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ORIGINAL ARTICLE

Systemic absorption of epinephrine compared between the intranasal and intramuscular routes of administration in healthy adults

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Abstract

Background: Epinephrine 5 mg administered via the intranasal (IN) route was shown to be bioequivalent to epinephrine 0.3 mg administered via the intramuscular (IM) route in our preliminary study.

Objective: To investigate the pharmacokinetics and pharmacodynamics of IN and IM epinephrine absorption in a larger group of healthy adults (n = 12).

Methods: Each subject was administered IN saline, IN epinephrine (5 mg), and IM epinephrine (0.3 mg) on 3 separate days. Plasma epinephrine levels were determined using liquid chromatography-tandem mass spectrometry.

Results: IN epinephrine administration showed significant systemic absorption compared to IN saline control with the areas under the curve ($AUC_{0\text{-}180\ min}$) of 4.4 (4.9) ± 4.0 and 0.2 (0.5) ± 0.3 ng.min/mL, respectively; the values are mean (median) ± standard deviation. IN epinephrine absorption was about 0.5-fold that of IM epinephrine ($AUC_{0\text{-}180\ min}$ 10.0 (9.2) ± 8.6 ng.min/mL), but the difference was not statistically significant (p = 0.16). The mean peak epinephrine concentration and the time to reach it were also not significantly different between the IN and IM routes. The corresponding values were 120 pg/mL and 41 min for IN, and 209 pg/mL and 41 min for IM, respectively.

Conclusion: The systemic absorption of IN epinephrine 5 mg was significantly different from the control IN saline and about 0.5-fold that of IM epinephrine 0.3 mg. Although epinephrine administration via the less invasive IN route is safe and feasible, further investigations are necessary to achieve an adequate and consistent systemic absorption comparable to that of the conventional IM injection.

Key words: epinephrine, intranasal administration, intramuscular injection, pharmacokinetics, pharmacodynamics, anaphylaxis

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Introduction

Epinephrine is the drug of choice for initial treatment of anaphylaxis. It is, therefore, strongly recommended that patients with a history of severe anaphylactic reaction (or their caregivers) have an epinephrine auto-injector readily available for intramuscular (IM) injection as first aid treatment.[1,2] However, IM epinephrine administration is often underused for various reasons, including unavailability of auto-injectors (particularly in developing countries) due to their relatively high cost;[3,4] lack of confidence in using the device, which requires proper instruction, repeated training, and practice;[5] and fear of needles.[6]

Alternative routes of epinephrine administration have been investigated to overcome the drawbacks of IM injection.[7] The intranasal (IN) route is a potential route of drug administration in this setting because the nasal mucosa consists of highly vascularized and permeable tissue with high absorption capability. Previous studies in canine model demonstrated that epinephrine administered via the IN route readily absorbed into the systemic circulation.[8,9] In humans, systemic epinephrine absorption was reported after topical application for endoscopic sinonasal surgery.[10-12] A preliminary study in a small group of healthy adults (n = 5) that was previously conducted by our group demonstrated that IN epinephrine 5 mg could be systemically absorbed, and the plasma concentration was bioequivalent to that of IM epinephrine 0.3 mg.[13] The aim of this study was to determine and compare the pharmacokinetics and pharmacodynamics of IN epinephrine 5 mg with those of IM epinephrine 0.3 mg in a larger group of healthy subjects (n = 12) to confirm our previous findings, and to evaluate for any side effects of IN epinephrine administration.

Methods

Materials and Reagents

Epinephrine bitartrate was purchased from Sigma-Aldrich (St. Louis, MO, USA). An internal standard (lamivudine) was obtained from the United States Pharmacopeial Convention, Inc. (Rockville, MD, USA). Cationic exchange cartridges (1 cc Oasis MCX Vac cartridges, cat. no. 186000252) were purchased from Waters Corporation (Milford, MA, USA).

