

RESEARCH ARTICLE

The Influences of Nitric Oxide, Epinephrine, and Dopamine on Vascular Tone: Dose-Response Modeling and Simulations

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ABBREVIATIONS:

ACE = angiotensin converting enzyme
ADRB2 = β 2-adrenergic receptors
AIC = Akaike information criterion
(a means for model selection)
CHF = congestive heart failure
ED50 = 50% effective dose
EMA = European Medicines Agency
GC = guanylyl cyclase
NO = nitric oxide
PK/PD = pharmacokinetic/
pharmacodynamic
SNP = sodium nitroprusside
SVR = systemic vascular resistance
SVR0 = effect at baseline dose
SVRmax = dose resulting in maximum
effect

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ABSTRACT

BACKGROUND: Sodium nitroprusside has successfully been an excellent choice when considering a decrease in systemic vascular resistance in the critical care setting. However, reflex tachycardia and ventilation-perfusion mismatch are possible side effects of this agent. To maintain cardiac output, cerebral perfusion pressure, and concurrently drop systemic vascular resistance (SVR), low-dose epinephrine or dopamine are viable options. The aim of this paper is to conduct dose-response simulations to identify the equivalent dopamine, epinephrine, and nitroprusside infusion doses to decrease the systemic vascular resistance by 20% and by 40% from baseline resting values.

METHODS: Three studies were identified in the literature which reported epinephrine, dopamine, and sodium nitroprusside infusion doses with corresponding SVR responses. Infusion doses were normalized to mcg/kg/min and SVR values were normalized and scaled to the percent decrease (%SVR) in SVR from baseline resting values. The original published studies were mathematically modeled and the Hill equation parameters used for further dose-response simulations of a virtual population. One-hundred patients were simulated various doses resulting in corresponding %SVR responses for each of the three drugs.

RESULTS: Equivalent infusion doses achieving an approximate 20-25% decrease in SVR from baseline, were identified for epinephrine, dopamine, and sodium nitroprusside. Moreover, equivalent infusion doses were identified for epinephrine and nitroprusside to decrease the SVR by 40% from baseline.

CONCLUSION: Even though sodium nitroprusside is traditionally used to decrease SVR, low doses of dopamine or epinephrine are viable alternatives to patients with contraindications to nitroprusside infusions or who will require prolonged infusions to avoid toxicity. The multiple comparisons procedure-modeling approach is an excellent methodology for dose-finding exercises and has enabled identification of equivalent pharmacodynamic responses for epinephrine, dopamine, and sodium nitroprusside through mathematic simulations.

INTRODUCTION

Sodium nitroprusside (SNP) is a nitric oxide (NO) releasing drug used in medicine to therapeutically decrease blood pressure in cases of malignant hypertension.^{1,2} Exogenous administration of nitric oxide elicits effects such as dilation of both arterial and venous vessels and adverse effects such as inhibition of platelet aggregation potentially leading to prolonged bleeding in patients; however, despite these effects, SNP maintains high efficacy in the clinical setting.^{3,4} From a signaling perspective, NO released from an SNP infusion interacts predominately with iron and heme leading to the activation of soluble guanylyl cyclase (GC) forming protein kinase G.⁵ Following a series of reactions, the eventual outcome is a decrease in calcium within the cytosol causing reduced smooth muscle contractions within the vasculature. As an endogenous substance, nitric oxide provides the body with antithrombotic, antiatherogenic, and vasodilating effects rendering tremendous latitude for the demands of daily life.³⁻⁵

The two other vasodilators, at low doses, presented in this paper, are the catecholamines dopamine and epinephrine. At low doses, epinephrine acts via the G-protein coupled β 2-adrenergic (ADRB2) receptors causing vasodilation through mediation by class CL-type calcium channels.⁶ There is much evidence describing polymorphisms associated with the ADRB2 gene potentially leading to varied clinical outcomes ranging from asthma, chronic obstructive pulmonary syndrome, labor pain and progress, to patient survival in patients receiving beta-blocker therapy after acute coronary syndrome.⁷⁻⁹ Despite these findings, low dose epinephrine stimulates the ADRB2 resulting in vasodilation, providing strong inotropic support post cardiac surgery while maintaining cerebral perfusion pressure, amongst other indications.

