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Is Epinephrine Administration by Sublingual Tablet Feasible for the First-Aid Treatment of Anaphylaxis? A Proof-of-Concept Study

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ABSTRACT: *Purpose*: In order to explore the feasibility of sublingual administration of epinephrine tablets as a non-invasive first-aid treatment for anaphylaxis, we studied epinephrine absorption from this dosage form in an animal model. *Methods*: In a prospective, randomized, four-way crossover study, six rabbits received epinephrine 2.5 or 10 mg as a sublingual tablet, epinephrine 0.03 mg (0.3 ml) by intramuscular (IM) injection (positive control), and 0.9% NaCl (0.3 ml) IM (negative control). Pre- and post-dose blood samples were obtained for measurement of plasma epinephrine concentrations by HPLC-EC. *Results*: After administration of epinephrine 2.5 mg as a sublingual tablet, the mean ($\pm$ SEM) C_{max} was 2369 $\pm$ 392 pg/ml, and the t_{max} was 20.8 $\pm$ 5.7 min. After administration of epinephrine 10 mg sublingually, the C_{max} was 10836 $\pm$ 2234 pg/ml, and the t_{max} was 21.7 $\pm$ 5.4 min. After IM epinephrine, the C_{max} was 6445 $\pm$ 4233 pg/ml, and the t_{max} was 15.8 $\pm$ 4.7 min. After IM 0.9% NaCl, the C_{max} (endogenous epinephrine) was 518 $\pm$ 142 pg/ml. The t_{max} after both of the sublingual epinephrine tablet doses did not differ significantly from the t_{max} after IM epinephrine, and the C_{max} after the 10 mg sublingual epinephrine tablet dose did not differ significantly from the C_{max} after IM epinephrine. *Conclusions*: In this proof-of-concept study, administration of epinephrine as a sublingual tablet formulation resulted in rapid achievement of peak plasma epinephrine concentrations. Absorption studies in humans are needed.

Definitions: HPLC—high performance liquid chromatography; EC — electrochemical detection; C_{max} — maximum plasma epinephrine concentration after dosing; t_{max} — time of maximum plasma epinephrine concentration.

Key words: epinephrine; adrenaline; anaphylaxis; sublingual tablet

Introduction

Prompt administration of epinephrine [1,2], preferably by intramuscular injection [3,4], is the cornerstone of systemic anaphylaxis treatment. Most episodes of anaphylaxis occur outside of a hospital setting; in this situation, death has been attributed to the patient's delay in self-injection of epinephrine for first-aid treatment [5,6]. In some instances, reluctance to self-inject epinephrine promptly may be due to anxiety about a 'needle' [7].

It is not practical to administer epinephrine orally because it is rapidly conjugated and oxidized by catechol-*O*-methyltransferase in the wall of the gastrointestinal tract, and by

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monoamine oxidase in the gastrointestinal tract wall and the liver [8]. Epinephrine inhalation from a pressurized metered-dose inhaler has been recommended as a non-invasive route of administration; however, the large number of inhalations required [9,10] may not be feasible to take during a medical emergency.

Drugs absorbed from the mucosa in the sublingual area pass directly into the systemic circulation, avoiding the first-pass effect [11]. We therefore hypothesized that epinephrine would be well absorbed and rapidly absorbed after sublingual administration in a tablet formulation, and that this route of administration might eventually prove to be a practical alternative to injection of epinephrine. We tested absorption of epinephrine from a sublingual tablet formulation in an animal model.

Methods

The research was conducted according to current guidelines published by the Canadian Council on Animal Care and was approved by the University of Manitoba (Fort Garry Campus) Protocol Management and Review Committee.

Tablets containing 2.5 and 10 mg epinephrine were formulated in the manufacturing laboratory of the Faculty of Pharmacy at the University of Manitoba. The principal non-medicinal ingredient was microcrystalline cellulose. They contained no lactose. They met USP standards for content uniformity, and had a disintegration time of less than 20 s *in vitro*.

Using a prospective, randomized, controlled, crossover study design, six New Zealand white rabbits (mean weight 4.2 ± 0.1 kg) were investigated on four different study days at least 1 week apart, using a protocol described previously [12]. Each rabbit received epinephrine 2.5 mg as a sublingual tablet, epinephrine 10 mg as a sublingual tablet, epinephrine 0.03 mg (0.3 ml) intramuscularly (IM) (Adrenalin® (1 mg/ml), diluted 1:10, Parke–Davis, Scarborough, ON, Canada) as a positive control, and 0.9% sodium chloride (0.3 ml) IM as a negative control. The IM injections were administered in the lateral aspect of the right thigh.

For sublingual epinephrine administration, one epinephrine tablet was placed under the rabbit's tongue using forceps. The rabbit's mouth was gently, but firmly held closed for 5 min to prevent it from chewing or swallowing the tablet. Through the corner of the closed mouth, 1 ml of water was administered by syringe immediately after placing the tablet under the tongue, and 1 ml of water was also administered by syringe just before the rabbit's mouth was released at 5 min.

In each rabbit on each study day, a 1.5 ml blood sample for measurement of plasma epinephrine was obtained from an indwelling catheter in an ear artery before and at 5, 10, 15, 20, 30, 40, 60, 90, 120, and 180 min after administration of epinephrine or NaCl [12]. After epinephrine administration, total exogenous and endogenous plasma epinephrine concentrations were measured using a previously described method [12]. At baseline on each study day, and after IM injection of saline, endogenous plasma epinephrine concentrations were measured.

