Clinical pharmacology of dobutamine and dopamine in preterm neonates

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Dobutamine is a β_1 selective stimulant. β Receptor agonists are used to stimulate the rate and the force of cardiac contraction. The chronotropic effect is useful for the treatment of arrhythmias whereas the inotropic effect is useful to augment the myocardial contractility. Dobutamine is about four times as potent as dopamine in stimulating myocardial contractility in low concentrations and increases left ventricular output in the hypotensive preterm infants. Dobutamine possesses a center of asymmetry. The $(-)$-isomer of dobutamine is a potent agonist of α_1 receptors and is capable of causing marked pressor responses. In contrast, $(+)$-dobutamine is a potent α_1 receptor antagonist which can block the effects of $(-)$-dobutamine. Dobutamine is relatively cardioselective at dosages used in clinical practice with its main action being on β_1-adrenergic receptors. Dobutamine and dopamine undergo intense metabolism in neonates where they are conjugated with sulphate and O-methylated. The clearance and the half-life of dobutamine and dopamine range over one order of magnitude in neonates. Dopamine is widely used to increase blood pressure, cardiac output, urine output and peripheral perfusion in neonates with shock and cardiac failure. Dopamine is more effective than dobutamine in the short-term treatment of systemic hypotension in preterm infants. High doses of dopamine cause vasoconstriction, increase systemic vascular resistance, and, eventually, decrease renal blood flow. Treatment with dobutamine is associated with a significantly greater increase in left ventricular output in the single study reporting that outcome. Dobutamine is indicated for the short-term treatment of cardiac decompensation.

KEYWORDS: dobutamine; dopamine; hypotension; metabolism; neonate; pharmacokinetics.

■ INTRODUCTION

β Receptor agonists may be used to stimulate the rate and the force of cardiac contraction. The chronotropic effect is useful in the emergency treatment of arrhythmias such as torsades de pointes, bradycardia, or heart block. The inotropic effect is useful when it is desirable to augment myocardial contractility.[1] Dobutamine is a β_1 selective stimulant[2] which resembles dopamine structurally, but possesses a bulky aromatic substituent on the amino group.[1] The pharmacological effects of dobutamine are due to direct interaction with β receptors. Its actions do not appear to result from release of norepinephrine from sympathetic nerve endings, nor are they exerted by dopamine receptors.[2] Dobutamine is a β_1 agonist like dopamine, but in high doses its β_2 effects can decrease rather than increase peripheral resistance.[3]

Dobutamine is about four times as potent as dopamine in stimulating myocardial contractility in low concentration, and of proven value in increasing left ventricular output in the hypotensive preterm infants. It has less effect than dopamine on blood pressure because it has little effect on systematic vascular resistance.[3] Tachycardia may occur, and increased pulmonary blood pressure leading to pulmonary edema has been observed when the dose exceeds 15 µg/kg per min.[3]

This drug onset of action is 1 to 2 min after intravenous administration, with peak effect in 10 min. Dobutamine must be administered by continuous intravenous infusion because of its rapid metabolism.[4]

Dobutamine possesses a center of asymmetry, and both enantiomeric forms are present in the mixture used clinically. The $(-)$-isomer of dobutamine is a potent agonist at α_1 receptors, and is capable of causing marked pressor responses. In contrast, $(+)$-dobutamine is a potent α_1 receptor antagonist, which can block the effects of $(-)$-dobutamine. The effects of these two isomers are mediated by β receptors.

Dobutamine is indicated for the short-term treatment of cardiac decompensation that may occur after cardiac surgery or in patients with congestive heart failure or acute myocardial infarction. Dobutamine increases cardiac output and stroke volume in such patients, usually without a marked increase in heart rate.[2]

This drug seems to be better than dopamine at improving systemic blood flow. There is a growing consensus that cardiac output and systematic tissue perfusion usually matter more than blood pressure.[3] Blood pressure rises significantly during the first week of life and then more slowly after that. The most likely value for a 6-day-old infant of 25 weeks' gestation is 50 mm Hg, and most will have a systolic pressure between 33 and 67 mm Hg.[3]

High doses of dopamine cause vasoconstriction, increase systemic vascular resistance, and, eventually, decrease renal blood flow. While a moderate dose increases myocardial contractility and cardiac output in adult and older children, a dose of more than 10 μg/kg per min can cause an increase in systemic resistance, a fall in gut blood flow, and a reduction in cardiac output in the neonate, especially in the first days of life.[3]

Dobutamine and dopamine are off-patent drugs prioritized by the National Institute of Child Health and Human Development of USA Food and Drug Administration for further study under the Best Pharmaceuticals for Children Act.[6] Both agents are used to manage cardiac insufficiency in preterm neonates, and are subject to controversy among neonatologists.[6] For the very-low-birthweight neonates, the probability of treatment with dopamine or dobutamine varied almost 10-fold from 4.4% to 38.4% at 11 hospitals. Treatment with dopamine alone was more common than treatment with dobutamine alone. There was no difference in mortality between neonates treated with dopamine compared to those treated with dobutamine, but access to charts and clinical details are required to conduct a comparative effectiveness study.

■ BIBLIOGRAPHIC SEARCH

The bibliographic search was performed using PubMed and EMBASE databases as search engines. The cutoff point was January 2014. The following key words were used: "dobutamine neonate", "dobutamine metabolism neonate", "dobutamine pharmacokinetics neonate", "dobutamine therapy neonate", "dopamine neonate", "dopamine metabolism neonate", "dopamine pharmacokinetics neonate" and "dobutamine dopamine neonate". The bibliography of each article was read carefully, and the selected articles were examined. In addition, the books "Neofax: a Manual of Drugs Used in the Neonatal Care" by Young and Mangum[4], and the "Neonatal Formulary"[3], were consulted. The findings of the bibliographic search gave rise to 40 original articles, 8 review articles and 4 book chapters. The publication years of this matter ranged from 1982 to 2012.