Dopamine, a precursor to both norepinephrine and epinephrine, stimulates the DA1 and DA2 receptors resulting in vasodilation at low doses.¹⁰ Just as with epinephrine, at higher doses, the alpha-adrenergic receptor mediated vasoconstriction predominates eliminating the vasodilating actions of the lower doses of both catecholamines. In the catecholamine synthesis pathway, phenylalanine is converted to tyrosine and subsequently dihydroxyphenylalanine, commonly referred to as dopa, an agent able to cross the blood brain barrier.^{11,12} Further, in the conversion from dopa to dopamine, vitamin B6 is the necessary cofactor.¹³ Similarly, for the conversion of dopamine to norepinephrine, vitamin C is the required cofactor. As with all reactions, deficiencies of these cofactors result in build-up of the precursor and decrease in the downstream product. The last conversion from norepinephrine to epinephrine requires S-adenosyl methionine (SAM) as a cofactor where the formation of methionine is dependent on vitamin B12, a cofactor, from the conversion from homocysteine to methionine.^{12,13} Thus, the common theme indicates that

nutrition has an obvious importance along the catecholamine synthesis pathway and vitamin deficiencies along the conversion steps may lead to a build-up or depressed levels of dopa, dopamine, norepinephrine, or epinephrine. Moreover, a recent review article summarizes ascorbate's role as a cofactor for enzymes in the catecholamine synthesis pathway and recommends ascorbate-dependent vasopressor support in patients with severe sepsis and septic shock.¹⁴

Dopamine DA1 and DA2 receptors are found in the brain, while higher receptor densities are located in the renal vasculature smooth muscle allowing for increased blood flow with low infusion doses of dopamine.^{15,16} Therefore, the drug effects of nitroprusside, epinephrine, and dopamine have varied mechanisms all allowing for dilation in the human vasculature. What are the equivalent doses allowing for decreasing vascular tone?

The aim of this paper is to use mathematical modeling of established dose-response parameter values to then conduct simulations to identify the equivalent doses of dopamine, epinephrine, and sodium nitroprusside to decrease the systemic vascular resistance (SVR) by 20% and by 40%. The hypothesis was that all three drugs would be capable of achieving a 20% and a 40% decrease in the change from SVR from resting values.

METHODS

LITERATURE-BASED DATA SOURCE

Dose-response data were derived from three publications evaluating the effects of epinephrine, dopamine, and sodium nitroprusside on systemic vascular resistance as well as other hemodynamic variables.¹⁷⁻¹⁹ Results were originally reported in dynes*sec/cm⁵ and were scaled from the resting/baseline SVR to each respective dose response. Drug doses were all normalized to microgram per kilogram per minute (mcg/kg/min) infusion doses. As a result of similar dose ranges, nitroprusside and dopamine results are illustrated on the same dose-response curves; however, epinephrine was reported on a single dose-response curve. Lastly, box and whisker plots depicting the equivalent doses resulting in an approximate 20% decrease in SVR, for all three drugs, and an approximate 40% decrease in SVR for epinephrine and sodium nitroprusside.

PHARMACOKINETIC/PHARMACODYNAMIC MODELING AND DOSE-RESPONSE SIMULATIONS

Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations were conducted in the R programming language (version 3.2.2, The R Foundation for Statistical Computing, Vienna, Austria).^{20,21} Specifically, the dose-response simulations were conducted using the Multiple Comparisons Procedure-Modeling package in R.²² This modeling package has been validated by the European Medicines Agency (EMA)

Committee for Medicinal Products for Human Use and is used during clinical trials.²³ Based on the EMA qualification report, the committee determined the R package an efficient statistical tool for Phase II dose finding studies. The Multiple Comparisons Procedure allows for population dose-response testing and estimation of model uncertainties by enabling researchers to design candidate models in clinical trial design.^{22,24} Lastly, for all dose-response simulations, a sample size of 100 virtual patients (n=100) was created at each infusion dose.

$$\% SVR = SVR_0 - \frac{SVR_{max} * Infusion Dose}{ID50 + Infusion Dose}$$

Equation 1: Pharmacodynamic modeling equation describing the percent decrease in the systemic vascular resistance (SVR) based on infusion doses of epinephrine, dopamine, or sodium nitroprusside.

