Short Communication

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Use of a liquid chromatography-tandem mass spectrometry method to assess the concentration of epinephrine, norepinephrine, and phenylephrine stored in plastic syringes

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Abstract

Objectives: There are concerns about the potency of epinephrine (EPI), norepinephrine (NE), and phenylephrine (PE) stored in syringes for later infusions in clinical care. The objective of our study was to optimize a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method to determine the concentrations EPI, NE, and PE dissolved in normal saline and stored in 50 mL 3-part Becton Dickinson syringes.
Methods: Medications were diluted in normal saline to 80 µg/mL for EPI and NE, and 100 µg/mL for PE. The solutions were stored in syringes for 0 (fresh), 3, and 7 days in a medical refrigerator. United States Pharmacopeia grade EPI, NE, and PE and their deuterium-labeled analogs were used as calibration standards. Stored samples and standards were diluted and analyzed by LC-MS/MS operated in selected reaction monitoring mode.
Results: The calculated limit of quantification for EPI, NE and PE were well below the concentrations used in clinical practice. The coefficient of variation remained below 12 % for all samples. The standard linear calibration regressions for EPI, NE, and PE had r^2 values of between 0.96 and 0.98 ($p < 0.001$). EPI and NE stored in the refrigerator remained within 10 % of the of their initial concentrations at all time points. The concentration of PE in syringe decreased by 19.85 % at 3 days, with no further decrease at 7 days, compared to fresh PE.
Conclusions: The sample preparation steps and optimized LC-MS/MS method allowed simple and reliable measurements of EPI, NE, and PE.

Keywords: adsorption; epinephrine; liquid chromatography-mass spectrometry; norepinephrine; phenylephrine; sympathomimetic; syringes.

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Introduction

Epinephrine (EPI), norepinephrine (NE), and phenylephrine (PE) are sympathomimetic medications commonly used in anesthesia and intensive care to help manage hypotensive states [1]. Traditionally, these vasoactive medications have been diluted to 10–20 µg/mL in sterile 0.9 % w/v solutions of NaCl, also referred to as normal saline (NS) [2]. These medications are usually prepared in plastic bags and administered to patients through high-volume infusion pumps. This procedure is currently being revised, and smart syringe infusion pumps containing higher concentrations of these medications (80–100 µg/mL) are being used. Low infusion rates have the advantage of decreasing the volume load in critically ill patients [3, 4].

The Food and Drugs Administration (FDA) and Health Canada received reports about decreased concentrations up to 50 % of multiple compounded medications stored in BD 3-part syringes because of adsorption of drugs in the

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rubber stoppers [5, 6]. As a result, those institutions do not recommend storing compounded medications in syringes. Although BD discontinued using the rubber stopper material in their syringes, concerns regarding drug potency remain unresolved [5]. As a result, many hospital pharmacies and the pharmaceutical industry have limited their pre-mixed presentations to mini-bags and glass syringes since there is lacking information on this subject.

In addition to the potential syringe interaction, these medications can degrade with basic pH, and exposure to heat and light [7–9]. Previous studies recommend their preparation with diluents in acidic pH, storage protected from UV light and refrigerated [10, 11].

Conflicting information regarding the stability of sympathomimetic medications has been previously reviewed [12] Stability studies have quantified these drugs using fluorometric analyses, high-performance liquid chromatography (HPLC), and HPLC coupled with electrochemical detections, or ultraviolet (UV) detection for drug quantifications [10, 11, 13–15]. Alternatively, liquid chromatography combined with mass spectrometry (MS) has been used. The strengths and weaknesses of MS compared to other detectors are well known [16]. Most importantly, quantification using LC-MSMS techniques are more resilient to cross-talk (false positive) signals from degradation products.

Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) has in fact already been used to accurately quantify catecholamines in biological samples such as urine and serum [17, 18]. However, the preparation steps required to produce LC-MS compatible samples use costly, time and labour-intensive procedures such as solid phase extractions, liquid-liquid extractions, solvent-based precipitations, derivations, filtrations, etc. [18].

