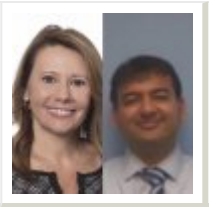
Cardiac Drugs: Vasopressors and Inotropic Agents

In this episode Drs. Weiner and Rajgarhia discuss commonly used vasopressors and inotropic agents used in neonates.



Featured Speaker:

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Transcription:

Julie Weiner, DO (Host): Hello everyone. And welcome to another edition of Neonatal Review Isolette to Crib. Welcome and thank you for joining us today. I will be your host for this podcast. I'm Dr. Julie Weiner, one of the Neonatologists and the Medical Director for the NICU at Children's Mercy Hospital in Kansas City. Fun fact, did you know that Walt Disney moved to Kansas City when he was nine years old and here is where Mickey Mouse was created?

Okay. Now, moving on, to help prepare for boards, the next few episodes, we'll focus on the cardiovascular section and this is a large part of boards. Today we are joined by Ayan Rajgarhia, MD. He is also one of the Neonatologists here at Children's Mercy Hospital, and he spends a lot of his clinical time caring for the cardiac babies.

He is joining us today to talk about vasopressers and inotropic agents that are commonly used in the NICU. Dr. Rajgarhia, thank you for joining us. And can you tell everybody hi out there?

Ayan Rajgarhia, MD (Guest): Hello everybody. And thank you for inviting me. Happy to be here.

Host: Well, we are happy to be talking about this topic today because it's not only important for boards, but managing babies too. So, we're going to move into the topic for today. And just to give you an idea how large the cardiovascular section is, is it represents 10% of the test. This is the second highest section with respiratory being number one at 14% of boards.

So Dr. Rajgarhia, what does the, ABP tell us we need to know?

Dr. Rajgarhia: The ABP, the American Board of Pediatrics wants us to know the mechanism of action, the therapeutic indications and toxicity of the commonly used adrenergic, vasoppressor, inotropic and chronotropic drugs.

Host: Before we dive into a discussion about vasopressors and inotropes, we need to spend a little time discussing how we define hypotension in neonates and its implications to managing critically ill newborns. Dr. Rajgarhia, tell us a little bit about hypotension.

Dr. Rajgarhia: Dr. Weiner, studies that have sought to determine normal ranges of blood pressure in newborns often have weaknesses such as retrospective data collection, small number of patients and use of both invasive and noninvasive blood pressure values. In most studies though, blood pressure is higher in larger, more mature infants, and there is an increase in blood pressure with increasing postnatal age.

The commonly used clinical tool of mean arterial blood pressure equals gestational age is applicable for maybe the first 72 hours of the life of a newborn. After which most babies should have a mean blood pressure that's at least 30 millimeters of mercury, which is the lower limit of the cerebral blood flow autoregulatory curve. Added to this problem, hypotension is often a late sign of shock in neonates. Given the uncertainty of accurate blood pressure values and the need to identify circulatory compromise early, we need to rely on a combination of signs rather than blood pressure alone, such as capillary refill time, heart rate, urine output, acidosis, central venous pressure, mixed venous saturation as well as newer strategies, such as functional echocardiography and near infrared spectroscopy to identify circulatory compromise. For the rest of the discussion, when we use the term hypotension it will be used to reflect a blood pressure value which is inadequate to maintain end-organ perfusion and leads to this circulatory compromise, which we've been talking about.

Host: Those are all very good points about hypotension and recognizing the implications for neonates. Dr. Rajgarhia, can you now move into discussing how we treat or manage hypotension in the NICU?

Dr. Rajgarhia: Now we will review the inotropes most commonly used in neonatology, focusing on their pharmacologic properties and clinical factors that affect the selection of these medications. And first up is dopamine. Dopamine is an endogenous sympathomimetic amine that potentiates the release of norepinephrine, in addition to its direct action on alpha, beta and dopaminergic receptors. The receptor effects of dopamine are dose dependent, which means that at a low dose of 0.5 to two micrograms per kilo per minute, it acts on dopaminergic receptors. At a medium dose of two to six micrograms per kilo per minute. It acts on cardiac beta one receptors and at higher doses of greater than six to 10 micrograms per kilo per minute, it acts on alpha one receptors.