RESULTS

The dose-response simulations resulted in 1100 samples for dopamine, 1000 samples for epinephrine, and 1300 samples for nitroprusside. The infusion doses normalized to mcg/kg/min with the corresponding SVR percent change from baseline are reported in Table 1. The original *Epinephrine* dose-response values were obtained from the Stratton et al¹⁸ 1985 study that was conducted in 10 healthy participants. This study evaluated the hemodynamic outcomes following infusion of three different epinephrine doses (25, 50, and 100 ng/kg/min). For the original *Sodium Nitroprusside* data, the values are referenced from the Gerson et al 1982 study in 20 adult patients undergoing elective open heart surgery.¹⁷ The original study methods indicate that none of the patients received any drug for at least 11 hours prior to the study period. Therefore, the dose-response simulations are based on a patient population, rather than in healthy participants.

As with the nitroprusside clinical population, the original

dose-response values referenced for the *Dopamine* data were obtained from the Elkayam et al 2008 study in 13 patients with a history of congestive heart failure (CHF).¹⁹ In these patients, CHF was due to left ventricular systolic dysfunction with moderate to severe symptoms (New York Heart Association functional class III or IV) with left ventricular ejection fraction ranging from 14% to 32%.¹⁹ Moreover, the underlying cause of CHF was coronary artery disease (n=5) and non-ischemic dilated cardiomyopathy (n=8).¹⁹ For the original dopamine study, all 13 patients were treated with diuretics, 10 were on ACE inhibitors (n=10), nine were medicated with digoxin (n=9), seven were on beta-blockers (n=7), and lastly, seven were treated with organic nitrates (n=7).¹⁹ Therefore, to summarize, healthy participants were evaluated in the epinephrine study, while both the dopamine and nitroprusside dose-response data were collected in patients with cardiovascular conditions.¹⁷⁻¹⁹

The R programming language scripts were written creating the resulting model parameters and model diagnostics Akaike Information Criteria (AIC) and fitted Log-likelihood. The results are provided in Table 2. Overall, the Emax model equation adequately described the dose-response data from the overall published studies. The best Log-likelihood fit in decreasing order is as follows: epinephrine, dopamine, and nitroprusside, respectively. The maximum decrease in the percent SVR model parameter (SVRmax) resulted in a very wide standard error for nitroprusside; this finding clinically makes sense due to the powerful vasodilating effects of the drug. At doses less than 2 mcg/kg/min, dopamine and nitroprusside exhibited a near parallel linear curve, however, at around 2 mcg/kg/min, the population dose-response simulations diverged resulting in dopamine’s vasodilation effects ending near 10 mcg/kg/min.

Figure 1 provides the dose response simulation results for both dopamine and sodium nitroprusside infusions to systemic vascular resistance. There is a clear dose dependent decrease in SVR as epinephrine is infused at doses lower than

TABLE 1. Normalized Published Dose-Response Data Sources Used for Modeling and Simulations. Systemic Vascular Resistance (SVR) Responses Represent % Vasodilation

Dopamine		Epinephrine		Sodium Nitroprusside	
Elkayam et al (2008) ¹⁹		Stratton et al (1985) ¹⁸		Gerson et al (1982) ¹⁷	
Dose (mcg/kg/min)	Response (% SVR)	Dose (mcg/kg/min)	Response (% SVR)	Dose (mcg/kg/min)	Response (% SVR)
0	100	0	100	0	100
1	83	0.025	69	1	94
2	82	0.050	58	1.5	87
3	81	0.100	52	2	82
10	77	--	--	--	--

TABLE 2: Calculated Dose-Response Modeling Parameters and Diagnostics

	Dopamine	Epinephrine	Sodium Nitroprusside
SVRmax (%) (S.E.)	-22.894 (2.037)	-59.0303 (2.75)	-52.2 (120.54)
SVR0 (%) (S.E.)	99.954 (1.384)	100.0420 (1.14)	101.3 (3.89)
ED50 (mcg/kg/min) (S.E.)	0.432 (0.177)	0.0218 (0.0034)	4.0 (13.39)
Akaike Information Criterion	20.8632	24.6809	14.8374
Fitted Log-likelihood	-6.4316	-3.4187	-8.3405

