A Clinical Trial Simulation Evaluating Epinephrine Pharmacokinetics at various Dosing Frequencies during Cardiopulmonary Resuscitation

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RUNNING TITLE
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KEYWORDS
epinephrine; pharmacokinetics; clinical trial simulation; CPR

WORD COUNT
2115

CONFLICT OF INTERESTS
no conflicts of interest

ABBREVIATIONS
ACLS-Adult Advanced Cardiovascular Life Support; AHA-American Heart Association; AUC-area under the concentration curve; CDC-Centers for Disease Control; COMT-catechol-O-methyltransferase, CPR-cardiopulmonary resuscitation; ICU-intensive care unit; PK-pharmacokinetic; PD-pharmacodynamic; PNMT-Phenylethanolamine N-Methyltransferase; ROSC-return of spontaneous circulation; SAPS-Simplified Acute Physiology Score

ABSTRACT
Objective: This article seeks to test the hypothesis that repeated 1mg intravenous epinephrine dosing intervals of 3-minutes and 5-minutes results in differences in the total drug exposure and the maximum epinephrine concentration using simulated cardiopulmonary resuscitation (CPR) dosing.

Methods: Published population pharmacokinetic parameters were identified in the literature and pharmacokinetic dosing simulations were conducted according to the 2015 American Heart Association guidelines for CPR in adults. The stochastic pharmacokinetic simulations were conducted in MATLAB and R for statistical programming.

Results: A total of 5000 simulations were conducted in MATLAB while 90,000 data points for the 3-minute dosing interval and 150,000 data points for the 5-minute epinephrine dosing interval resulted from pharmacokinetic simulations in R. The difference between the 3-minute and 5-minute dosing intervals for patients with a SAP score of 30, were found to be: Male
ΔAUC=2416 and ΔCmax=71, Female ΔAUC=1422 and ΔCmax=41, and for a 70kg patient ΔAUC=2968 and ΔCmax=90. While in virtual healthy participants, the differences were calculated to be ΔAUC=2658 and ΔCmax=81 for 3-minute and 5-minute dosing frequencies.

Conclusions: Epinephrine plasma levels during a simulated CPR scenario in a virtual patient population are dependent upon intravenous dosing intervals of either 3-minutes or 5-minutes. Based on the results of this clinical trial simulation, implications may exist that may require clinical studies investigating the influence of the 1mg epinephrine dosing frequency on the return of spontaneous circulation.

INTRODUCTION

This article seeks to identify if differences exist in epinephrine blood levels in virtual patients who are administered epinephrine at a dosing interval of either 3-minutes or 5-minutes. According to the most recent, 2015 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) epinephrine remains the primary drug of choice during resuscitation with a fixed dose of 1mg for Adult Advanced Cardiovascular Life Support (ACLS) every three to five minutes [1]. Do differences exist in epinephrine kinetics during simulated CPR scenarios in virtual adult patients of varying health backgrounds? This article will used published population pharmacokinetic parameters and dosing simulations will be conducted according to the 2015 AHA adult guidelines. Prior to the pharmacokinetic simulations, this article will review the reported sources of variability influencing epinephrine pharmacokinetics.

Endogenous epinephrine is produced by chromaffin cells, which are embryological neural crest in origin, and are located in the medullary region of the adrenal glands just superior to the kidneys [2,3]. Epinephrine is a catecholamine that stimulates both β1 and β2 adrenergic receptors which at low doses induces vasodilation and higher doses causes alpha adrenergic mediated vasoconstriction [4,5]. In the catecholamine synthesis pathway, as shown in Figure 1, epinephrine is the product of the conversion from norepinephrine to epinephrine via the Phenylethanolamine N-Methyltransferase (PNMT) enzyme. Exogenously administered epinephrine, via the intravenous route, undergoes extensive hepatic metabolism by the catechol-O-methyltransferase (COMT) enzyme that methylates the meta-hydroxyl group of the catechol nucleus [6]. Further, oxidative deamination of the side chain occurs by the two mitochondrial oxidase MAO-A and MAO-B enzymes [7]. The remaining metanephrine metabolites undergo renal elimination from the body [3].

There is published evidence suggesting that a gender difference in the metabolism of epinephrine exist. In an article by Boudikova and colleagues reported that men have a 30% greater COMT enzymatic activity when compared to women using hepatic tissue [8]. Further, an article by Worda and colleagues reported that the COMT codon 158 polymorphism effects the basal estrogen levels in women, further suggesting greater variability in COMT metabolism and influences of gender [9]. In psychiatry, COMT activity has also been found to be significantly higher in the erythrocytes of male patients when compared to female patients [10,11].