Intranasal Epinephrine Spray Formulation and Administration

Intranasal (IN) epinephrine spray was freshly prepared before use by the Pharmacy Department of Siriraj Hospital (Bangkok, Thailand). A specified amount of epinephrine bitartrate was dissolved in normal saline solution to a final concentration of 40 mg/mL and filter-sterilized. The nasal spray device dispensed 5 mg of epinephrine in 125 ± 4 µL volume per puff (coefficient of variation of device output = 4%). Before IN administration, subjects underwent nasal irrigation with normal saline solution. To deliver the nasal spray, the tip of the device was inserted into the nasal cavity adjacent to the inferior turbinate and the spray was administered into one nostril.

Subject Selection

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Siriraj Institutional Review Board (SiRB) of Faculty of Medicine Siriraj Hospital, Mahidol University (approval no. SI258/2007). The study protocol was also registered in the ClinicalTrials.gov website (reg. no. NCT01432522). Twelve healthy subjects (4 males, 8 females) aged 18-30 years were recruited and informed consent was obtained from all subjects involved in the study. Subjects were determined to be healthy based on evaluation of normal medical history, physical examination, and laboratory investigations, including electrocardiographic (ECG) study and routine hematological, biochemical, and urinary analyses. Subjects were excluded if they had underlying diseases (e.g., cardiovascular disease, hypertension, or systemic diseases), history of smoking, use of any drug, or recent upper respiratory tract infection.

Study Design and Outline

On 3 separate days (at least 14 days apart), each subject was given the following treatments: 1) IN spray of normal saline solution as a negative control; 2) IM injection of epinephrine USP 1:1,000 at 0.3 mg (0.3 mL) in the lateral part of the right thigh as a positive control; and, 3) IN spray containing 5 mg of epinephrine bitartrate. Foods containing methylxanthine, such as chocolate, cocoa, and cola, were disallowed for at least 24 hours before each study day. On each study day, an indwelling venous catheter was inserted for blood sample collection, and blood pressure, heart rate, and ECG were continuously monitored. Venous blood samples were collected from the indwelling venous catheter for plasma concentration measurement at various time points, including at 30 and 15 minutes before the treatment (as baseline or time 0), and at 5, 10, 15, 20, 30, 45, 60, 90, 120, and 180 minutes after the treatment. For each collection, 10 mL of whole blood was mixed in a heparin tube containing 75 µL of EGTA-glutathione solution (9.5% EGTA and 3% glutathione, pH 6-7). All samples were put on ice and processed within 1 h after collection by spinning down at 1,600 g for 10 min at 4°C to collect plasma, which was then stored in light-resistant polypropylene tubes at -80°C until analysis.

Determination of Plasma Epinephrine Using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Method

Frozen plasma was thawed at room temperature before sample preparation by solid phase extraction (SPE). Briefly, 500 µL of plasma, 20 µL of 0.5 µg/mL lamivudine (internal standard), and 550 µL of deionized water were gently mixed and transferred into an SPE cartridge (Oasis MCX 1 cc; Waters Corporation) that was pre-conditioned with methanol and deionized water. The sample-loaded SPE cartridge was then washed with 3 mL of 2% formic acid. The analytes were eluted with 1 mL of 5% NH_4OH in methanol. The eluate was evaporated under nitrogen stream at 30°C and reconstituted in 100 µL of 0.1% formic acid before quantification using LC-MS/MS method.

For LC-MS/MS analysis of epinephrine, the liquid chromatographic separation was performed using an Acquity™ Ultra Performance LC (Waters Corporation) and a C18 column (Gemini® NX C18, 3 µm, 150 × 2.0 mm Phenomenex, Torrance, CA, USA). The mobile phase consisted of 2% formic acid in water (A) and 100% acetonitrile (B). The separation was run at a flow rate of 0.2 mL/min using the following gradient elution profile: 0-2 min, 2% B; 2-3 min, 2%-10% B; 3-3.5 min, 10% B; 3.5-4.5 min, 10%-2% B; and 4.5-6 min, 2% B (for a total run time of 6 minutes). The retention times for epinephrine and lamivudine were 2.2 minutes and 4.3 minutes, respectively. For mass spectrometry (MS) analysis, the mass spectra were analyzed using a Quattro Premier™ XE Tandem Quadrupole Mass Spectrometer (Waters Corporation). Multiple reaction monitoring (MRM) mode was used with electrospray ionization (ESI) source in positive mode. The mass transition ion-pairs