■ RESULTS

Dose and monitoring of dobutamine in infants

Young and Mangum[4] suggest starting with an intravenous continuous infusion of 2 μg/kg per min of dobutamine, increasing to 25 μg/kg while titrating the response. The Neonatal Formulary[3] states that the right dose of dobutamine needs to be individually assessed because the clearance of dobutamine is very variable in children. The Neonatal Formulary[3] suggests starting with a continuous intravenous infusion of dobutamine 10 μg/kg per min. This dose is adjusted as necessary after 20 min because of the drug's variable half-life. A few infants may need twice as much drug. Ultrasound must be used to check the hemodynamic

response when using a dose of more than 10 μg/kg per min. Urine output and peripheral perfusion must be frequently assessed.

The heart rate and arterial blood pressure must be continuously monitored. The intravenous site must be checked for signs of extravasation.[4] Dobutamine may cause hypotension if the patient is hypovolemic. Tachycardia occurs at high dosage. Arrhythmias, hypertension, and cutaneous vasodilation increase myocardial oxygen consumption. Tissue ischemia occurs with infiltration.[4]

Sulphation and methylation of dobutamine and dopamine in neonates and adult subjects

Berg and Padbury[5] measured the simultaneous plasma free and sulfoconjugated dobutamine and dopamine in urine and plasma of 47 stable critically ill neonates and children, aged between 1 day to 17 years (mean ± SD = 37 ± 7 months). Nine infants received dopamine only, 27 infants received dobutamine only, and 11 infants received both simultaneously. The fractions of plasma dobutamine and dopamine sulfoconjugated were 0.73 ± 0.05 and 0.76 ± 0.05, respectively.[5] Free dobutamine plasma clearance was not different among patients receiving dobutamine and dopamine versus patients receiving dobutamine only (83 ± 13 versus 114 ± 13 ml/kg per min.[6]).

Very little is known about the metabolism of dopamine in neonates. In adults, dopamine is metabolized rapidly by both monoamine oxidase and catechol-O-methyl transferase present in circulating blood to 3,4-dihydroxyphenyl acetic acid (DOPAC), homovanillic acid (HVA), and 3-methoxytyramine (for review see[7]). The few data published on the metabolism of dopamine in neonates deal with the sulfation of this drug. Hepatic SULT1A3, the enzyme that sulphates dopamine, is expressed at high levels early in development, but decreases in late fetal/early neonatal life, and is essentially absent from the adult liver.[8] In the lung, significant SULT1A3 activity is observed in the fetus, but neonatal levels are considerably lower. In the brain, the highest activity is observed in the choroid plexus for SULT1A1, with low and widespread activity for both SULT1A1 and SUT1A3 in other brain regions.[7]

Plasma free and sulfoconjugated dopamine concentrations were not different in neonates and healthy adult volunteers. The percentage free to total dopamine recovered in urine was 1.5 ± 1.1%. These data suggest that the majority of plasma dopamine is sulphated.[9]

Dobutamine is methylated by catechol-O-methyltransferase. Raxworthy et al.[6] investigated dobutamine and isoprenaline as substrates for purified pig-liver catechol-O-methyltransferase. The apparent first-order rate constant (Vmax/Km) was derived. Dobutamine was a 5-fold better substrate for catechol-O-methyltransferase than isoprenaline.

Yan et al.[10] stated that the main catabolic fate of dobutamine in humans is the formation of 3-O-methyldobutamine. They described the isolation and identification of 3-O-methyldobutamine in the urine of children receiving infusion of racemic dobutamine. Forty-seven percent of infused dobutamine was identified as 3-O-methyldobutamine and its acid-hydrolyzed derivatives, the latter mostly conjugated with sulphate (33%). Thus the formation of 3-O-methyldobutamine constitutes a major pathway of dobutamine in neonates.

In another investigation, Yan et al.[11] studied the in-vitro kinetics of dobutamine and dopamine as substrates and inhibitors of each other, i.e., the apparent Vmax and Km, and Ki, in crude preparation of human adult blood mononuclear cell catechol-O-methyltransferase. The Vmax for dopamine and dobutamine as substrates for catechol-O-methyltransferase were 0.45 and 0.59 nmol of catechol-O-methyltransferase product formed per mg of protein per min, whereas the values for Km were 0.44 and 0.05 mM, respectively. Dopamine and dobutamine were competitive inhibitors of each other in this reaction. The Ki for dopamine as an inhibitor of dobutamine methylation was 1.5 mM, whereas that for dobutamine as an inhibitor of dopamine methylation was 0.015 mM. The Ki for dopamine as an inhibitor of dobutamine is thus 100-fold lower than the Ki of dobutamine as an inhibitor of dopamine methylation.

Pharmacokinetics of dobutamine and dopamine in neonates

Free plasma dobutamine and dopamine clearances are 102 ± 15 and 250 ± 38 ml/kg/min, respectively ($p < 0.01$).[5] Linear regression analyses demonstrated relationships of the fraction of plasma dobutamine and dopamine sulfoconjugated to the respective free plasma clearances ($r^2 = 0.30$; $p < 0.001$, and $r^2 = 0.29$, $p < 0.05$, respectively).[5]

Infants with serum creatinine concentrations >2 mg/dl had lower free plasma dobutamine and dopamine clearance rates than those infants with serum creatinine levels <2 mg/dl (6 ± 1 versus 107 ± 15, $p < 0.05$ ml/kg/min for dobutamine and 40 ± 38 versus 270 ± 39 ml/kg/min for dopamine, respectively, $p < 0.05$). Renal excretion is an important determinant of the wide interindividual variability in plasma free dobutamine and dopamine clearance rates.[7]

There is significant inter- and intra-individual variability in the dose of dopamine required to elicit cardiovascular responses of similar magnitude in preterm infants. Possible explanations for this phenomenon include the differences in the metabolism of dopamine,[11–13] the production of local vaso-regulatory hormones, the state of expression[14] and down-regulation[15] of cardiovascular adrenergic receptors, and the differences in adrenal function.[16,17]