ED50 = 50% effective dose; SE = standard error; SVR = systemic vascular resistance; SVR0 = effect at baseline dose; SVRmax = dose resulting in maximum effect

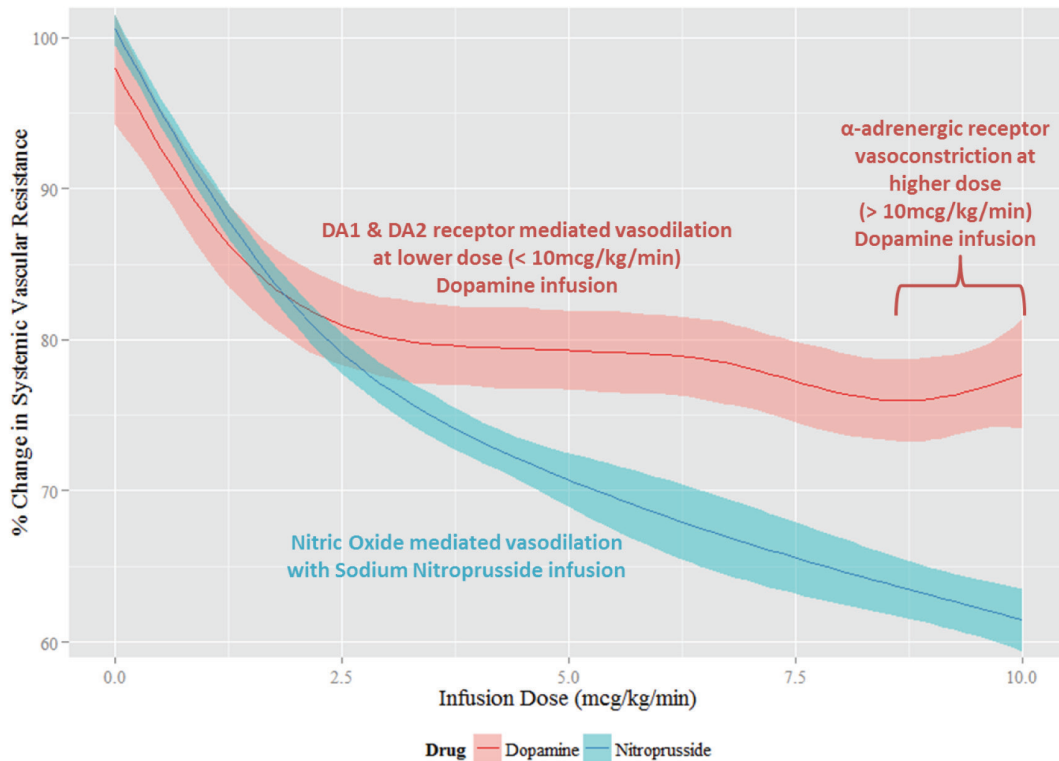


FIGURE 1. Dose-response simulation results comparing the effect of *Dopamine* and *Sodium Nitroprusside* on the percent change, from baseline, of systemic vascular resistance. The solid line describes the population mean while the shaded error bands represent the 95% confidence intervals.

0.010 mcg/kg/min. It is important to note that the epinephrine dose-response model parameters are valid for doses at or below 0.010 mcg/kg/min. Higher simulation doses were attempted and, as expected, an increase in the %SVR was seen with wider shaded confidence interval bands. Therefore, due to the predominant alpha-adrenergic receptor effects at higher epinephrine infusion doses, the mathematical model becomes unstable and is therefore recommended for infusion doses of less than 0.10 mcg/kg/min. However, despite the higher dose simulation findings, the mathematical model allowed

for appropriate hypothesis testing and addressing the aim of identifying doses resulting in a 20% and 40% decrease in systemic vascular resistance.