for epinephrine $[M + H]^+$ ions were selected as 184.07 > 106.98 and 184.07 > 166.07 m/z. For lamivudine, the mass transition ion-pair was 230.11 > 111.97 m/z. Data acquisition was performed using MassLynx 4.1 mass spectrometry software (Waters Corporation).

Data Analysis

To determine the rate and extent of epinephrine absorption, the area under the plasma concentration-time curve at time 0-180 minutes ($AUC_{0\text{-}180\ min}$) was calculated using the linear trapezoid method. In this calculation, the difference between the plasma epinephrine concentration at each time point and the baseline plasma epinephrine concentration was used to determine the baseline-adjusted $AUC_{0\text{-}180\ min}$. Statistical analysis was performed using GraphPad Prism 9.1.0 (GraphPad Software Inc., San Diego, CA, USA). The pharmacokinetic parameters $C_{baseline}$, T_{max} and $AUC_{0\text{-}180\ min}$ were analyzed using Dunnett's T3 post hoc test following Brown-Forsythe analysis of variance (ANOVA). For C_{max}, the values of which were not normally distributed, Kruskal-Wallis test followed by Dunn's multiple comparison test was used. Differences were considered statistically significant at a *p*-value less than 0.05.

Results

In this study, 12 healthy adults were recruited, and each subject received IN saline, IN epinephrine 5 mg, and IM epinephrine 0.3 mg on separate days (at least 14 days apart). As shown in **Figure 1A and 1B**, IN epinephrine 5 mg showed significantly higher systemic absorption over 180 minutes compared to that of IN saline. The corresponding $AUC_{0\text{-}180\ min}$ (mean [median] ± standard deviation) was 4.0 (4.9) ± 4.0 and 0.2 (0.5) ± 0.3 ng.min/mL respectively; $p = 0.02$). Epinephrine absorption was not significantly different between the IN route and the IM route ($p = 0.16$); however, the $AUC_{0\text{-}180\ min}$ for IN epinephrine was about 0.5-fold that for IM epinephrine (10.0 [9.2] ± 8.6 ng.min/mL). The other pharmacokinetic parameters, i.e., plasma epinephrine concentration at baseline ($C_{baseline}$), peak plasma epinephrine concentration (C_{max}), and time to reach C_{max} (T_{max}), were also not significantly different between the IM and IN routes of epinephrine administration (**Figure 1C-E**). The C_{max} values for the IM and IN groups were 209 ± 228 and 120 ± 53 pg/mL, and the T_{max} values were 41 ± 41 and 41 ± 34 minutes, respectively. All pharmacokinetic parameters for the three administrations are summarized in **Table 1**.

During the study, increases in heart rate and blood pressure (both diastolic and systolic) were consistently observed at the time of peak plasma epinephrine concentration during both IN and IM epinephrine administrations. Transient and mild adverse reactions were observed after IN epinephrine treatment in this study. One subject experienced short-term palpitation during the study period, ten subjects felt transient nasal stinging, and another had bloody mucus nasal discharge. All adverse reactions were resolved within one day. For IM epinephrine injection, a serious adverse event was observed in one female subject. She developed hypotension, bradycardia and chest pain within 5 minutes after the injection, which was treated with intravenous saline loading. After consultation with cardiologists, a right coronary artery spasm was suspected; however, her symptoms resolved spontaneously and no further treatment was required.