The objective of this study was to optimize a LC -MS/MS method for the quantitative analysis of EPI, NE, and PE diluted in NS solution at concentrations of 80 µg/mL, 80 µg/mL, and 100 µg/mL respectively, measured at 0, 3 and 7 days, and stored in 3-part BD syringes refrigerated and protected from ultraviolet light (UV). In addition, this study aimed to conduct a statistical power analysis to estimate the sample size in future stability studies up to fourteen days as stated by the USP <797>, which accepts sterile compounded medications preparations to be used without microbiologic or toxins testing [19]. To our knowledge, the study presented herein is the first quantitative study showing the detection of EPI, NE, and PE in clinical formulations (0.9 % saline solution) using LC-MS/MS.

Materials and methods

Approval from the Nova Scotia Health Authority Research Ethics Board was waived for this non-clinical laboratory-based study. Medication concentration measurements were performed at the Biological Mass Spectrometry Core Facility located at the Dalhousie University Life Sciences Research Institute.

Calibration standards

Research grade (purity >99.9 %) NE, EPI, and PE (MilliporeSigma, Part Numbers: 489,350, E-4250, and PHR1017, respectively), and their respective deuterium-labeled “heavy” analogs (MilliporeSigma, Part Numbers: N-069-1ML, E-077-1ML, and PN: P-079-1ML) were used to obtain calibration curves. For reference, the molecular structures and expected mass-to-charge (*m/z*) values of the protonated $[M+H]^+$ molecular ions for each drug are shown in Figure 1. Fresh stock solutions of NE, EPI, and PE were prepared at a concentration of 1 mg/mL in H_2O. Stock solutions of each drug were diluted using normal saline solution. The final calibration standards for EPI, NE and PE were 80, 70, 60, 40 µg/mL, 42, 37, 32, 21 µg/mL and 100, 90, 80, 60 µg/mL, respectively. It should be noted that the NE standard (Sigma PN 489350) is sold as a bitartrate salt whereas the clinical drug (Levophed, Pfizer Canada Inc. Kirkland, Quebec) concentrations are expressed in its base form; therefore, the concentration of NE standards had to be adjusted accordingly.

Sample preparation

The experimental test samples were prepared using commercially available vials of EPI 1 mg/mL (Alveda Pharmaceuticals Inc. Toronto, Ontario), NE 4 mg/4 mL (Hospira, Pfizer Canada Inc. Kirkland, Quebec), and PE 10 mg/mL (Sandoz Canada Inc. Boucherville, Quebec). Four vials of EPI (4 mg), one vial of NE (4 mg), and 0.5 mL of the vial (10 mg/mL) of PE were individually diluted with NS solution (100 mL bags, Baxter Corporation Mississauga, Ontario) to complete a solution of 50 mL, for concentrations of 80 µg/mL for EPI and NE, and 100 µg/mL for PE. These concentrations are used in our clinical practice. A staff anesthesiologist (VN) performed all dilutions using routine aseptic technique. Diluted medications were stored in 3-part Becton Dickinson 50 mL syringes (Product N. 309653, Mississauga, Ontario, Canada), protected from UV radiation with plastic amber bags, and stored in a medical refrigerator (5 °C–8 °C) for 3 and 7 days before testing. In addition, fresh samples were prepared on the day of analysis (less than 4 h before testing). Staggered sample preparation allowed all samples to be analyzed on the same day, thus reducing operator and instrumental variability. Randomly labeled samples were prepared in triplicate, with analytical LC-MS/MS operators blinded to the preparation date.

A 15:85 v/v mixture of 30 mM ammonium formate pH 3.0 and acetonitrile was prepared and named the dilution buffer (DB). Both the working calibration solutions and syringe samples of EPI, NE, and PE were further subjected to two consecutive dilutions with DB, as described in Supplementary Table 1.