Data analysis

Only the maximum epinephrine concentration (C_{max}) and the time of maximum epinephrine concentration (t_{max}) could be calculated using WinNonlin® (Pharsight, Mountain View, CA), since the variations in plasma epinephrine concentrations did not permit curve fitting.

Mean plasma epinephrine concentrations obtained at the various times after administration of epinephrine or NaCl and the pharmacokinetic parameters were compared using ANOVA and the Tukey and Bonferroni multiple-range tests (PC-SAS). Differences were considered to be significant at $p < 0.05$.

Results

Mean plasma epinephrine concentration versus time plots are shown in Figure 1. There was considerable variation in the plasma epinephrine concentrations. After administration of epinephrine 2.5 mg as a sublingual tablet, the mean ($\pm$ SEM) C_{max} was 2369 ± 392 pg/ml, reached at a mean t_{max} of 20.8 ± 5.7 min. After

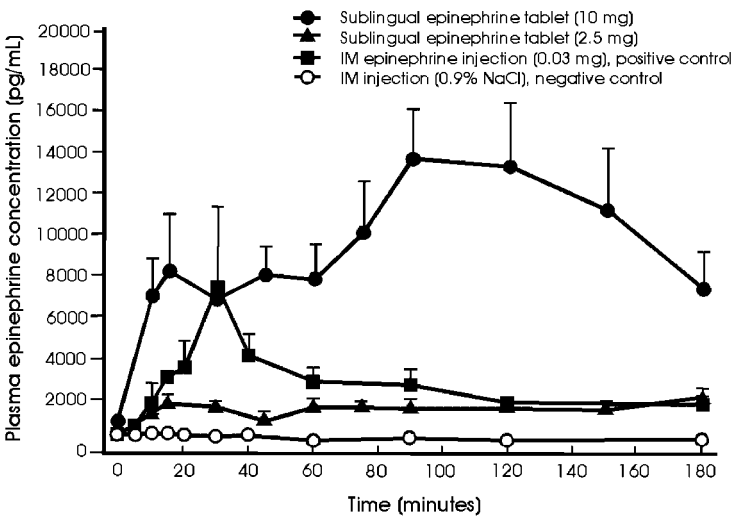

Figure 1. Plasma epinephrine concentrations (pg/ml) versus time (min) are shown after epinephrine 2.5 mg as a sublingual tablet, epinephrine 10 mg as a sublingual tablet, epinephrine 0.03 mg (0.3 ml) by intramuscular injection (IM) (positive control), and 0.9% NaCl (0.3 ml) by intramuscular injection (negative control). After NaCl injection, endogenous epinephrine concentrations were measured. The mean $\pm$ S.E.M. plasma epinephrine concentrations were calculated by averaging the epinephrine concentrations at each sampling time after epinephrine or NaCl. The mean C_{max} values reported in the text were the average of the C_{max} values for each individual animal during each study calculated using WinNonlin®

administration of epinephrine 10 mg as a sublingual tablet, the C_{max} was 10836 $\pm$ 2234 pg/ml, reached at a t_{max} of 21.7 $\pm$ 5.4 min. After IM injection of epinephrine, the C_{max} was 6445 $\pm$ 4233 pg/ml, reached at a t_{max} of 15.8 $\pm$ 4.7 min. After IM injection of 0.9% NaCl, the C_{max} (endogenous epinephrine) was 518 $\pm$ 142 pg/ml. The t_{max} after both of the sublingual tablet doses of epinephrine did not differ significantly from the t_{max} after IM epinephrine, and the C_{max} after the 10 mg sublingual tablet dose of epinephrine did not differ significantly from the C_{max} after IM epinephrine. No adverse effects were observed.

Discussion

In the first-aid, out-of-hospital treatment of anaphylaxis, delay in epinephrine self-administration is common, and increases the risk for fatality [5,6]. A common reason for delaying epinephrine injection is anxiety about the 'needle' involved [7]. An important therapeutic goal is therefore to develop non-invasive, user-friendly, effective and safe epinephrine formulations for use in first-aid, out-of-hospital treatment. Since it is not practical to give epinephrine by the oral route or by the inhaled route, other routes of administration need to be investigated.

The sublingual area provides an ideal site for epinephrine administration, as it is a readily accessible and highly vascularized mucosal surface that facilitates rapid drug absorption directly into frenular and sublingual vessels. In hospitalized patients in whom intravenous access is compromised, there is a precedent for administration of epinephrine sublingually either by injection or by application of epinephrine solution to the mucosa [13]. There is also an obvious precedent for patients to take sublingual tablets in a medical emergency: in the first-aid treatment of angina, nitroglycerin tablets, self-administered every 5 min sublingually, are more effective than long-acting nitrate formulations administered by patch, paste, chewing, or swallowing [14].

In this proof-of-concept study, after administration of epinephrine 10 mg in a sublingual tablet formulation, the C_{max} and t_{max} were similar to those achieved after epinephrine 0.03 mg IM,

and from 90 to 180 min, high plasma epinephrine concentrations were maintained. This was attributed either to ongoing absorption from the sublingual mucosa, absorption of swallowed non-metabolized epinephrine, or possibly, as noted in previous studies [3,4,10,12], to rebound of endogenous epinephrine secretion after suppression by exogenous epinephrine administration. The optimal concentrations of epinephrine required in plasma and tissue for successful treatment of anaphylaxis are unknown; however, it is logical to expect that achieving high tissue and plasma concentrations rapidly is important for decreasing release of chemical mediators of inflammation from mast cells and basophils, and for down-regulating the ensuing allergic reaction including laryngospasm, bronchospasm, and hypotension [15]. Studies to define the appropriate dose for epinephrine sublingual tablet administration in humans are needed.

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