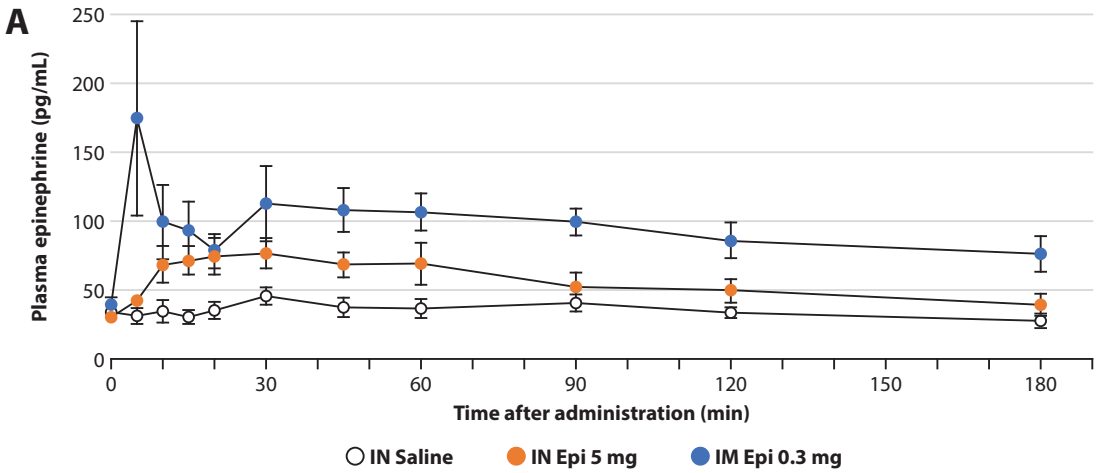

Figure 1. The pharmacokinetics of epinephrine (EPI) after administration of intranasal (IN) saline, IN epinephrine (5 mg), and intramuscular (IM) epinephrine (0.3 mg). A) Plasma epinephrine concentrations at different time points after saline or epinephrine administration (mean ± standard error of the mean). B) Area under the plasma concentration-time curve from t = 0 to 180 minutes ($AUC_{0\text{-}180\ min}$). C) Baseline plasma epinephrine concentration ($C_{baseline}$). D) Maximum plasma epinephrine concentration (C_{max}). E) Time at which maximum plasma epinephrine concentration is achieved (T_{max}). The plots are shown as individual values and mean ± standard deviation. Significant difference is indicated as follows: $^*p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. (Abbreviation: ns, non-significant).