In adults, Leier et al.[18] found a linear relationship between dobutamine dose and the resulting plasma concentration, and between the plasma concentration and the resulting hemodynamic response. The mean calculated threshold values (the minimum concentration necessary for a change in cardiac output) were 39 ng/ml[19] and 33 ng/ml.[20] A higher threshold value of 50 ng/ml was found for heart rate in normal children and adolescents.[20]

Martinez et al.[19] studied the pharmacokinetics and pharmacodynamics of dobutamine in 13 critically ill neonates requiring inotropic support. Dobutamine was administered as a constant intravenous infusion in increasing doses of 2.5, 5, and 7.5 μg/kg per min. The plasma dobutamine levels showed a progressive stepwise increase, with mean levels of 21 ± 3 ng/ml at the 2.5 μg/kg per min dose, 49 ± 4 ng/ml at the 5 μg/kg per min dose, and 68 ± 4 ng/ml at the 7.5 μg/kg per min dose. Of interest, the actual infusion rate represented $74 \pm 3\%$ (range: 39% to 108%) of the desired infusion rate when dobutamine concentration was measured in the infusate.

Dobutamine is a racemic mixture of enantiomers with a complex mechanism of action.[21,22] The racemic mixture used in clinical practice leads to myocardial α_1-receptor-mediated inotropic effects and increased blood pressure as well as β-receptor mediated chronotropic effects and decreased peripheral vascular resistance.[23] This is in contrast to dopamine, which is believed to act through an indirect action with increased norepinephrine release from cardiac sympathetic nerves, as well as a direct action on β-adrenergic and dopamine receptors of the renal and splanchnic vasculature.[24–26]

During dobutamine infusion, there were significant increases in cardiac output measurements above infusion values. There was no statistically significant change in systolic or diastolic blood pressure, or of heart rate during infusion. The minimum plasma concentration necessary for a change in cardiac output was 39 ± 7 ng/ml. The plasma clearance rate was 90 ± 38 ml/kg per min. Plasma catecholamines levels were unchanged during dobutamine infusion. The data by Martinez et al.[19] suggest that dobutamine is an effective but limited inotropic agent in neonates. Dobutamine may be most beneficial when cardiogenic failure is presented.

Banner et al.[27] evaluated a linear kinetic model for dobutamine clearance in 12 patients aged between 2 days to 9 years. The infusion rates for dobutamine ranged from 2 to 15 μg/kg per min. The serum concentrations of dobutamine varied from 6.4 to 347 ng/ml. A trend of increasing concentration with dose was observed ($p < 0.001$). Contrary to the behaviour of a first-order model, the slope of this relationship is significantly negative ($p < 0.001$). The concentration of dobutamine increased with the dose of this drug. The values for clearance varied from 32 to 625 ml/kg per min. However, the relationship of clearance to steady-state concentration had a negative slope. Multiple analyses of variance on age, weight, and co-infused dopamine showed that these factors did not influence the relationship of clearance to steady-state. Analysis to show an underlying model failed to differentiate Michaelis-Menten from non-linear binding or mixed models on the basis of these data. These findings show that the pharmacokinetics of dobutamine do not appear to follow a simple linear model. Based on these data, neither age nor the added infusion of dopamine affects the clearance of dobutamine. Banner et al.[27] state that an appropriate model describing drug pharmacokinetics of dobutamine must be validated.

Schranz et al.[28] studied the pharmacokinetics of dobutamine in 27 children and infants aged between 0.13 and 16.6 years. Seventeen patients received dobutamine for treatment of shock secondary to sepsis, while 10 patients received dobutamine for treatment of post-cardiac surgery. The duration of dobutamine infusion before sampling was 1.87 ± 0.29 days (range: 0.2 to 5.5; median: 1 day). There was considerable variation in the concentration-time profile among patients. The kinetic parameters are summarised in Tables 1 and 2.

Table 1 summarizes the pharmacokinetic parameters of dobutamine in 27 patients. Some patients demonstrated a remarkably high clearance rate while others cleared dobutamine relatively slowly. A complete time-concentration profile was obtained in 10 patients. Of these 10 patients, 5 appeared to exhibit a simple (monoexponential) log-linear decline in plasma concentrations, while the other five patients exhibited a biphasic decline suggestive of a two-compartment model. Neither age, weight, sex, disease state, duration of infusion, nor blood measures of renal or hepatic dysfunction were found to be covariates of the above

Table 1 - Pharmacokinetic parameters for infused dobutamine in a heterogeneous population of critically ill children. Data are the mean ± SEM.

Number of patients = 27
Duration (days) = 1.87 ± 0.29 days (range 0.20 to 5.50 days)
Dose (µg/kg per min) = 7.47 ± 1.23 (range: 1.0 to 25.0 µg/kg per min)
Distribution phase α (min^{-1}) = 0.49 ± 0.07 (range: 0.20 to 1.09 min^{-1})
Elimination phase β (min^{-1}) = 0.060 ± 0.025 (range 0.010 to 0.152 min^{-1})
$t_{1/2}$ α (min) = 1.65 ± 0.20 (range: 0.64 to 3.01 min)
$t_{1/2}$ β (min) = 25.8 ± 11.5 (range: 4.6 to 68.6)
Cp^{o} (ng/ml) = 165 ± 42.1 (range: 3.79 to 696 min)
Cl (ml/kg per min) = 151.1 ± 47.5 (range: 12.5 to 1319 ml/kg per min)
Vd (l/kg) = 1.3 ± 0.70 (0.09 to 5.64 l/kg)
AUC (ng.min/ml) = 386 ± 125 (46.8 to 1277 ng.min/ml)

Table 2 - Pharmacokinetic parameters for patients from which a full concentration-time profile (post-infusion) was obtained. Figures are the mean ± SEM.