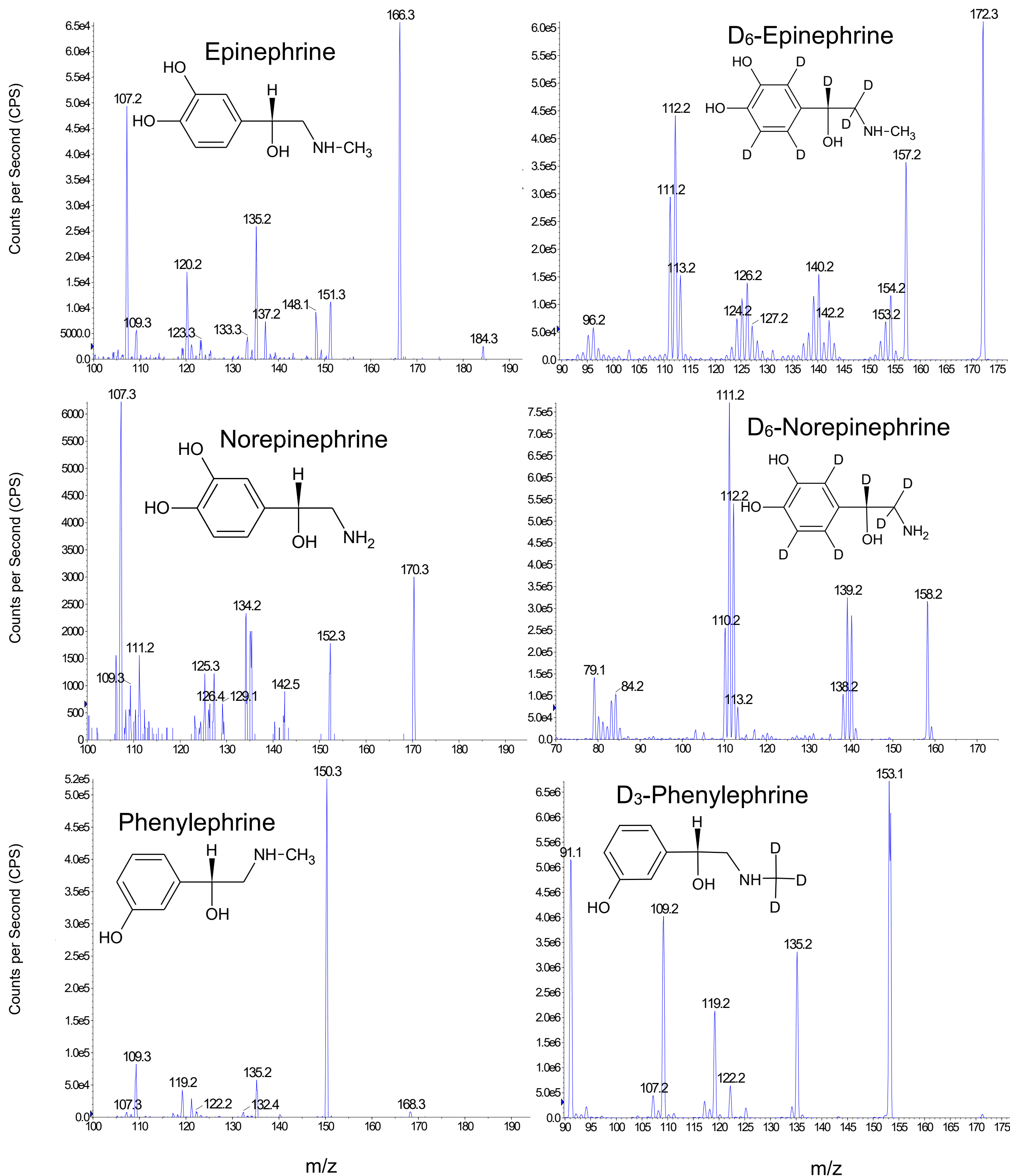

Figure 1: Product ion spectra of EPI, NE, and PE (left top, middle, and bottom left panes, respectively) obtained from CID fragmentation of the $[M+H]^+$ precursor ions at *m/z* 184.1, 170.1 and 168.1. The product ion spectra of deuterated standards (D_6-EPI, D_6-NE, and D_3-PE) are observed in right top, middle, and bottom right panes, respectively. The latter were obtained by the CID fragmentation of the $[M+H]^+$ precursor ions at *m/z* 190.1, 176.1 and 171.1, respectively.