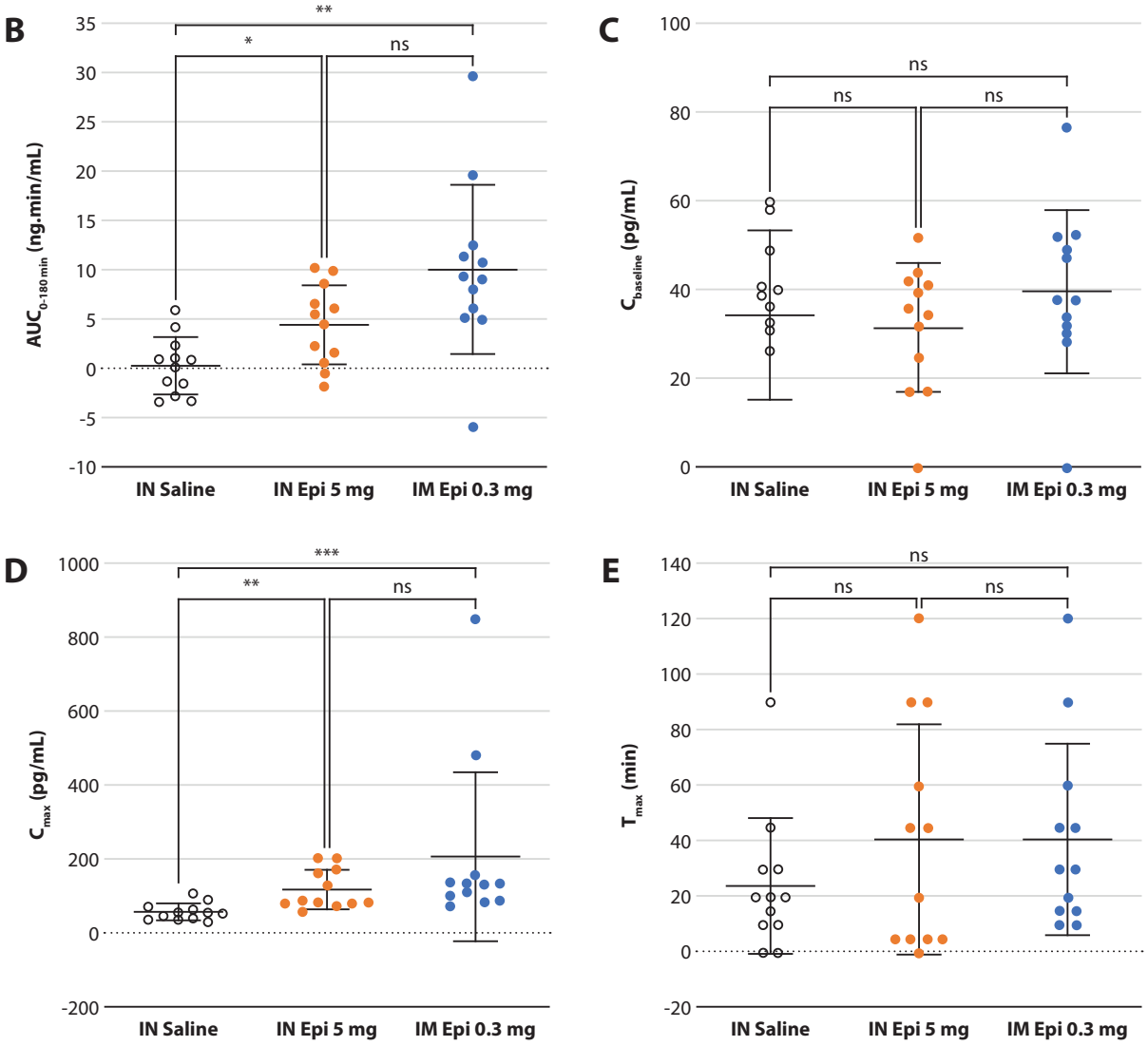

Figure 1. (Continued)

Table 1. Pharmacokinetic parameters of epinephrine after administration of intranasal saline, intranasal epinephrine (5 mg), and intramuscular epinephrine (0.3 mg)

Parameters	Intranasal Saline	Intranasal Epinephrine 5 mg	Intramuscular Epinephrine 0.3 mg
$C_{baseline}$ (pg/mL)	34 (38) ± 19	32 (35) ± 14	40 (38) ± 18
C_{max} (pg/mL)	61 (57) ± 23	120 (88) ± 53	209 (136) ± 228
T_{max} (min)	24 (20) ± 24	41 (30) ± 34	41 (33) ± 41
$AUC_{0\text{-}180\ min}$ (ng.min/mL)	0.2 (0.5) ± 0.3	4.4 (4.9) ± 4.0	10.0 (9.2) ± 8.6

Data presented as mean (median) ± standard deviation

Discussion

Nasal mucosa is a promising site for systemic drug absorption because it is rich in vasculature and is highly permeable. Our previous study in 5 healthy adults[13] showed that epinephrine 5 mg can be well absorbed into the systemic circulation via nasal mucosa, and that its bioavailability is comparable to that of IM epinephrine 0.3 mg. In the present study, which was conducted in a larger group of 12 healthy subjects, we confirmed the previous findings. Several studies in dogs also showed comparable systemic absorption between IN epinephrine 5 mg and IM epinephrine 0.3 mg.[14,15] However, we found that although the pharmacokinetic parameters (i.e., $AUC_{0\text{-}180\ min}$, C_{max} and T_{max}) of the IN 5 mg and IM 0.3 mg groups were not significantly different (p values of 0.16, > 0.99 and > 0.99, respectively), the amount of epinephrine absorption via IN, based on the average $AUC_{0\text{-}180\ min}$ and C_{max}, was about 0.5-fold that via IM. It is possible that the systemic

absorption of epinephrine via IN at 5 mg might not be comparable to that via IM at 0.3 mg but the differences could not be statistically detected due to the seemingly inadequate number of subjects. Therefore, further studies in larger sample sizes are needed to confirm this notion.