Number of patients = 10
Dose (µg/kg per min) = 4.1 ± 0.57 (range: 1.0 to 5.0 µg/kg per min)
Cp^{o} = 77.12 ± 20.00 (range: 27.9 to 245 ng/ml)
Cl (ml/kg per min) = 65.66 ± 14.08 (range: 20.4 to 180 ml/kg per min)
$t_{1/2}$ α (min) = 1.69 ± 0.21 (range: 0.64 to 3.00 min)
$t_{1/2}$ β (min) = 25.83 ± 11.5 (range: 9.18 68.6 min)*
Vd (l/kg) = 0.96 ± 0.54 (0.09 to 5.64 l/kg)
Duration of the infusion (days) = 2.20 ± 0.47 (range 1.0 to 5.0 days)

*Data for only 5 patients were available.
Cp^{o} = Concentration at steady state.

parameters. It was found, however, that the concomitant administration of dopamine altered dobutamine pharmacokinetics, indicating the possible presence of a competitive component in dobutamine's disposition. The kinetic parameters of these 10 patients are summarized in Table 2.

There was no correlation between clearance and dose of dobutamine. The steady-state levels are a linear function of infusion rate for a given patient. Schranz et al.[28] normalized the steady-state plasma concentrations to a 5 µg/kg per min dose to see whether there was a decrease in variability. Despite this, there was still a considerable variation of steady-state concentrations among patients (3.8 to 400 ng/ml). Thus, the clearance rates for the patients ranged over more than on order of magnitude (Table 1).[28] The volume of distribution (Vd) showed a similarly large variability, as did the AUC (Table 1). AUC, normalized to a dose of 5 µg/kg per min, also showed a large variability. Additionally, clearance was not correlated with blood urea nitrogen levels or plasma creatinine.

Dopamine pharmacokinetics were investigated in 14 critical newborn infants ranging from 27 to 43 weeks of gestational age.[38] Dopamine was infused at the rate of 8 µg/kg per min. Steady-state plasma dopamine concentrations and plasma clearance rates were observed 20 min after infusion. Plasma dopamine concentration ranged from 0.5 ng/ml before infusion to almost 70 ng/ml at an infusion rate of 4 to 8 µg/kg per min. There was a linear correlation between infusion rate and plasma dopamine concentration (r = 0.68; p < 0.001).

The clearance of dopamine varies widely in the pediatric population, depending on age. Its elimination half-life is approximately 2 min in fullterm infants, and may be as long

as 4-5 min in preterm infants.[7] Due to immaturity of the autonomic nervous system, the drug may produce some adverse respiratory responses at high doses in neonates, the most common being tachycardia and cardiac arrhythmias.

Dobutamine is relatively cardioselective at dosages used in clinical practice, with its main action being on β1-adrenergic receptors. Unlike dopamine, it does not have any effect on specific dopaminergic receptors. Dobutamine is used to increase cardiac output in infants with circulatory failure. Its elimination half-life is about 2 min in adults and older infants. In neonates, the half-life of dobutamine is 5.8 ± 1.3 min (see Table 3).

Plasma dopamine clearance was determined in 27 acutely ill infants and children who were receiving a continuous intravenous infusion of dopamine.[30] Dopamine clearance was 60.7 ± 28.1 ml/kg per min. There was a negative correlation between the patient age and dopamine clearance (r = -0.63; p < 0.05), and dopamine clearance was nearly twice as rapid in children younger than 2 years than it was in older children (87.3 ± 27.7 ml/kg per min versus 45.9 ± 17.0 mg/kg per min; p < 0.05). Conjugated bilirubin exerted an age-independent effect on clearance of dopamine: clearance was 44.8 ± 28.6 ml/kg per min in children with abnormal conjugated bilirubin (greater than or equal to 0.9 mg/dl) and 70 ± 2.56 ml/kg/min in children with normal conjugated bilirubin (less than 0.9 mg/dl). Clearance was lowest (29.8 ± 5.7 ml/kg per min) in the four children who had both hepatic and renal dysfunction. Age is an important determinant of dopamine clearance, explaining, in part, the clinical observation that infants and young children require higher infusion rate.

In adults, dopamine follows a biphasic pattern, with an initial distribution phase (α-phase) of 1 min and a terminal elimination phase (β-phase) of approximately 9 min. The total body clearance is about 70 ml/kg per min when administered at a rate of 2 µg/kg/min, 75 ml/kg per min when administered at a rate of 8 µg/kg per min.[37]

In neonates, a log-linear relationship was shown to exist between plasma dopamine concentration and response. The thresholds of the concentrations were 14 ± 3.5 ng/ml for increase in mean blood pressure, 18 ± 4.5 ng/ml for increase in systolic blood pressure, and 35.0 ± 5.0 ng/ml for increase in heart rate. The baseline dopamine plasma concentration was 32.0 ± 16.0 ng/ml, and rose to 70.0 ng/ml with rates of 4 and 8 µg/kg per min.

Dopamine is frequently used in critically ill newborn infants for treatment of shock and cardiac failure.[29] Steady-state arterial plasma concentrations of dopamine were

Table 3 - Pharmacokinetic parameters for patients on dobutamine alone versus patients receiving concomitant dopamine. Figures are the mean ± SEM.

