Stop and Go: Titration of IV Drip Medication

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Objectives
• Discuss the pharmacology of common inotropic agents used in the treatment of shock in children
• List the indications for inotropic, chronotropic drugs used in post op pediatric heart patients.
• Discuss how to avoid the common errors in adjusting IV drip medications

Disclosures
• Nothing to disclose

Way’s to cause Trouble
• Treating Numbers instead of the patient!
• Look at the whole patient.
• Why is this patient hypertensive?
Way’s to cause Trouble

• Changing too many things at once.
• Giving pain medication, turning down the dopamine and increasing the nipride!

Ways to cause Trouble

• Tweaking too often, too soon or too much
• Give the patient’s body a chance to respond and react.
• The patient should prove himself worthy!

Ways to cause Trouble

• Not knowing why drugs were started and what the goal is for their use.

Myocardial Contraction

• Contractility increases over 1st months of life along with:
  – #’s of sympathetic nerve fibers within myocardium
  – Total concentration of endogenous norepinephrine
• There is a greater dependence of CO on HR than contractility during this time

Immature Heart

• Limited responsiveness to medications
  – ↑ noncontractile content
  – ↓ availability of releasable NE
  – Less mature sympathetic system
  – Underdeveloped intracellular calcium regulatory mechanisms
  – ↓ functional reserve capacity
  – more sensitive to the depressant effects of rapid infusions of platelets and fresh frozen plasma, as a result of chelation of Ca²⁺ by the citrate in banked blood

Age Related Differences

• Calcium – the calcium channels are a major source of intracellular calcium
• Reduced sensitivity of heart and peripheral vasculature to adrenergic agents
• Impaired preload reserve
• Limited chronotropic reserve
Immature Myocardium

Newborn

2 year old

Human myocardium preparations

Calcium

• THE ION OF GOD

When a ball is thrown someone must be there to catch it!

Receptors

• Adrenergic – catecholamines work by interacting with specific receptors
  – α
  – β
  – Need G proteins
  – Activate cAMP – causes a specific cellular response based on the target cell

Receptors

• α-1 receptor
  – "Classic" alpha receptor
  – Post-synaptic receptor on vascular smooth muscle
  • CONTRACTION
**Alpha-1 receptor**

- **What to Expect:**
  - Vascular smooth muscle → contraction → increases vascular resistance → increases blood pressure → Baroreceptor - mediated increase in vagal tone → slowed heart rate

**Alpha-1 receptor**

- **Agonists**
  - Phenylephrine
  - Norepinephrine
  - Epinephrine

**Alpha Effects Case Study**

- 1 mos old POD #10 Norwood with Sano.
- Develops fever, erythematous sternal wound and ↑WBC
- Taken to OR for washout on POD #12.
- Post op – hypotensive in OR
- Started on phenylephrine, epinephrine
- HR 90 sinus, BP 86/36

**Beta-1 receptors**

- **Mechanism of Action**
  - Activation
  - Bind and activate adenylate cyclase → increases cAMP in cell → activation of protein kinase → open Ca channels

**Beta-1 receptors**

- **Agonists**
  - Dobutamine
  - Epinephrine
  - Isoproterenol
- **Antagonists**
  - Metoprolol
  - Esmolol
  - Labetalol
Case Study

- 2 week old, returning from OR after coarctation repair.
- Flushed, warm
- BP 50/36, HR 160
- Lactic Acidosis
- Left ventricle decompensating, poor function

Receptors - β-2 receptors

- Mechanism of Action - Activation
  - stimulates adenylate cyclase → cAMP produced
  - protein kinase activated → RELAXATION of vascular smooth muscle

Beta-2 receptors

- Distribution
  - Vessels in skeletal muscles → relaxes → decreases systemic resistance
  - Bronchiolar smooth muscle → relaxes
  - Smooth muscle in the walls of GI and bladder → relaxes
  - Pregnant uterus → relaxes
  - Cardiac muscle – mechanism is not completely known