LC-MS/MS analysis

LC-MS/MS methods were based on previously published methods on quantification of urinary catecholamines with the following adaptations [17]. The calibration standards and the syringe samples prepared at different time points were analyzed through LC-MS/MS using a 1,290 Infinity II Liquid Chromatograph (Agilent Technologies, Santa Clara, CA, USA) coupled to a Qtrap5500 (Sciex, Framingham, MA, USA) triple quadruple linear ion trap tandem mass spectrometer equipped with a turbo electrospray ion source, operated in selected reaction monitoring (SRM, also known as MRM, multiple reaction monitoring). Chromatographic separation was performed by injecting a 10 µL sample onto a Hypersil GOLD hydrophilic interaction chromatography (HILIC) (150 × 1 mm, 3 µm) column heated at 40 °C across a 2-min gradient starting at 15 % Buffer A (100 % water containing 30 mM ammonium formate, pH 3.0) and 85 % of Buffer B (100 % acetonitrile), ending under the same conditions. The detailed chromatographic gradient conditions and SRM transition list are included in Supplementary Tables 2 and 3. The starting LC flow rate was set to 200 µL/min. A 500 °C heat-assisted electrospray source (Turbo Ion Spray) was used for ionization; curtain gas was kept at 20 units and Gas 1 and 2 at 30 units (Analyst 1.6.3 software arbitrary units). The ionization spray voltage was set to 4.5 kV for the positive ionization mode. Isotope-labeled internal standards were spiked into each sample. Each target was identified using a diagnostic transition within a particular retention time window [17].

To optimize the collision energy (CE) for SRM, we used Skyline Software (see Data Analysis) to generate an acquisition method containing ramped CEs for each of the transitions (Supplementary Material Table 3). This temporary method was used on the LC-MS/MS system to analyze EPI, NE, and PE standards prepared at 100 µg/mL concentrations.

Data analysis

Data were acquired using the Analyst 1.6.3 software (Sciex, Framingham, MA, USA) and later analyzed using Skyline© [20]. The area under the curve (AUC) corresponding to the SRM transitions for the unlabeled "light" target drugs (NE, EPI, or PE) and their corresponding isotope-labeled "heavy" analogs was measured for both syringe experimental samples and calibration standards. The light/heavy AUC ratios were calculated and used as dependent variables to construct the calibration curves. The concentrations of EPI, NE, and PE in the stored syringe samples were computed by interpolating the experimental AUC light/heavy values on the corresponding linear regression curves [20], The anticipated precision and accuracy of the analysis using stable isotope-labeled standards is <5 % (average intra-assay variations <2.9 % and inter-assay variations <4.6 %) based on the existing literature [17].

Statistical analysis

Linear regression analysis of the calibration curves with 95 % confidence intervals (CIs) for the calibration standard was performed using RStudio 2021.09.0 + 351. Data from this study were used to calculate the sample size for a future study to analyze the stability of these three medications over four time periods—0 (fresh), 3, 7, and 14 days—using three syringe brands. Power analysis was performed using the R package pwr©.

Results

As a first step toward the development of the LC-MS/MS method, we initially analyzed the unlabeled (referred herein as "light") and deuterated "heavy" standards acquiring the product ion spectra (MS/MS) of the corresponding $[M+H]^+$ precursor ion. The MS/MS spectra for both light and heavy standards prepared at 100 ug/mL are shown in Figure 1. The product ion spectra obtained using our instrument show the same characteristic fragment ions as those observed in the mzCloud ms/ms spectrum library repository (http://www.mzcloud.org/).