Parameters	Dobutamine alone	Dobutamine + Dopamine
Age (years)	5.8 ± 1.3	4.9 ± 1.2
Weight (kg)	17.7 ± 3.7	19.1 ± 3.8
Dose (µg/kg/min)	5.0 ± 0.7	8.5 ± 1.8
Duration (days)	1.8 ± 0.4	1.9 ± 0.4
Cp^{o} ng/ml	94 ± 28	199 ± 60*
Clearance (ml/kg per min)	135 ± 41	160 ± 71
$t_{1/2}$α (min)	1.78 ± 0.26	1.31 ± 0.11*
$t_{1/2}$β (min)	30.0 ± 19.6	19.5 ± 10.3*

*p < 0.05

measured in 11 seriously ill infants receiving dopamine infusion at the rate of 5 to 20 µg/kg per min, for presumed or proven sepsis and hypotensive shock. Steady-state concentrations of dopamine ranged from 0.013 to 0.3 µg/ml. Total body clearance averaged 115 ml/kg/min. The apparent volume of distribution and the elimination half-life averaged 1.8 l/kg and 6.9 min, respectively.[30] No relationship was observed between dopamine pharmacokinetic parameters and gestational and postnatal ages or birthweight. Substantial interindividual variation was seen in dopamine pharmacokinetics. Plasma concentrations could not be predicted accurately from its infusion rate. Marked variation in clearance explains, in part, the wide dose requirements of dopamine needed to elicit clinically response in critically ill newborn infants.

Padbury et al.[12] compared the clinical responses with plasma dopamine concentration and compared dopamine pharmacokinetics in 14 infants of different gestational ages (range: 27 to 42 weeks) or different clinical conditions. Dopamine infusion was increased stepwise from 1 to 2, or 2 to 4, or 4 to 8 µg/kg per min. Plasma dopamine concentration was compared with blood pressure, heart rate, and Doppler cardiac output. Plasma clearance rate was calculated from steady-state plasma concentrations and was 60 ± 12 ml/kg per min at two lower dosages, and decreased to 48 ± 6 ml/kg per min at the highest dosage. The average threshold for increases in mean arterial pressure was 50% below that for increases in cardiac heart rate. Improvements in arterial pressure were noted before, and at lower thresholds, than increases in heart rate. Serial echography data showed dose-dependent increases in cardiac output and stroke volume without significant changes in heart rate or systemic vascular resistance. Thresholds and plasma clearance values were similar in infants of 27 to 42 weeks, and birth weights 900 to 4300 g. Administration of dopamine at initial dosages lower than commonly recommended,

followed by incremental increase in dose, may be associated with improved left ventricular performance with avoidance of undesirable tachycardia and arrhythmias.

Effects of dobutamine and dopamine in the hypotension of neonates

Shock develops when oxygen delivery becomes inadequate to satisfy tissue oxygen demand. Rozé et al.[29] performed a randomized double blind study in 20 hypotensive preterm infants to evaluate the hemodynamic response to dobutamine and dopamine. Initially, both drugs were administered at 5 µg/kg per min, and their dose was increased up to 20 µg/kg per min if mean arterial pressure remained blow 31 mm Hg. The pharmacological and therapeutic profile of dobutamine and dopamine in neonates are summarised in Table 4.

Dobutamine does not stimulate the cardiovascular dopaminergic receptors (Table 5). In the most effective dose range of 2 to 15 µg/kg per min, dobutamine increases cardiac output, mainly through the augmentation of stroke volume.[7,23] In children with septic and cardiogenic shock, at doses between 0.5 and 20 µg/kg per min, dobutamine caused increases in cardiac index and left ventricular strike work index.[21,30]

The normal physiologic range for blood pressure is best defined by the presence of intact organ blood flow autoregulation. However, the lower and upper limits of this developmentally regulated physiological blood pressure range have not been determined in the preterm or term infant.[32,33,34] Instead, the "normal" blood pressure limits have been defined as the gestational- and postnatal-age-dependent blood pressure values between the 10th and 90th percentiles. Thus, the decision to treat hypotensive non-acidosic preterm infants is based on arbitrary blood pressure limits without proven physiologic relevance.

Table 4 - Pharmacologic and therapeutic profile of dobutamine and dopamine in neonates.

Drug	Main effect	Therapeutic use	Drawbacks, Risks	Future
Dobutamine	β_1-receptors: increased myocardial contractibility. $\beta2$-receptors: peripheral vasodiltion.	Neonatal circulatory failure with significant cardiac dysfunction	Tachycardia with increased myocardial oxygen demand and decreased stroke volume	Evaluation of effects on systemic and local circulation with focus on cerebral flow.
Dopamine	2-5 µg/kg/min – D1 receptors, mesenteric vasodilation, renal vasodilatation.	First line vasopressor agent in neonatal hypotension	Pharmacokinetics: high interindividual variability	Evaluation of clinical outcome.
	5-10 µg/kg/min, α_1 receptors. Vasoconstriction	Questionable use for promotion of renal perfusion and filtration	Suppression of prolactin, growth hormone and thyroid secretion.	Catecholamines stay the mainstream of therapy.
	10-20 µg/kg/min, β_2 receptors, positive inotropic effect			

Table 5 - Adrenergic and dopaminergic receptor-dependent cardiovascular actions of dobutamine and dopamine.

	Cardiac receptors				Peripheral vascular receptors	
Agent	α_1*	β_1 and β_2*	Dopamine	α_1/α_2	β_2	Dopamine
Dobutamine	Increase contractility	Increase rate, conduction, contractility	No effect	Modest peripheral vaso-constriction	Peripheral vasodilation	Vasodilation in renal, mesenteric, and coronary circulation
Dopamine**	Increase contractility	Increase rate, conduction, contractility	Increase contractility	Peripheral vaso-constriction	Modest peripheral vasodilation	No effect

*The relative contribution of the α_1 and β_1 adrenergic receptors and the myocardial dopamine receptors to the increase in myocardial contractility in the neonate is unknown.
**Dopamine stimulates the α- and β-adrenergic and dopaminergic receptors in a dose-dependent manner.