Beta-2 receptors

- Agonists
  - Terbutaline
  - Metaproterenol (alupent)
  - Albuterol
  - Levalbuterol (xopenex)

Receptors - Dopamine

- Mechanism of Action - Activation
  - stimulates adenylate cyclase → cAMP

Dopamine- receptors

- Distribution
  - Brain
  - vascular smooth muscle of renal, mesentery and coronary arteries
- Infants respond at lower doses
Dopamine -1 receptors

- Agonist
  - Dopamine
  - Fenoldopam

<table>
<thead>
<tr>
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<tbody>
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<td>↑↑ SVR</td>
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<tr>
<td>BETA 1</td>
<td>Heart</td>
<td>↑↑ heart rate &amp; contraction</td>
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<tr>
<td>BETA 2</td>
<td>Vascular smooth muscle</td>
<td>↓ SVR</td>
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<tr>
<td>DOPAMINE</td>
<td>Smooth muscle</td>
<td>↑ renal Na excre.</td>
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<tr>
<td></td>
<td>&amp; nerve endings</td>
<td>↑ contraction &amp; heart rate</td>
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<td>↑ SVR</td>
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Vasopressin Receptors

- Three types of receptors which respond to AVP – arginine vasopressin
- Located in Renal collecting duct, vascular beds of kidney, bladder, spleen, liver, and brain
- Stimulated by changes in osmolarity or hypotension

- Effects:
  - Vasoconstriction in skin, skeletal muscle, fat
  - Vasodilatation in renal, pulmonary and cerebral vasculature
  - Increases PVR – vasoconstriction
  - Systemic corticosteroids have been shown to suppress endogenous vasopressin production and release
  - Play a part in crucial for pair bonding in voles

Phosphodiesterase

Breaks down cAMP
- PDE3 – cardiac myocytes and vascular smooth muscle

Phosphodiesterase Blockers – Milrinone & sildenafil
- Positive inotropic effect – myocardium
- Vasodilatation in systemic and pul vasculature
- Augments left ventricular relaxation - lusitrophy
Case Study

- 6 year old with presumed myocarditis
  - cool extremities, poor cap refill, HR 145, BP 100/50
  - Echo – poor ventricular function

- What is your goal for therapy
- So now, what?

Consequences

- For every ACTION there is a REACTION!

CONSEQUENCES

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<th>↑ Demands on heart, reflex brady</th>
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<td>↑↑ heart rate &amp; contraction</td>
<td>↑ Oxygen needs, vent ectopy</td>
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<td>↓ SVR</td>
<td>Reflex tachycardia</td>
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<td>DOPAMINE</td>
<td>↑ contraction &amp; heart rate ↑ SVR</td>
<td>Depends on rate of infusion</td>
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Inotropes, Chronotropes, Vasopressors, OH MY

When to Use & When to Wean Norepinephrine

- Warm Septic Shock – vasodilated, hypotensive.
- Head Injury – hypotension related to pentobarbital used to keep ICP’s in control. Wean to keep CPP > 60-65.
  CPP = MAP – ICP
- Anaphylactic reaction
  Half Life 2-2.5 minutes

NOREPINEPHRINE

- Activates α > β-1; very little β-2 effect
- Major effect in animals is alpha
- Inc. Contraction → Vasocostriction → Inc. BP → Vagal reflex (baroreceptors) slow down heart rate
- Little HR or CO affect
- Consequences - inc myocardial oxygen demand

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Norepinephrine Case Study
• 6 yr old admitted with hypotension 70/35, fever x3 days and petechial rash, WBC 23
• Echo with normal cardiac contractility
• Warm shock
• Norepinephrine started at 0.1mcg/kg/min
• 12 hrs later, not acidotic, HR 90, BP 124/88.

What can we consider?