The sensitivity and detection limits of the SRM methods depend on the signal-to-noise ratio produced for each transition. The signal produced for each transition depends on the CE applied to fragmentation during collision-induced dissociation (CID). Therefore, we optimized the CE for each transition by analyzing EPI, NE, and PE standards using a stepped CE acquisition method, as shown in Supplementary Figure 1A, B, and C. The normalized peak areas for each CE (vertical bars) are shown in the inset of each figure. The optimal CEs for each transition were selected as the most intense among these signals. In addition, as observed in these figures, NE (retention time: 0.8 min) was chromatographically resolved from PE and EPI (retention time: ~0.6–0.7 min).

Once the optimization of the LC-MS/MS parameters was finalized, we continued analyzing the calibration standards and test samples from the study. The AUC ratios (light/heavy) for the EPI, NE, and PE calibration standards showed a strong linear signal-to-concentration correlation. Linear regression analysis for EPI, NE, and PE calibration revealed r^2 values of 0.96, 0.97, and 0.98, respectively ($p<0.001$ for each; see Figure 2). In addition, the r^2 values are improved when the light/heavy AUC ratios are used compared to those obtained from the identical graph in which the absolute AUC intensity signal of the light standard is used as the dependent variable.

The calculated limits of detection (LoD) for EPI, NE and PE were 7.9, 6.4 and 14.0 µg/mL as recommended by published guidelines [21]. Briefly, the LoD=LoB + 1.645 × SD [low concentration sample], where the interpolated concentration of blank samples was used for limit of blank (LoB), and the 40 µg/mL standard were used as low concentration points. The limits of quantification (LoQs) for EPI, NE and PE were 26.0, 21.2 and 46.3 µg/mL, respectively. These were calculated as LoQ=3.3 × LoD as reported in literature [22].

The reproducibility of the method was estimated by monitoring the signal of the internal standards that were spiked in equal amounts to all calibration standards and