3-O-methyldopamine, the major dobutamine metabolite, is a relatively potent and highly selective α_1-adrenoreceptor antagonist.[23]

Dopamine exerts direct beneficial renal[30,31] and endocrine[28] actions in preterm infants. Via its epithelial effects in the renal tubules, dopamine increases sodium, phosphorus, and free water excretion.[28,31]

The beneficial and complex mechanisms of actions of dopamine and the pathophysiology of neonatal hypotension explain why dopamine has become the drug of choice in the treatment of hypotensive preterm infants.[28] Dopamine should be started early at low to medium doses, and the dose escalated in a step-wise manner to achieve sustained normalization of the blood pressure.[28,31]

Dobutamine is a frequently used positive inotropic in children. Isoproterenol increases heart and cardiac output but has no independent effect on renal blood flow. Dobutamine increases cardiac output with less chronotropic effect than isoproterenol but, unlike dopamine, does not have an independent effect on renal and mesenteric profusion.[7]

It is possible to detect and treat low systemic and organ blood flow in preterm infants in the first day after birth.[37] Preterm infants are at risk of low systemic blood flow in the first day of life. Risk factors for low systemic blood flow include low gestational age, ventilation with higher mean airway pressure, large diameter ductus arteriosus, higher calculated systemic vascular response, and poor myocardial contractility. Blood pressure and clinical signs such as capillary refill times do not accurately detect infants with low systemic blood flow, and result in delayed treatment when treatment is targeted at hypotension. Although dobutamine is better at increasing systemic blood flow and dopamine is better at increasing blood pressure, neither has been shown to improve mortality or long-term outcomes.

The function of the newborn heart is characterized by a relatively high resting cardiac output with little contractile reserve, due to the presence of more non-contractile fibrous tissue, which results in high sensitivity to any increase in afterload. Newborn infants can increase their cardiac output by tachycardia, but severe tachycardia may result in decreased stroke volume. Inotropic drugs, such as dopamine or epinephrine increase afterload in the newborn, counteracting the beneficial cardiac effect by a secondary fall in cardiac output.[33]

Dobutamine is widely used for the treatment of acute cardiac failure and hypotension in adults and children.[34,35] As a sign of the efficacy of dobutamine on the left ventricular function, a significant decrease of left ventricular post-ejection pressure was measured within the first 20 min of dobutamine infusion. The reduction of post-ejection pressure may reflect an increased preload, decreased after load, or increased contractility, due to a β_1-adrenergic effect on the heart.[36] An increased heart rate can be a compensatory mechanism to improve cardiac output in cases with myocardial dysfunction.[37] Robel-Tilling et al.[38] conclude that dobutamine has an influence on the left ventricular function in sick preterm neonates with typical signs of myocardial dysfunction. Within 20 min after the start of a dobutamine infusion, a significant improvement in the hemodynamic situation was observed with progressively increased cardiac output.

In hypotensive states, oxygen supply to the gut is critical.[39] Among high-risk patients, this is thought to play a major role as an ischemic factor in the pathogenesis of necrotizing enterocolitis.[34] For dobutamine, a marked β_1-adrenergic effect on the heart with inotropic effect is documented even in moderate doses.[37] In contrast to dopamine, only a minor α_1-receptor stimulation leading to peripheral vasoconstriction is observed.

The effect of dopamine is strongly dose dependent. Moderate doses lead to β_1-adrenergic effects, but in higher doses, α_2-adrenergic effects lead to increased systemic vascular resistance and cardiac output decreases in preterm infants.[37] In addition to adrenergic receptors, a specific dopaminergic receptor exists on splanchnic and renal vessels, which leads to vasodilation.

The hemodynamic effects of dobutamine or dopamine ($10\,\mu g/kg$ per min) in 20 preterm infants with median gestational and postnatal ages of 28 weeks (range: 26 to 32 weeks) and 1 day (range: 2 hours to 17 days), respectively, who had protracted arterial hypotension refractory to volume therapy were studied. Hypotension was defined as mean arterial pressure $\leq$10th percentile of normal values. Mean arterial pressure increased during dobutamine and dopamine therapy ($p < 0.05$). Blood flow velocity increased. None of the 20 infants studied developed necrotizing enterocolitis. Both dobutamine and dopamine increased mean arterial blood pressure and heart rate.[43]

Trials comparing dobutamine and dopamine in preterm infants

Subhedar and Shaw[40] compared the effectiveness and safety of dopamine and dobutamine in the treatment of systemic hypotension in preterm infants. They conclude that dopamine is more effective than dobutamine in the short term treatment of systemic hypotension in preterm infants. However, in the absence of data confirming the long term benefit and safety of dopamine compared to dobutamine, no firm recommendations can be made regarding the choice of drug to treat hypotension.

There was no evidence of a significant difference between dopamine and dobutamine in terms of mortality, incidence of periventricular leukomalacia, or severe periventricular hemorrhage.[50] No adverse long-term neurodevelopment outcome was observed. Subhedar and Shaw[40] conclude that dopamine is more effective than dobutamine in the short-term treatment of systemic hypotension in preterm infants. There was no evidence of an effect on the incidence of adverse neuroradiological sequelae, or on the incidence of tachycardia. However, in the absence of data confirming long-term benefit and safety of dopamine compared to dobutamine, no firm recommendation can be made regarding the choice of drug to treat hypotension.

Osborn et al.[44] performed a randomized and double-blind study in 42 very preterm infants during the first 24 hours of life to determine if dobutamine or dopamine result in greater improvements in systemic blood flow. The infants were treated with $10\,\mu g/kg$ per min of dobutamine or dopamine. Dobutamine resulted in a significantly greater increase in the blood flow in the superior vena cava than did dopamine (mean, $+9.9$ versus $-3.2\,ml/kg$ per min; $p = 0.02$). Dopamine resulted in a significantly greater increase in blood pressure. Infants receiving dobutamine only at 24 hours had a greater right ventricular output than infants receiving dopamine (mean: 295 versus $167\,ml/kg$ per min; $p < 0.001$). Forty percent failed to increase or maintain superior vena cava flow in response to either inotrope.

No significant differences in mortality or morbidity were found. Osborn et al.[50] conclude that dobutamine produced a greater increase in blood flow than dopamine.