When considering drug interaction influences on epinephrine metabolism, Stratton and colleagues reported basal epinephrine plasma concentrations in ninety-five normal participants to be (mean ± standard deviation) 50 ± 22 pg/mL in supine rest, but 30 ± 4 pg/mL if study participants were receiving alprazolam, a benzodiazepine [12]. Further, during maximal exercise epinephrine plasma concentrations are reported to be 970 ± 324 pg/mL in healthy participants without co-administered drugs, but 520 ± 125 pg/mL (p=0.13) if the subject was undergoing alprazolam treatment during the same maximal exercise [12]. Therefore, various factors may contribute to variability in plasma concentrations.

During CPR cardiac output is of great interested. Cardiac output is influenced by heart rate, stroke volume, left-ventricular capacity, systemic vascular resistance, and the underlying autonomic (sympathetic and parasympathetic) nervous system regulation in patients [13]. Further, β1 and/or β2 adrenergic receptor polymorphisms may influence hemodynamic response to epinephrine stimulation in the systemic circulation [14,15]. However, when considering the clear average anatomical differences between genders, cardiac output variability may be evident simply due to left ventricular filling capacity; where men have larger filling volumes than women due to average size.

This may explain the reported gender differences in the rates of return of spontaneous circulation (ROSC) [16–18]. Herlitz and colleagues analyzed the results from 557 patients, with 39% being women, who underwent CPR during a five-year period in Sweden and found that the female gender had an improvement in survival, after correcting for baseline characteristics [18]. In a study by Yuen and colleagues that compared 473 patients, with 52% being women, who suffered from in-hospital cardiac arrest in Chicago Illinois, found a trend difference in ROSC favoring women, 60% of whom were of African-American [17]. In a larger study totaling 10,862 patients found that there was no difference in ROSC between men and women [16]. However, the study found as a woman’s age increases her probability of survival decreased, with her highest probability of survival being prior to age 47 [16]. Contrastingly, for men, survival actually
increased with age until 65-years-old and then decreased after the age of 65-years-old [16].

With this information as a background, the specific aim of this article is to test the hypothesis if repeated 1mg intravenous epinephrine dosing intervals of 3-minutes and 5-minutes results in differences in the total drug exposure and the maximum epinephrine concentration using simulated CPR scenarios. To do so, a clinical trial simulation will be conducted, using Monte-Carlo methods, evaluating the two dosing frequencies of 3-minutes and 5-minutes using AHA guidelines for adult CPR. The outcome of the dosing simulations will allow the quantification of the total epinephrine exposure, as area under the concentration curve (AUC), and the maximum epinephrine concentrations (Cmax). A final analysis evaluating the epinephrine plasma concentrations at the 10-minute time point and the 40-minute time point will be reported using the same virtual patient population pharmacokinetic parameters as in the AUC and Cmax analysis.

MATERIAL AND METHODS

Literature based Model Parameters
Pharmacokinetic model parameters are referenced from two published studies [19,20]. The first study is referenced from Abboud and colleagues in a patient population undergoing treatment for septic shock in the intensive care unit (ICU) and includes the following pharmacokinetic parameters: Vd=7.9 L, CL=127 L/hr/70kg/50 Simplified Acute Physiology Score (SAPS II units) (CV=33%).

The second study is referenced from population pharmacokinetic and pharmacodynamic (PK/PD) study published in the FASEB Journal, by Eugene and colleagues [20]. The Eugene et al parameters for healthy adults are: Vd=22.8 L (CV=28%), Ke=8.8 hr-1 (CV=13%), serum concentration at half-maximal cardiac output EC50=2486 pg/mL (CV=6%), resting cardiac output E0=4.94 L/min (14%), and the maximum cardiac output Emax=35 L/min (39%) from twenty-four healthy adult participants [20]. For simulations, patient demographics of body weight will be referenced from the average male and female in the United States of America, as reported by the Stratton and colleagues article [12].