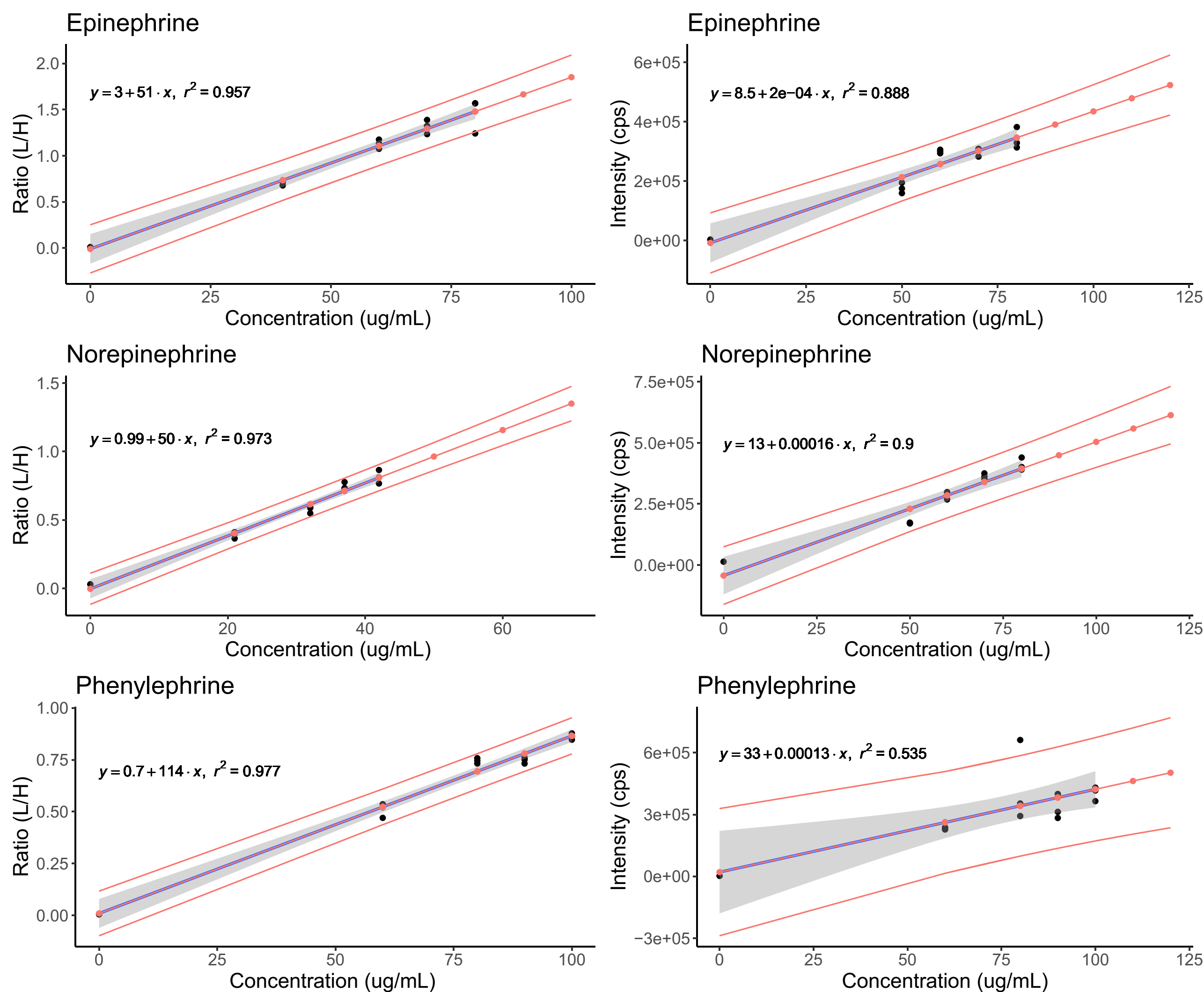

Figure 2: Linear regression calibration curves of epinephrine (top), norepinephrine (middle), and phenylephrine (bottom). The L/H AUC ratios (left column) show improved r^2 when compared to the absolute AUC intensity values of the light standards using identical datasets. Black dots represent triplicated experimental values obtained from the pure standard dilutions. Red dots and inner line correspond to extrapolated values along the regression equation. Outer red lines represent 95 % confidence intervals.

samples. These values were also used as surrogate quality controls signal and retention time parameters (Electronic Supplementary Material Table 4). The coefficient of variation (CV) % for EPI, NE and PE were 11.4, 5.5 and 20.9 %, respectively. Note that the CV% for PE dropped to 8.9 % when one replicate (Standard at 80 µg/mL) outlier was removed.

The mean concentrations of EPI, NE, and PE on day 0 (fresh) were 104.63, 80.45, and 118.97 µg/mL, respectively. The percent change in concentration at 3 and 7 days of storage for EPI and NE compared to the fresh drug concentrations was less than 10 %. However, the PE samples showed a 19.85 % after 3 days of storage but no further decrease at 7 days (Supplementary Table 5 and Figure 3).

The statistical power analysis determined a sample size of four syringes for each of the three syringe brands and for each time of the four periods of time (fresh, 3, 7, and 14 days) to identify a 10 % decrease in the concentration of the medication, with an alpha of 0.05 and power of 0.8.

Discussion

The sample preparation of the NS solutions turned out to be one of the most challenging steps of our method development. The intravenous formulations of EPI, NE, and PE used in anesthesia are commonly prepared in NS solution. This relatively simple matrix presents a challenge to LC-MS/MS, as the high sodium chloride concentration of NS solution produces precipitation in the MS ionization source and reduces the signal due to ion suppression and formation