Klarr et al.[45] compared the efficacy of dopamine and dobutamine for the treatment of hypotension (mean arterial blood pressure ≤ 30 mm Hg) in 63 hypotensive preterm infants with a gestational age ≤ 34 weeks. All hypotensive infants first received intravascular volume expansion. Intravenous study drug infusions were initiated at 5 µg/kg per min and then increased in increments of 5 µg/kg per min at 20 min intervals until a mean arterial blood pressure >30 mm Hg was attained and sustained for ≥ 30 min (success) or a maximum rate of 20 µg/kg per min was reached without resolution of hypotension (failure). The study drug was administered by umbilical or peripheral vein. The treatment failure was 0 following dopamine and 5 (16%) following dobutamine (p = 0.028). Success was 30 (97%) following dopamine and 22 following dobutamine (69%; p = 0.008). Heart rate >180 beats/min was 16% (dopamine) and 22% (dobutamine, NS). These results show that dopamine was more successful than dobutamine, at commonly used infusion rates, in acutely increasing mean blood pressure to >30 mm Hg in infants at ≤ 34 weeks of gestation with respiratory distress syndrome. The apparent enhanced efficacy of dopamine in comparison with dobutamine may reflect underlying differences in mechanisms of action, pharmacodynamics, other pharmacological properties, or undetected disparities between the two groups.

Miall-Allen et al.[36] measured the mean arterial blood pressure and heart rate in 12 hypotensive preterm infants given dopamine. A significant, although temporary, elevation in mean blood arterial pressure occurred in five neonates in response to 5 µg/kg per min, but an increase in mean arterial blood pressure was found in all infants (11 ± 6 mm Hg; p < 0.01) when the infusion rate was doubled. Heart rate was unaffected except for an increase of 22 ± 12 beats/min (p < 0.01) in the five showing sustained mean blood arterial pressure elevation with 10 µg/kg per min. Dobutamine failed to raise mean blood arterial pressure in the 7 who relapsed, and refractory shock resulted. They conclude that time should not be wasted in starting dopamine at less than 10 µg/kg per min in hypotensive preterm infants, as lower rates are unlikely to produce a response and delay may cause further compromise.

Greenough and Emery[46] compared the efficacy of two inotropic infusions in treating low arterial blood pressure in preterm infants. Forty infants with median gestational age of 27 weeks (range: 23 to 33 weeks) were studied. At trial entry, the infants, who all had a systolic arterial blood pressure <40 mm Hg receiving a colloid infusion, were randomized to receive either a dopamine or dobutamine infusion. The infusions were commenced at a rate of 5 µg/kg per min and, if necessary, this was increased over the 3 hour study period to 15 µg/kg per min. There was no significant difference in the gestational or postnatal age or baseline arterial blood pressure of the infants who received dopamine or dobutamine. Three hours after commencing the infusion, the infants who received dopamine had a significantly higher systolic arterial blood pressure, a median of 39 mm Hg compared to a median of 34 mm Hg in the dobutamine group (p < 0.05). In addition, 10 infants who received dopamine, but only 3 who received dobutamine,

had a systolic arterial blood pressure >40 mm Hg (p < 0.05). Greenough and Emery.[46] conclude that dopamine rather than dobutamine infusion is more efficient in improving the arterial blood pressure of preterm neonates.

Rozé et al.[29] performed a randomized double blind study to evaluate hemodynamic response to dobutamine and dopamine in 20 hypotensive preterm infants of less than 32 weeks of gestation. Neonates initially received dopamine or dobutamine 5 µg/kg per min. They found that dopamine is more effective than dobutamine in raising and maintaining arterial blood pressure above 30 mm Hg; however, dopamine did not increase left ventricular output.

Filippi et al.[42] compared the endocrine effects of dopamine and dobutamine in 35 hypotensive, very low birthweight infants who received dopamine or dobutamine. Hemodynamic variables and serum levels of thyroid stimulating hormone (TSH), total thyroxine (T4), prolactine and growth hormone were assessed during the first 72 hours of treatment and the first 72 hours after stopping treatment. Necessary cumulative and mean drug doses and maximum infusion required to normalise blood pressure were significantly higher in the dobutamine than in the dopamine group (p < 0.01). Suppression of TSH, T4 and prolactine was observed in dopamine-treated newborns from 12 h of treatment onwards, whereas levels of growth hormone reduced significantly only at 12 hours and 36 hours of treatment (p < 0.01). TSH, T4 and prolactine rebound was observed from the first day onwards after stopping dopamine. Dobutamine administration did not alter the profile of any of the hormones, and no rebound was observed after stopping treatment. Filippi et al.[42] conclude that dopamine and dobutamine both increase the systemic blood pressure, though dopamine is more effective. Dopamine reduces serum levels of TSH, T4 and prolactin in very low birthweight infants, but such suppression is quickly reversed after treatment is stopped.

■ DISCUSSION

The adrenergic and dopaminergic receptor-dependent cardiovascular actions of dobutamine and dopamine are summarised in Table 6. Catecholamine agents are the most widely used drugs for the treatment of circulatory failure in newborn infants. Indeed, catecholamines were introduced to the care of critically ill neonates based on adult experience, using adult doses, without any clear evidence for their usefulness as regards clinical outcome. Blood pressure has long been used as a measure of therapeutic effectiveness, with no clear ranges established for critical organs. Today, systemic and local blood flow parameters should also be evaluated in order to establish goal-directed therapeutic guidelines for catecholamine therapy.

Dobutamine is a relatively cardioselective sympathomimetic amine with significant α and β-adrenoceptor-mediated direct inotropic effects and limited chronotropic actions.[25,33] Dobutamine administration is usually also associated with a variable decrease in the total peripheral resistance.[7,25,40] Dobutamine increases myocardial contractility exclusively through the direct stimulation of the myocardial adrenergic receptors.[45] Since myocardial norepinephrine stores are immature and rapidly depleted in the neonate;[33] and dobutamine may decrease afterload,[17,25,46] preterm infants with primary myocardial dysfunction and elevated

Table 6 - Cardiovascular actions of dopamine in preterm infants.