Now, what do these receptors do? Dopaminergic receptor stimulation increases renal blood flow through renal vasodilatation. It changes, renal tubular absorption, and causes positive inotropy. The net effect is increased renal blood flow. Stimulation of dopaminergic receptors is also responsible for the endocrine effects of dopamine, which we see. Including a decrease in the levels of thyrotropin, prolactin and thyroxin hormones. Beta one receptor stimulation increases cardiac output through positive inotropy, that is myocardial contractility and chronotropy, that is heart rate. And lastly, alpha one receptor stimulation produces systemic vasoconstriction.

Host: So, how do we use dopamine in the NICU?

Dr. Rajgarhia: Dopamine would fall in the category of a vasopressor inotrope that increases systemic vascular resistance and cardiac contractility. It is the most commonly used drug for the management of hypotension in newborns. It also increases peripheral perfusion and cerebral blood flow in very low birth weight infants. It is more effective than dobutamine in increasing mean blood pressure and has a comparable effect when compared to epinephrine in increasing blood pressure and urine output. But in a nutshell, dopamine can be used for practically any indication in the NICU.

Host: So now that we know dopamine is the most commonly used drug, are there side effects that we need to worry about or be aware?

Dr. Rajgarhia: As we discussed earlier, Dr. Weiner, while we discussed its mechanism of action, potential negative effects of dopamine include abnormalities of the endocrine system, arrhythmias and an increase in pulmonary vascular resistance. This effect on pulmonary vascular resistance limits its use in pulmonary hypertension. Higher doses of dopamine can also significantly increase systemic vascular resistance causing impairment of cardiac contractility and cardiac output.

Next we will discuss dobutamine. Dobutamine is a synthetic sympathomimetic amine that acts directly on alpha and beta receptors without the release of norepinephrine. This is different from the mechanism of action of dopamine. This synthetic catecholamine has a relative affinity for beta one cardio receptors leading to increased myocardial contractility and beta two receptors leading to vasodilation of the peripheral vasculature. It also has some peripheral vasoconstriction action through its effect on alpha receptors, but the overall net effect is systemic vasodilation.

Host: So, how is dobutamine used in the NICU?

Dr. Rajgarhia: Dr. Weiner, dobutamine is an inotrope vasodilator, which is used primarily for the treatment of decreased myocardial contractility, and low cardiac output. It has been the drug of choice for hypotension during the transition period in premature neonates secondary to its ability to improve contractility of the immature myocardium and decrease afterload.

And although dopamine is more effective at increasing mean blood pressure, dobutamine is more effective in increasing systemic blood flow. Dobutamine is also used in the treatment of pulmonary hypertension due its ability to increase myocardial function and decrease pulmonary vascular resistance.

Host: So now, what we dobutamine for, are there specific side effects or worries with dobutamine we should be aware of?

Dr. Rajgarhia: The possible negative effects of dobutamine are again, based on its mechanism of action. And include peripheral vasodilation and associated hypotension as well as arrhythmias.

Moving on to the next class of drugs, we'll talk about epinephrine. Now, epinephrine is an endogenous catecholamine that stimulates alpha one and two and beta one and two receptors. The beta receptor effect is seen at lower doses of 0.01 to .1 micrograms per kilo per minute and causes an increase in myocardial contractility with associated peripheral vasodilation. High-dose epinephrine of and doses of more than 0.1 microgram per kilo per minute is associated with increased systemic vascular resistance due to alpha receptor mediated peripheral vasoconstriction.

Host: So epinephrine is another one of the drugs that seems to be used pretty commonly. Can you talk about the use in the NICU?

Dr. Rajgarhia: Absolutely. Epinephrine like dopamine would be classified as a vasopressor inotrope, and it's primarily used to treat hypotension, which is refractory to first-line medications and therapies.