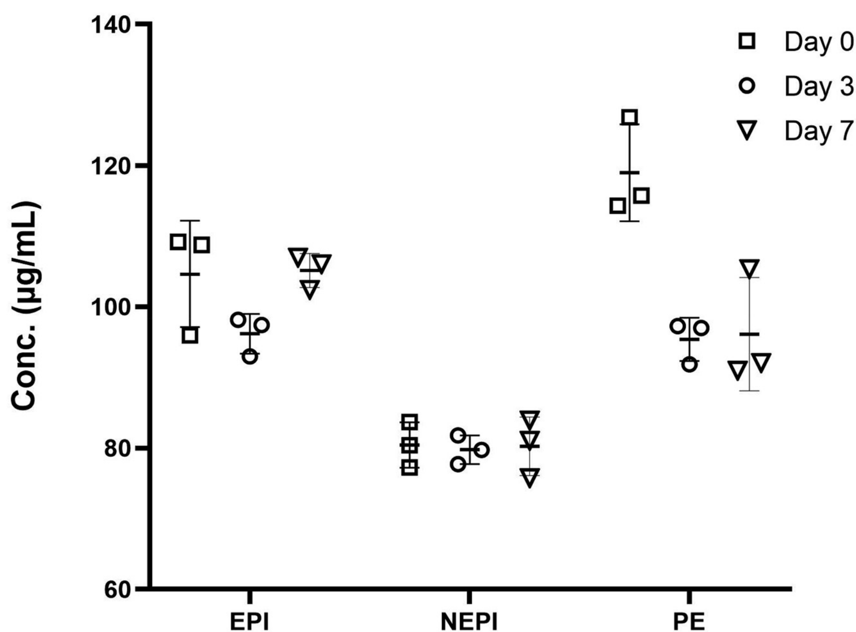

Figure 3: Concentrations and standard deviations (±1SD) of epinephrine, norepinephrine, and phenylephrine at days 0 (fresh), 3, and 7 days.

of sodium adducts. We empirically tested a variety of dilutions that would provide both a strong signal-to-noise ratio and concomitantly reduce the saline (NaCl) concentration to levels that would not compromise the performance of the LC-MS/MS system.

Various stationary phases have been used for the chromatographic separation of these drugs. Many of the studies found in the literature have employed C18 based reversed-phase LC to separate these compounds [18, 23]. In our experience, polar compounds are better resolved using a HILIC stationary phase, which uses an ethylene-bridged hybrid (BEH) amide column.

The MS parameters must also be carefully selected and optimized to improve the analytical results. Although most of the published studies using LC-MS/MS have relied on single SRM transitions, we decided to increase the number of transitions per molecule to increase specificity. Two product ions per precursor ion were selected for each drug to develop the final SRM method (see Supplementary Table 3).

As commonly observed in LC-MS/MS studies, the use of stable isotope-labeled internal standards reduces the variability introduced by the LC auto-sampler and corrects for instrumental signal drift across the entire data acquired. An example of this phenomenon can be seen in the PE calibration curve (Figure 2-Bottom), where an outlier corresponding to the 80 µg/mL standard (right panel) is corrected when the light to heavy ratio is computed as the dependent variable (left panel). In the present study, all internal standards were individually spiked into each tube by manual pipetting in the last step prior to LC-MS/MS analysis (see Supplementary Table 1, dilution II). Since then, we have improved this procedure by using a stock solution of the final dilution buffer containing an equivalent concentration of internal standards, thus further reducing the variability caused by pipetting.

Finally, the analysis of the fresh samples for EPI (104.63 µg/mL) and PE (119.97 µg/mL) showed higher than the intended concentrations (80 and 100 µg/mL, respectively). This result could be explained by the overfilling factor, i.e., commercially available medication vials often contain more than the stated dose. The four vials of EPI were found to exhibit a final volume of 5 mL instead of 4 mL, with a concentration of 1 mg/mL; this finding explained the final concentration of the mixture at approximately 100 µg/mL. All medications were prepared following current clinical practices measuring medications with graduated syringes, not laboratory calibrated pipettors. This could explain the variation in the concentration of the fresh PE preparation being higher than expected since all syringes were prepared with 0.5 mL of PE stored in vials at the 10 mg/mL concentration. The U.S. Pharmacopeia recommends up to an additional 0.1 mL or 10 % overfill for a 1 mL dose vial [19]. The amount of overfill is different between products and depends on vial size, dose, and other factors [24].