Based on the mathematical simulations, the doses resulting in an equivalent infusion response leading to decreased systemic vascular resistance by 20-25%, are 5 mcg/kg/min for dopamine, 0.015 mcg/kg/min for epinephrine, and lastly 2.5 mcg/kg/min for sodium nitroprusside. These results are based on the median simulated population response rate and variations with infusion outcomes would potentially be

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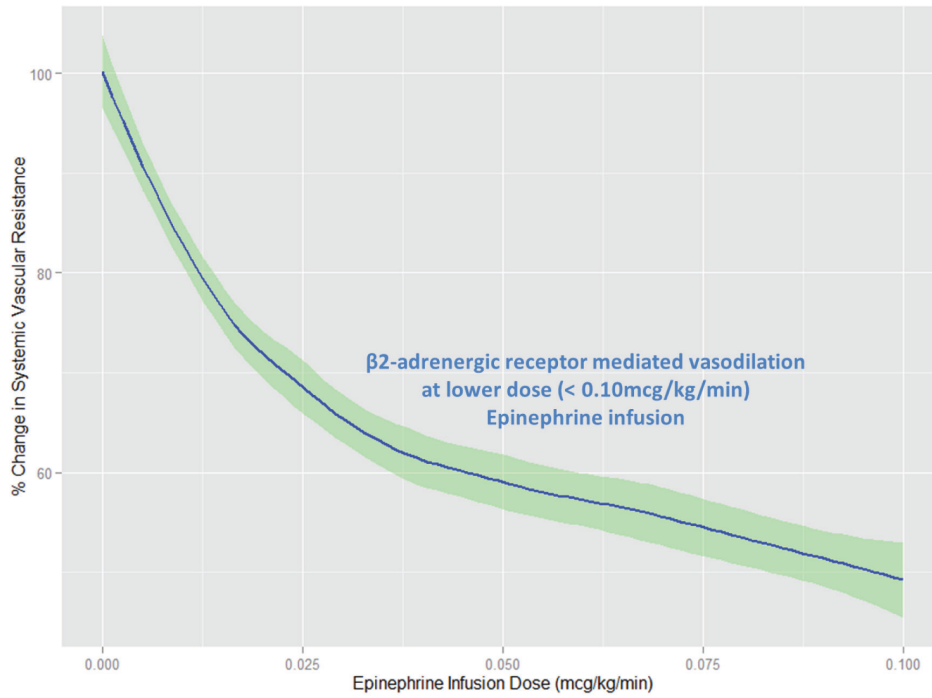


FIGURE 2. Dose-response simulation results comparing the effect of *Epinephrine* on the percent change, from baseline, of systemic vascular resistance. The solid line describes the population mean while the shaded error bands represent the 95% confidence intervals.