RESULTS

Based on the United States Centers for Disease Control, the average weight for a male is 195.5 pounds (89kg) and 166.2 pounds (75.6kg) for women. Using the Abboud et al population parameters for an adult patient with a SAPS II score of 30, indicating a predicted mortality of only 10%, the following are the pharmacokinetic parameters for average sized American men and women: Vd=7.9 L, CL-Male=96.88 L/hr, CL-Female=82.3 L/hr, and CL-70kg=76.2 L/hr. The Eugene et al parameters for healthy adults are: Vd=22.8 L and CL=200.64 L/hr due to (CL = Vd * Ke). Figure 2 and Figure 3 illustrate the results for the dosing simulations comparing the aforementioned virtual patient characteristics studies at 3-minute and 5-minute dosing intervals.

Results of the total epinephrine drug exposure and maximum plasma concentrations are shown in Table 1. The difference between the 3-minute and 5-minute dosing intervals, for patients with a SAP score of 30, were found to be: Male ΔAUC=2416 and ΔCmax=71, Female ΔAUC=1422 and ΔCmax=41, and for a 70kg patient ΔAUC=2968 and ΔCmax=90. Using the Eugene et al healthy participants, the differences were calculated as to be ΔAUC=2658 and ΔCmax=81 for the 3-minute and 5-minute dosing frequencies using a healthy patient population pharmacokinetic model.

The results of the individual simulated epinephrine plasma levels in R resulted in 22,500 data points re-
presenting 50 virtual patients at the 3-minute epinephrine CPR dosing frequency and 37,500 data points for each 5-minute dosing frequency. The final total of simulated epinephrine plasma concentrations totaled 90,000 data points for the 3-minute file and 150,000 data points for the 5-minute file. Results of the virtual population plasma levels at the 10-minute time point are shown in Figure 4, while the results for the 40-minute time point is shown in Figure 5.

At the 10-minute time point, epinephrine plasma levels were estimated to be (mean ± s.d.) for simulated patients with SAPS scores of 30 as: average weight American females 3-minute 240.6 ± 19.6 ng/mL vs. 80.9 ± 9.1 ng/mL at 5-minutes, average weight American male at 3-minutes 217.6 ± 22.1 vs. 69.9 ± 9.4 ng/mL at 5-minutes, a 70kg patient at 3-minutes 246.2 ± 19.7 ng/mL vs. 89.2 ± 10.9 ng/mL at 5-minutes, and in a healthy study participant population at 3-minutes 96.9 ± 10.7 ng/mL vs. 35.1 ± 4.6 ng/mL at 5-minutes. The following are the virtual patient epinephrine concentrations for the forty-minute point in time: average weight American females 3-minute 308.3 ± 61.4 ng/mL vs. 110.5 ± 20.2 ng/mL at 5-minutes, average weight American male at 3-minutes 267.5 ± 61.3 vs. 93.2 ± 25.5 ng/mL at 5-minutes, a 70kg patient at 3-minutes 312.3 ± 52.4 ng/mL vs. 129.8 ± 34.5 ng/mL at 5-minutes, and in a healthy study participant population at 3-minutes 117.9 ± 13.0 ng/mL vs. 46.2 ± 6.4 ng/mL at 5-minutes.

**DISCUSSION**

This paper illustrated that epinephrine pharmacokinetics during a dosing simulation of repeated 1mg intravenous doses have great variability depending on a 3-minute or 5-minute dosing interval. The pharmacokinetic simulations show that epinephrine dosing at 5-minute intervals will result a large portion of the population not achieving the median epinephrine plasma concentration of 136.3ng/mL that Prengel and colleagues identified in patients who experienced successful resuscitations [23]. Further, at 5-minute intervals approximately half of the patients weighing less than 70kg will achieve the desired median plasma concentration of 136.3ng/mL, as found by Prengel and colleagues [23]. Target blood epinephrine concentrations may serve as a useful starting point and then appending multivariate factors to achieve successful patient reanimation may alleviate the known variability in CPR outcomes.

The average American male and female body-weights did not appear to significantly alter the maximum plasma concentrations during the simulations. However, extremely low and high body weights will result in varied volumes of distribution and thus affect the overall Cmax. In a study (n=836,289) that investigated if obesity influenced survival found that obese patients had improved survival to hospital discharge when compared with non-obese patients after experiencing in-hospital cardiac arrest [24]. Thus, considering a dosage adjustment based on the body-weight may not be warranted based the clinical trial simulation results. However, what appears to result in variability is the dosing interval at which epinephrine is administered. Thus, targeting a more precise dosing frequency may influence the outcome parameter of return of spontaneous circulation (ROSC) in patients. Further studies investigating the influence of epinephrine dosing intervals and plasma concentrations on the successful ROSC, during CPR, may improve cardiopulmonary resuscitation outcomes for the population and patient subgroups.