Dose	Receptors	Vascular effects	Cardiac effects
Low dose (0.5 to 2 µg/kg/min)	Dopamine α (Serotonin)	Increase renal blood flow Increase total peripheral vascular resistance	Increase myocardial contractility
Medium dose (2 to 10 µg/kg/min)	Dopamine β-Receptors α (Serotonin)	Increase renal blood flow Increase peripheral vasodilation Increase total peripheral vascular resistance Net effect on blood pressor	 Increase myocardial contractility Increase venous return
High dose (> 10 µg/kg/min)	Dopamine β-Receptors α (Serotonin)	Increase renal blood flow Increase peripheral vasodilation Increase total peripheral vascular resistance	Increase myocardial contractility Increase heart rate Increase conduction velocity Increase myocardial contractility Increase venous return

peripheral vascular resistance should be treated with dopamine alone.

In the majority of preterm infants, hypotension results from a decrease in the afterload with or without myocardial dysfunction. Dopamine is the initial drug of choice in the treatment of hypotensive preterm infants. Several randomized, blinded, controlled clinical trials have documented the superiority of dopamine over dobutamine in this patient population.[40] However, if signs of myocardial dysfunction persist or develop during dopamine treatment, the addition of dobutamine is recommended. Dobutamine is the drug of choice in asphyxiated hypotensive preterm infants with myocardial dysfunction who present with elevated peripheral resistance.[38]

Dopamine is the sympathomimetic amine most frequently used in the treatment of hypotension in preterm infants.[44] It exerts its cardiovascular actions via the dose-dependent stimulation of the cardiovascular dopaminergic, α and β-adrenoceptors (see Tables 5 and 6[44]). Dopamine affects all three major determinants of cardiovascular function (preload, myocardial contractility and afterload). By decreasing venous capacitance, dopamine augments preload.[44] However, the majority of its actions on raising blood pressure are due to the drug-induced increases in both myocardial contractility[13,40,44] and peripheral vascular resistance (afterload).[13,40,44] with some of the α- and β-adrenergic cardiovascular effects resulting from its partial conversion to norepinephrine.[13,40,44] Through its selective renal vascular effects, dopamine increases total blood flow[33] and glomerular filtration rate.[44,46] In preterm patients, the effect on filtration rate occurs as early as 23 weeks of gestation. Dopamine does not appear to selectively increase the mesenteric blood flow in the immature infant,[33] suggesting the absence of a functional mature mesenteric dopaminergic vasodilator response in this patient population.

Dopamine is the most widely used catecholamine in hypotensive newborns when they fail to normalize blood pressure after fluid boluses. The so-called renal dose of dopamine is theoretically not expected to exert its dopaminergic renal vasodilator effect because of the aforementioned resistance to receptor stimulation. However, many neonatologists still use low dose dopamine therapy for infants with decreased urine flow rate in the belief that it improves renal perfusion. Dopamine is, however, able to stimulate, in higher doses, vascular α_1 receptors causing vasoconstriction, and to a lesser extent myocardial β-receptors. Thus, higher doses of dopamine increase vascular resistance and blood pressure, with an accompanying decrease in cardiac output. The pharmacokinetics of

dopamine show higher inter-individual variability, leading to highly variable clinical effectiveness in newborns. If dopamine is administered for several days, endocrine effects could be present, such as suppression of prolactin, growth hormone, and thyroxin secretion, which may negatively influence early neurodevelopment.[41,42]

Dobutamine has the clear advantage over dopamine in enhancing myocardial contractility by stimulating β_1 receptors, albeit it clinically cannot always be translated into increased blood pressure. Dobutamine has also a vasodilator effect mediated by β_2 receptors. Moreover, it could cause significant tachycardia with increased myocardial oxygen demand and decreased stroke volume. The expected net effect of dobutamine is an increased systemic and local blood flow, and not a significantly changing blood pressure.

Myocardial dysfunction is one of the most frequently encountered pathophysiologic backgrounds of hypotension in severely asphyxiated premature infants. However, in preterm neonates without postnatal asphyxia, myocardial dysfunction can be observed without hypotension.[44]

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■ RESUMO

A dobutamina é um estimulante seletivo β1. Agonistas de receptores β são usados para estimular a taxa e a força de contração cardíaca. O efeito cronotrópico é útil para o tratamento de arritmias e o efeito inotrópico é útil para aumentar a contratilidade do miocárdio. A dobutamina é cerca de quatro vezes mais potente que a dopamina para estimular a contratilidade miocárdica em baixas concentrações e o volume de ejeção ventricular nos prematuros hipotensos. A dobutamina possui um núcleo de assimetria. O (−) – isômero da dobutamina é um agonista potente dos receptores α1 e é capaz de provocar respostas pressoras marcados. Em contraste, o isômero (+) – A dobutamina é um potente antagonista de dobutamina que pode bloquear os efeitos de (−)-dobutamina. A dobutamina é relativamente cardiosseletiva em dosagens utilizadas na prática clínica; sua ação principal incide sobre os receptores β1-adrenérgicos.

A dobutamina e a dopamina sofrem intenso metabolismo em recém-nascidos, onde são conjugados com sulfato e orto-metilados. A depuração e a meia-vida de dobutamina e dopamina apresentam variações de uma ordem de grandeza em recém-nascidos. A dopamina é amplamente utilizada para aumentar a pressão arterial, o débito cardíaco, a produção de urina e a perfusão periférica em recém-nascidos com choque e insuficiência cardíaca. A dopamina é mais eficaz do que a dobutamina no tratamento a curto prazo de hipotensão sistêmica em prematuros. Altas doses de dopamina causam vasoconstrição, aumento da resistência vascular sistêmica e, eventualmente, diminuem o fluxo sanguíneo renal. O tratamento com dobutamina está associada com um aumento significativamente maior na vazão do ventrículo esquerdo no único estudo relatando esse resultado. A dobutamina é indicada para o tratamento de curto prazo da descompensação cardíaca.

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