Epinephrine increases blood pressure with an efficacy that is similar to dopamine, although producing an increase in heart rate, plasma lactate level and blood glucose level.

And we'll talk about some of these effects in a little more detail later. It also has a greater effect in increasing cerebral blood flow when compared to dopamine. In pulmonary hypertension, epinephrine increases cardiac output, similar to dopamine with preferential systemic vasoconstriction. Although its utility is limited because of its effects in increasing heart rate and lactic acidosis.

Host: With epinephrine like the other medications are there side effects we should be aware of?

Dr. Rajgarhia: It's possible negative effects are those that we've discussed previously and include tachycardia or increase in heart rate, arrhythmias, peripheral ischemia, lactic acidosis, and hyperglycemia. When you look at its side effect profile, tachycardia that we see is most likely attributable to the beta two receptor stimulation in the heart while the lactic acidosis and hyperglycemia that we see are most likely attributable to the beta two receptor stimulation in the liver.

Excessive vasoconstriction leading to ischemia occurs predominantly at very high doses and does not represent the most likely cause of these adverse effects, at least in routine clinical practice. So, unfortunately there is no drug without side effects.

Our discussion of epinephrine isn't complete without discussing, norepinephrine. And norepinephrine is an endogenous catecholamine as well that increases systemic vascular resistance and cardiac output by activation of alpha one and two and beta one receptors. As with epinephrine, norepinephrine constricts systemic vasculature to a greater degree than pulmonary vasculature. Norepinephrine also increases cardiac output by increasing contractility via the beta one receptors. Although this effect is less pronounced in the setting of potent alpha receptor mediated vasoconstriction and increase in afterload.

Host: Dr. Rajgarhia, thank you for bringing up norepinephrine during this discussion. Can you also comment on how we use it in the NICU?

Dr. Rajgarhia: Dr. Weiner norepinephrine is a vasopresser that is used for the management of hypotension, seen secondary to vasodilatory septic shock due to its preferential alpha action. It has been shown to increase mean blood pressure, reduce oxygen requirement and improve tissue perfusion. In pulmonary hypertension, it has been shown to decrease oxygen requirement, improve cardiac output and blood flow to the lungs. And there is some preliminary data that suggests that independent alpha two mediated pulmonary vasodilation is the contributor to these results.

Host: So is there side effects for norepinephrine that we should be aware of?

Dr. Rajgarhia: The potential negative effects of norepinephrine include excessive peripheral vasoconstriction which leads to tissue ischemia.

Shifting gears a little, we will now talk about milrinone. Milrinone is a phosphodiesterase type three inhibitor with inotropic inodilator that is promotes myocardial contractility and produces vasodilation, and lusitropic. That is, promotes myocardial relaxation properties. The inotropic effect results from decreased breakdown of cyclic adenosine monophosphate, biphosphodiesterase type three, which

perpetuates calcium influx into myocardial cells and results in myocardial contraction. The inodilator effect results from a similarly derived influx of calcium into smooth muscle cells, increasing relaxation and leading to peripheral vasodilation.

Finally the lusitropic effect is caused by myocardial relaxation due to actine myosine complex breakdown. Cumulatively, milrinone increases cardiac output without an increase in myocardial oxygen demand all the while decreasing afterload by decreasing systemic vascular resistance.

Host: Milrinone as one of the other common cardiovascular medication shoes in the NICU, especially for the cardiac babies. Can you tell us a little bit more in detail how it's used in the NICU?

Dr. Rajgarhia: You're absolutely right, Dr. Weiner. Milrinone is used primarily for the prevention and treatment of low cardiac output after cardiac surgery. It's use has been expanded a little bit outside of patients who undergo surgery. And it has also been evaluated for the treatment of PPHN or persistent pulmonary hypertension. Through phosphodiesterase inhibition, milrinone, augments pulmonary vasodilation, which is induced by nitric oxide, a drug commonly used to treat PPHN. Use is not without side effects though. And it should be used with caution in patients with PPHN, because of associated hypotension and potential decreased coronary perfusion.