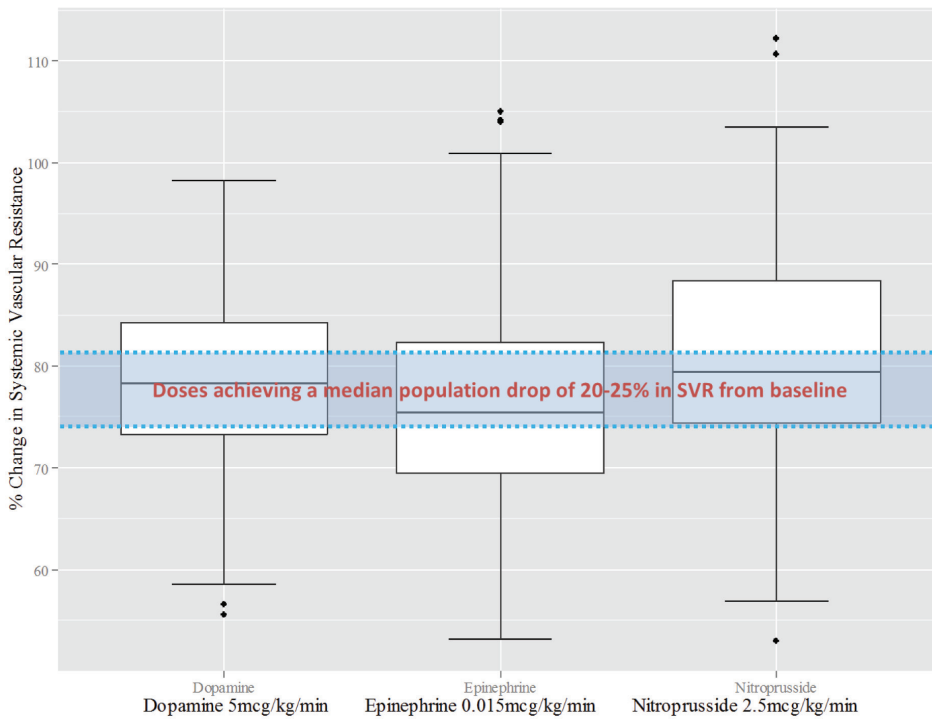


FIGURE 3. Approximate equivalent doses resulting in a 20-25% decrease in systemic vascular resistance for *Dopamine* (5 mcg/kg/min), *Epinephrine* (0.015 mcg/kg/min), and *Sodium Nitroprusside* (2.5 mcg/kg/min). The box plots represent 25%, 50% (median), and 75th percentile values, while the whisker lines represent the 10th and 90th percentile results. The dots represent the population outliers.

associated with gender and/or genotype status of the Catechol-O-methyltransferase (COMT) and/or Monoamine oxidase (MAO) enzymes when using dopamine or epinephrine.²⁵ Due to the effect on cardiac output by epinephrine and dopamine, cases necessitating maintenance of cerebral perfusion pressure, these two catecholamines are therapeutic alternative vasodilators to sodium nitroprusside.

After analyzing the response rates of the dopamine infusion simulations, the results suggest that the alpha-1 receptor vasoconstriction effects at around 10 mcg/kg/min. Therefore, in addressing the second aim, the equivalent dose resulting in a 40% decrease in SVR from baseline is 0.040 mcg/kg/min of epinephrine and a maximum infusion dose of 10 mcg/kg/min for sodium nitroprusside. As with any drug, population outliers are evident, and therefore, careful titration of these aforementioned infusion doses will be critical due to the extreme and rare instances when a 40% drop of SVR from baseline may be desired by the clinical staff. The dopamine simulation dose findings are consistent with the package insert for nitroprusside indicating a maximum infusion dose at 10 mcg/kg/min.²⁶

DISCUSSION

This paper described the dose-matched vasodilating prop-

erties of epinephrine, dopamine, and sodium nitroprusside based on dose-response simulations. These three drugs, all allowing for the same outcome variable of a decrease in systemic vascular resistance (SVR), all work with various mechanisms allowing for the same response. These principles highlight the role that endogenous nitric oxide, epinephrine, and dopamine play in maintaining vascular tone and further suggest the possibility to investigate a multi-mechanism approach for drug development to combat treatment resistant hypertension.

Understanding the mechanisms underlying essential hypertension has been investigated and treatments have been proposed for several decades using various medical and surgical approaches. The first measurement of blood pressure was accomplished in 1733 by Stephen Hales, an English clergyman²⁷ and has remained key pillar of human health since that time. In the 1930s, nearly 200 years later from the first blood pressure measurement, a common approach to management of hypertension was renal sympathectomy,²⁸ the approach of surgically denervating the kidney. Other approaches at the time were inducing high fevers in patients by using the typhoid bacilli or malaria related substances.^{29,30} Since then, pharmacological approaches have been quite successful; however, in select patients even individual combination of anti-hypertensive medications are of no help. These patients are classified as having resistant essential hypertension and often suffer from