**CONCLUSION**

Epinephrine plasma levels during simulated CPR scenarios in a virtual patient population are dependent upon intravenous dosing intervals of either 3-minutes or 5-minutes. When stratifying by intravenous epinephrine dosing frequency, virtual patients administered intravenous doses at 3-minute intervals achieved greater plasma concentrations as compared to the 5-minute dosing frequency. Based on the results of this clinical trial simulation, pharmacokinetic implications exist that may require further clinical studies investigating the influence of 1mg epinephrine dosing frequencies on the rate of return of spontaneous circulation in patients.

**ACKNOWLEDGMENTS**

Research reported in this publication was supported by National Institute of General Medical Sciences of the National Institutes of Health under award number T32 GM008685. I would like to thank Dr. B. Eugene for providing help with this manuscript.

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MEDtube Science 2016, Jun 2(4), 8 - 15

**BIBLIOGRAPHY**


The catecholamine synthesis pathway with cofactors resulting in the formation of epinephrine.

Results of the 5000 stochastic pharmacokinetic simulations, in Matlab, illustrating the epinephrine concentration during cardiopulmonary resuscitation. The shaded regions depict the 10th to 90th percentiles of epinephrine plasma levels while the solid line illustrates the population mean. The results are for the following populations: (a) a three-minute epinephrine dosing frequency in patients weighing 70kg and a Simplified Acute Physiology Score II (SAPS II) score of 30; (b) a five-minute epinephrine dosing frequency in patients weighing 70kg and a SAPS II score of 30; (c) three-minute epinephrine dosing frequency in an average weight (65.6kg) American female with a SAPS II score of 30; (d) and a five-minute epinephrine dosing frequency in an average weight (65.6kg) American female with a SAPS II score of 30.

**Fig. 4.** Epinephrine plasma concentrations (ng/mL) at the 10-minute time point during the clinical trial simulation, in R, comparing the 3-minute and 5-minute epinephrine dosing frequencies during cardiopulmonary resuscitation among virtual patient groups. Epi: epinephrine, SAPS: Simplified Acute Physiology Score II.

**Fig. 5.** Epinephrine plasma concentrations (ng/mL) at the 40-minute time point during the clinical trial simulation, in R, comparing the 3-minute and 5-minute epinephrine dosing frequencies during cardiopulmonary resuscitation among virtual patient groups. Epi: epinephrine, SAPS: Simplified Acute Physiology Score II.
FIG 1. THE CATECHOLAMINE SYNTHESIS PATHWAY WITH COFACTORS RESULTING IN THE FORMATION OF EPINEPHRINE.

FIG 2. RESULTS OF THE 5000 STOCHASTIC PHARMACOKINETIC SIMULATIONS...
FIG 3. RESULTS OF THE 5000 STOCHASTIC PHARMACOKINETIC SIMULATIONS...

![Graphs showing results of stochastic pharmacokinetic simulations.]

FIG 4. EPINEPHRINE PLASMA CONCENTRATIONS (NG/ML) AT THE 10-MINUTE TIME...

![Graphs showing epinephrine plasma concentrations at the 10-minute time point.]

**Epi Dosing Frequency**
- 3_minutes
- 5_minutes

**Virtual Patient Groups at 40-minute time point during CPR**
- 65.6kg_Female_SAPS30
- 70kg_SAPS30
- 89kg_Male_SAPS30
- Healthy
FIG 5. EPINEPHRINE PLASMA CONCENTRATIONS (NG/ML) AT THE 40-MINUTE TIME POINT

TAB 1. EPINEPHRINE DOSING SIMULATION RESULTS

<table>
<thead>
<tr>
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<th>AUC (ng/mL*min)</th>
<th>Cmax (ng/mL)</th>
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<tbody>
<tr>
<td></td>
<td>3-minute Epinephrine Dosing (1mg)</td>
<td>5-minute Epinephrine Dosing (1mg)</td>
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<tr>
<td>Male (89kg) SAPS=30</td>
<td>8674.91</td>
<td>6259.22</td>
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<tr>
<td>Female (65.6kg) SAPS=30</td>
<td>9951.36</td>
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<td>70kg SAPS=30</td>
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