In contrast to the IM epinephrine absorption, high variability in IN absorption among the subjects was observed. As shown in **Figure 2**, some subjects had epinephrine absorption via IN comparable to or even better than that via IM. However, about one-thirds of the subjects (i.e., no. 2, 4, 6, and 10) showed poor nasal epinephrine absorption with the level comparable to that of the control IN saline. The inadequate systemic absorption would be of great concern as it might result in treatment failure particularly during life-threatening anaphylaxis. The inter-subject variation could be due to histological, anatomical, and physiological differences in the nasal cavity among our healthy subjects, and these factors have been reported to impair IN epinephrine absorption.[16] One of the physiological factors, i.e., the nasal cycle, which causes alternating partial congestion and decongestion of the nasal cavities in humans and other animals,[17] has been shown to affect mucociliary clearance and IN absorption.[18,19] In this study, epinephrine was applied into one randomly-selected nostril, which might be more or less optimal for drug delivery, resulting in low epinephrine absorption in some subjects. Furthermore, variability of IN absorption could be more pronounced if it is applied in the general population because the prevalence of common nasal disorders,

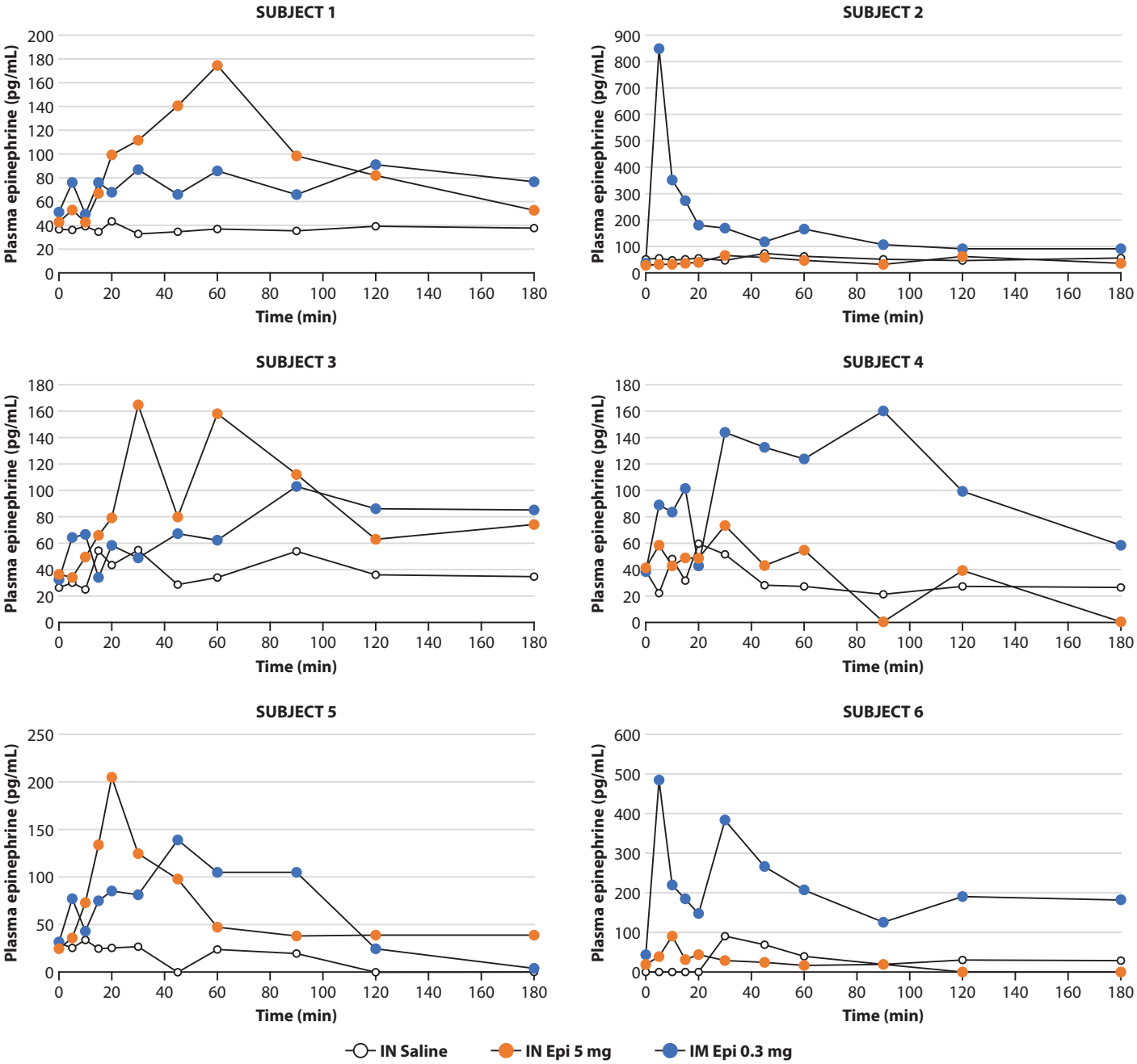

Figure 2. Plasma epinephrine concentrations at different time points of each subject (no.1–12) after administration of intranasal (IN) saline, IN epinephrine 5 mg, and intramuscular (IM) epinephrine 0.3 mg.