Another potential source of error could be explained by the preparation of the calibration standards. In the present study, EPI, NE and PE standards were prepared using very small quantities (around 10 mg each) of research-grade drugs in 10-mL volumetric flasks. We suggest the following recommendation to improve the accuracy and precision: research-grade standards should be replaced with USP-grade drugs, and final calibration solutions should be

prepared in larger volumetric flasks (25 or 50 mL volumetric flasks).

The highest concentration of NE used to create the calibration curve was 42 µg/mL; as such, we extrapolated our calibration curve to 80 µg/mL (Figure 2, middle pane) under the assumption we are working within the linear response of the MS detector. This oversight was the consequence of using research-grade norepinephrine bitrate monohydrate (molar mass=337.28 g/mol), which has a considerably higher molar mass than the clinical NE base (molar mass=169.18 g/mol). In spite of this, the NE values obtained from our study fell within the expected 80 µg/mL range. Our calibration standards for NE will be adjusted accordingly in future studies.

Although this study was not powered to demonstrate the stability of the medications tested, the average phenylephrine concentration was 19.85 % lower in samples stored for 3 days than in fresh preparations and was well below the USP standard of 10 % of the fresh preparation but still within ±10 % of the expected concentration. This decrease in concentration could have multiple explanations, including the adsorption to the syringe plungers, pre-analytical and analytical errors.

Sample preparation for the LC-MS/MS methods demonstrated high throughput (acquisition times <2 min per sample) and good reproducibility. All our samples were acquired within a few hours of LC-MSMS instrument time. Intra-day instrumental variability was estimated on the signal produced by the labeled -heavy- drugs, which were equally spiked to all samples and standards (Supplementary Material Table 4). We recommend the use of external Quality Control (QC) pooled samples to assess inter-day variability.

A future study is planned with a larger sample size and three syringe brands to determine sympathomimetic medication stability when stored for up to 14 days. The maximum time for pharmacy-compounded sterile injectable medications accepted by the USP<797> without sterility or toxin testing is 14 days [19]. This future study will include the same medications at the same concentrations but will be adequately powered to determine stability based on the current study results. If these medications remain stable for 14 days, we can obtain useful information regarding their preparation by clinical pharmacists and storage for future use. Compounding these medications by pharmacists can decrease several safety issues related to the point of care medication preparation: errors in concentration, labeling, stability, sterility; preventing waste; and improving availability for emergencies [25].

In conclusion, a simple two-serial dilution step was compatible for quantitative determination of EPI, NE and PE by LC-MS/MS. All the medication preparations were found at the expected concentration range taking to account the over-filling factor. These findings will be further studied with a larger number of samples, multiple syringe brands and longer storage periods.

Availability data and materials

The datasets used and/or analysed during the current study are available from the Electronic Supplementary Material Table 4. The following link is for access to the public repository of mass spectrometry data: https://panoramaweb.org/cB9AvZ.url

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Author contributions: Alejandro Cohen Methodology, validation, formal analysis, investigation, resources, writing, review, editing, visualization, project administration. Luke Wiseman: Investigation, validation, writing, and editing. Ahmed Al Faraj: Investigation, validation, writing, and editing. Pantelis Andreu: Conceptualization, software, validation, formal analysis, writing editing. Richard Hall: Conceptualization, supervision, writing, editing. Victor Neira: Conceptualization, methodology, validation, investigation, writing, review, editing, project administration, funding acquisition. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Alejandro Cohen: Declares no conflicts of interest. Luke Wiseman: Declares no conflicts of interest. Ahmed Al Faraj: Declares no conflicts of interest. Pantelis Andreu: Declares no conflicts of interest. Richard Hall: Declares no conflicts of interest. Victor Neira: Declares no conflicts of interest.

Informed consent: Non-applicable for this laboratory based study.

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