent pattern of absorption has consistently been observed in pharmacokinetic studies of epinephrine in animal models and in human subjects, regardless of the route of epinephrine administration. In animal models it has been reported previously after sublingual administration, intramuscular injection, subcutaneous injection, and

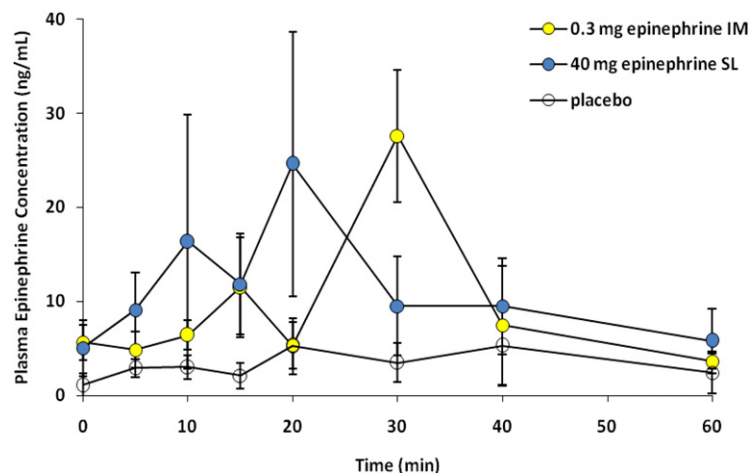


FIG 1. Plasma epinephrine concentration (mean $\pm$ SD) versus time plots after administration of epinephrine sublingual (SL) tablets, epinephrine by intramuscular (IM) injection, or placebo sublingual tablets.

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

	Epinephrine from sublingual tablets	Epinephrine from an EpiPen	Placebo sublingual tablets
Epinephrine dose (mg)	40	0.3	0
C _{baseline} (ng/mL)	5.0 $\pm$ 3.0	5.6 $\pm$ 1.9	1.1 $\pm$ 1.2*
C _{max} (ng/mL)	31.7 $\pm$ 10.1	27.6 $\pm$ 7.0	7.5 $\pm$ 3.0*
T _{max} (min) [†]	20.0 $\pm$ 7.1	30.0 $\pm$ 0.0	33.3 $\pm$ 17.5
AUC _{0-1 h} (ng/mL/min)	678.0 $\pm$ 149.0	592.0 $\pm$ 122.3	220.1 $\pm$ 78.0*

Values are presented as means $\pm$ SDs (n = 5).

AUC, Area under the plasma concentration versus time curve (mean $\pm$ SD of individual AUC values from each rabbit); C_{baseline}, baseline plasma concentration reflecting endogenous epinephrine; C_{max}, maximum plasma concentration (mean $\pm$ SD of individual C_{max} values from each rabbit, regardless of the time at which C_{max} was achieved); T_{max}, time at which maximum plasma epinephrine concentration was achieved (mean $\pm$ SD of individual T_{max} values from each rabbit).

*P < .05.

[†]T_{max} is the time at which the highest peak epinephrine concentration occurred in each rabbit, regardless of the time elapsed since dosing. T_{max} is limited by experimental design because it is a discrete variable based on predefined times of blood sampling.

inhalation. In human subjects it has been reported after intramuscular injection, subcutaneous injection, and inhalation.^{2,3,6-8}

The initial peak is likely due to rapid epinephrine absorption, followed by vasoconstriction at the site of administration, such as the sublingual mucosa or skeletal muscle, which leads to a temporary reduction in absorption and accumulation of epinephrine at the site. Subsequently, vasodilation and a second phase of rapid epinephrine absorption occur, leading to a second and higher epinephrine peak in the systemic circulation. After sublingual administration, the magnitude of this second peak depends on the epinephrine dose and the concentration gradient created, as previously reported.³

The pharmacologic effects of epinephrine are both time and concentration dependent. Ideally, as soon as anaphylaxis is recognized, high epinephrine concentrations need to be achieved rapidly in the systemic circulation and in target organs to decrease release of mediators of inflammation⁹ and prevent escalation of the anaphylaxis symptoms.

In this study we have shown that epinephrine is rapidly absorbed in the first 20 to 30 minutes after administration through either the sublingual or intramuscular route. The new-generation, taste-masked sublingual epinephrine tablets have similar bioavailability to epinephrine injected intramuscularly in the thigh. They are potentially suitable for phase I studies in human subjects and might eventually be useful for the first-aid treatment of anaphylaxis in community settings.

Ousama Rachid, BPharm, MSc^a
Mutaseem M. Rawas-Qalaji, PhD^b
F. Estelle R. Simons, MD^{c,d}
Keith J. Simons, PhD^{a,c}

From ^athe Faculty of Pharmacy and the Departments of ^cPediatrics and Child Health and ^dImmunology, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada, and ^bthe College of Pharmacy, Nova Southeastern University, Fort Lauderdale, Fla. E-mail: umrachid@cc.umanitoba.ca.

Disclosure of potential conflict of interest: F. E. R. Simons is on the ALK-Abelló Medical Advisory Board, the Mylan Medical Advisory Board, and the Sanofi Medical Advisory Board. The rest of the authors declare that they have no relevant conflicts of interest.

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