Host: Besides hypotension and the decreased coronary perfusion are there side effects with the use of milrinone?

Dr. Rajgarhia: Yes, Dr. Weiner, other than systemic hypotension, tachycardia,tachyarrhythmias, and thrombocytopenia can also be seen with the use of milrinone.

We're in the home stretch here and next, we will talk about vasopressin. Endogenous arginine vasopressin is a neuropeptide that increases vascular tone and regulates fluid homeostasis by binding to the vasopressin one and vasopressin two receptors in smooth muscle, the V one or the vasopressin one receptors mediate vascular tone, platelet function, and release of aldosterone and cortisol. Whereas the vasopressin two, V2 receptors influence fluid balance and vascular tone.

Host: So, how is vassopressin used in the NICU?

Dr. Rajgarhia: Vasopressin has been studied as a rescue therapy in refractory hypotension, which is primarily seen due to vasodilatory shock, and has been shown to increase vascular tone that eventually promotes coronary and pulmonary vasodilation. The clinical effects include increase in blood pressure, cardiac output, and a decrease in catecholamine requirement. We also see selective pulmonary vasodilatory effects, which make it a useful drug in the treatment of PPHN.

Host: Are there side effects for vassopressin?

Dr. Rajgarhia: The potential negative effects of vasopressin include tissue ischemia because of vasoconstriction and necrosis, liver ischemia, and hyponatremia.

Lastly, we will talk about hydrocortisone. Relative or absolute adrenal insufficiency may be present in neonates with refractory hypotension, secondary to decreased cortisol stores and the decreased ability

to increase cortisol in response to stress. Corticosteroids aid in the management of hypotension by decreasing the breakdown of catecholamines, increasing calcium levels in myocardial cells and upregulating adrenergic receptors.

Host: Thank you, Dr. Rajgarhia for mentioning hydrocortisone. And although it's not one of the cardiac drips commonly used, hydrocortisone seems to have a common use in the NICU. Can you tell us a little bit more about the use?

Dr. Rajgarhia: Hydrocortisone is used usually as an adjunct to conventional therapies. One of the problems with hydrocortisone though, is that it increases blood pressure and decreases catecholamine usually after a time lag, which can be up to 24 to 48 hours. It has been used in septic shock and pulmonary hypertension and its utility has been established in premature infants who are more at risk of developing adrenal insufficiency.

Host: For hydrocortisone, are there side effects that the listeners should be aware of?

Dr. Rajgarhia: Some of the adverse effects of corticosteroids include hyperglycemia, gastric irritation, and fluid retention. And this is common to any steroid that is used. Long-term exposure to steroids increases risk of osteopenia and overall inhibits the immune function and somatic growth.

Host: Dr. Rajgarhia, thank you for going over these medications. It has been very helpful. And so in review, the main medications, not counting fluid resuscitation, dopamine, dobutamine, epinephrine, norepinephrine, vasopressin, hydrocortison and milrinone are very important in the management of infants in the NICU that have hypotension. Can you give a quick summary for our listeners?

Dr. Rajgarhia: So to summarize what we just discussed, due to limitations and estimating accurate values of blood pressure that lead to a decrease in end organ perfusion, instead of one, a constellation of signs and symptoms should be used when assessing a patient. And although dopamine and epinephrine are considered natural first and second choice of drugs for most clinical indications, other drugs should be considered.

For example, dobutamine should be considered in hypotension during the transitionary period. Norepinephrine and vasopressin should be considered in cases of vasodilatory shock, sepsis and pulmonary hypertension and milrinone should be considered in cases of pulmonary hypertension with overall hemodynamic stability.

Host: Dr. Rajgarhia, thank you again for joining us today. Hopefully this information will give our listeners a better understanding on hypotension and the cardiac drugs use to manage this in the NICU. This is Neonatology Review Isolette to Crib and I'm Dr. Julie Weiner. Thank you for listening to us today and please join us next time when we will continue discussing the cardiovascular section for boards.