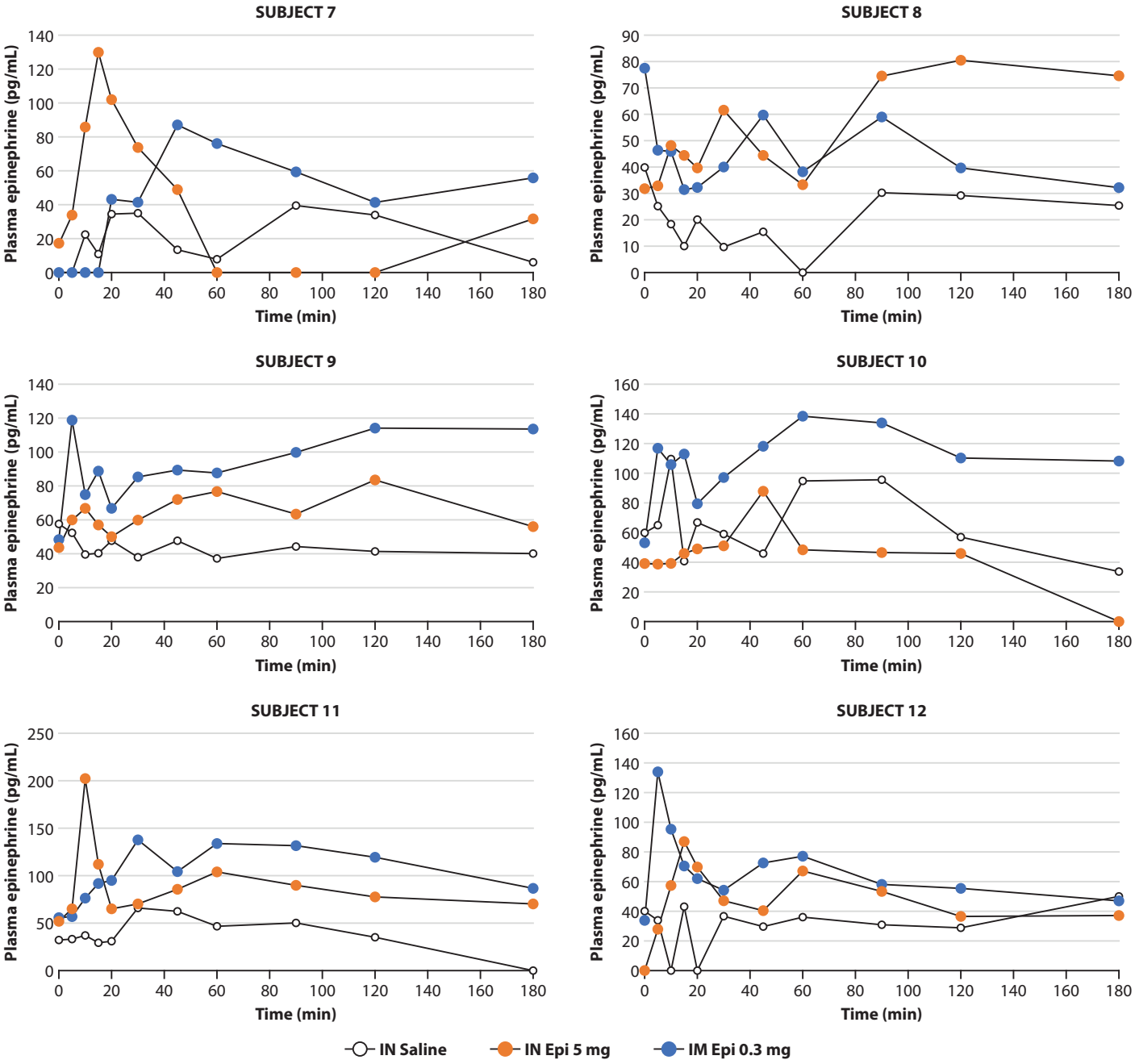

Figure 2. (Continued)

e.g., nasal polyps, allergic and non-allergic rhinitis, is quite high (up to 40% of the population).[20] These disorders affecting nasal mucosa could potentially interfere with the IN absorption of epinephrine. Thus, the roles of these factors, both physiological and pathological, in IN epinephrine absorption require further investigations to ascertain that systemic absorption via IN is adequate and consistent in all subjects.

Several approaches could be used to improve the IN epinephrine absorption to achieve the bioavailability comparable to that of the conventional IM injection. For example, IN epinephrine at higher doses (> 5 mg) and concentrations (> 40 mg/mL) should be studied; more epinephrine could theoretically be absorbed across the nasal mucosa due to the increased amount and concentration gradient. In addition, the nasal spray should be prepared using formulations that offer superior physicochemical stability of epinephrine, both ex-vivo and in-vivo (e.g., using a buffer solution with an optimal pH and/or addition of antioxidants). Drugs with vasodilatation effect (e.g., alpha-adrenergic receptor antagonist, such as phentolamine) might be added into the formulation to reduce the vasoconstriction effect of epinephrine, which prevents its own systemic absorption.[9] Moreover, the use of absorption enhancers may increase intranasal epinephrine absorption. Several different absorption enhancers have been used to improve intranasal delivery of various drugs in preclinical studies.[21-24] Recent studies investigated intranasal epinephrine absorption of an epinephrine nasal spray (ARS-1) that includes an absorption enhancer (Intravail™) in the formulation.[25] The nasal spray demonstrated enhanced nasal absorption of epinephrine. Even at an IN dose as low as 1 mg,

the absorption was comparable to that of an IM dose of 0.3 mg, and absorption occurred more rapidly,[26,27] suggesting the potentially important role of absorption enhancers in facilitating transmucosal delivery of epinephrine.

Conclusion

Epinephrine can be significantly absorbed via the IN route in humans. IN administration of epinephrine seemed to be feasible, less invasive, and not associated with serious adverse effects. Although the bioavailability of IN epinephrine 5 mg was not statistically different from that of IM epinephrine 0.3 mg, the amount of epinephrine absorption via IN was about 0.5-fold that via IM. In addition, high variability in IN absorption among subjects was observed with about one-thirds of them showing poor nasal absorption. Thus, further studies are needed for IN epinephrine administration to achieve an adequate and consistent systemic absorption comparable to that of the conventional IM injection.

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Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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