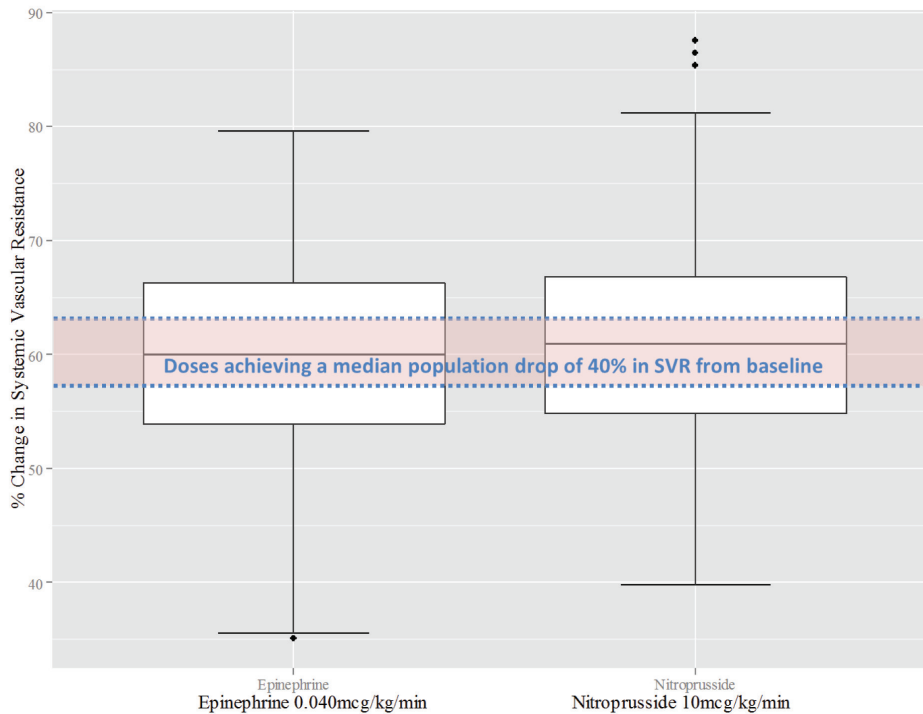


FIGURE 4. Approximate equivalent doses resulting in nearly a 40% decrease in systemic vascular resistance for *Epinephrine* (0.040 mcg/kg/min) and for infusions of *Sodium Nitroprusside* (10 mcg/kg/min). The box plots represent 25%, 50% (median), and 75th percentile values, while the whisker lines represent the 10th and 90th percentile results. The dots represent the population outliers.

the deleterious effects on various organs of the body due to chronically high blood pressures.

Mathematically, the change in pressure equals the blood flow multiplied by the vascular resistance, parameters that are all dependent on the vasodilatory capacity of the vessel and also organ-dependent. The brain and kidney have a low vasodilatory capacity and therefore have low vascular tone. In contrast, the heart and skeletal muscle are capable of high vasodilatory capacity resulting in high vascular tone. Thus, the modulation of resting vascular tone varies depending on the organ of interest, which in turn, is influenced by both endogenous substances (i.e. nitric oxide, epinephrine, etc.) and is regulated by sympathetic neurons located in the medulla regulating changes in vascular diameter.

Endogenous and exogenous substances, emotional well-being, environmental influences, and lifestyle factors all result in competing mechanisms resulting in essential hypertension. In this paper, the primary summarized dependent variable was systemic vascular resistance relative to the drug dosing (independent variable). As stated by the EMA report, there is a clear role for the mathematical simulations throughout the drug development and dose-finding process. This exercise clearly exhibited the cost-savings involved using interdisciplinary skills in computer programming, mathematics, and medicine to make recommendations for drug doses. The results are not supporting any of the three vasodilators over the other; however, there are clear physiologic benefits to choosing any of the three vasodilators in the appropriate clinical indication.

Based on the results, the hypothesis-testing results indicate that clearly epinephrine, dopamine, and sodium nitroprusside are able to decrease SVR by 20%. However, due to the increased alpha-1 vasoconstriction effects of dopamine near 10 mcg/kg/min, a 40% decrease in SVR was not evident based on the dose-response simulations. Rather, a 0.040 mcg/kg/min infusion of epinephrine provided the dose-response equivalence results to a 10 mcg/kg/min of nitroprusside.

CONCLUSION

Equivalent pharmacodynamic SVR responses have been identified for epinephrine, dopamine, and sodium nitroprusside using the multiple comparisons procedure-modeling approach. Based on the simulations, low-dose epinephrine or low-dose dopamine may provide clinicians without access to nitroprusside with more options to decrease patients' SVR and maintain adequate cerebral perfusion pressure, for the appropriate clinical indications.

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