EPINEPHRINE
One Stop Shopping
– Activates α and β1 = β2
– At High [conc.] → alpha effects dominate → vasoconstriction → inc. BP
– At Low [conc.] → Beta effects dominate:
  • β1 → Heart rate and contractility Increase
  • β2 → Vasodilatation of skeletal vessels, increase venous return → Cardiac output increases w/ widened pulse pressure

Epinephrine
• Sepsis with hypotensive shock
• Poor Cardiac Output
  – Post by-pass
  – Sepsis
  – LV dysfunction
  – Bradycardia

Epinephrine Case Study
• 1 month old, POD #0 s/p Norwood with central shunt. On Milrinone
• Becomes hypotensive, acidotic. ECHO reveals poor RV function.
• Epinephrine started at 0.05mcg/kg/min

Where do we want to go? How will we know when we get there? What other things cause hypotension and acidosis?

Vasopressin
• Main Function is to preserve fluid balance
• Hemodynamic Effects - ↑ Ca
  – Potent vasoconstrictor in high concentrations
• Levels are low post by-pass and septic shock
• Potentiates norepinephrine
• Blocks pathway for vasodilatation
• Half life – 10-20 minutes

Vasopressin Case Study
• 6 yr old with septic joint who presents with hypotension and metabolic acidosis.
• On Epinephrine gtt at 0.1mcg/kg/min.
• Started on vasopressin at 0.0015 units/kg/min
• Hypotension resolves, acidosis clears.
• What to wean first?
DOPAMINE
- Activates α-1, β-1, D-1, and D-2 receptors
- Potency: D receptors > β > α
- Half life – ill child 26 min, neonates 5-11
- Also it is an indirect acting sympathomimetic agent
- Doses higher than 20mcg/kg/min?
- Half life – 2 min

MILRINONE
Phosphodiesterase Enzyme Inhibitor.
↑ contractility
↓ SVR
Lusitrophy

Milrinone Case Study
• Post Op  ROSS procedure with moderate mitral regurgitation post op.
  Milrinone 0.5mcg/kg/min to improve contractility and reduce afterload.
  If you reduce workload and improve forward flow you improve regurg.
  Long acting - half life infants – 3 hrs children - 2 hrs (much longer in heart failure or renal failure)

Vasodilators
• Nitroglycerine – hypertension post by-pass half life 1-3 minutes, initial dosing 0.25-0.5mcg/kg/min titrate to 1-3 mcg/kg/min
• Nipride – hypertension post by-pass half-life is < 10 minutes. Initial dosing 0.5-1mcg/kg/min titrate to max 5mcg/kg/min. Monitor thiocyanate levels if > 24 hrs use

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Beta Blockers
• Esmolol – selective beta 1 blocker
  - 50 – 250 mcg/kg/min
• Labetalol – has some alpha blocking ability, beta blocker - 0.4 – 1 mg/kg/hr. IV bolus of 0.3-1mg/kg/dose
RULES of the ROAD

• Know your GOAL
• Know your drugs
• Adjust one drip at a time
• Treat the Patient not the numbers
• When you reach the fork in the road sometimes the best thing is to stop for lunch.

WHAT IS YOUR GOAL?

• 18 month old, 2 hrs post bypass for TOF repair. Pt is cold, base deficit -5, poor pulses, hypotensive 65/45. On Dopamine 5mcg/kg/min, milrinone .3mcg/kg/min and esmolol 50mcg/kg/min

• Improved perfusion
  – Increase contractility
  – Increase preload
  – Decrease SVR

WHAT IS YOUR GOAL?

• 7 month old presumed sepsis. Pt is warm, tachycardic, poor pulses, hypotensive, base deficit -8.

• Improved Perfusion
  – Increased SVR
  – Increase preload

WHAT IS YOUR GOAL?

• 4 yr old with ABI, Pentobarb gtt with continuous EEG monitoring, for 6 bursts/minute. Norepinephrine gtt started at 0.05mcg/kg/min. CPP >65.

• ICP increases to 20, MAP 60
• Increase SVR to preserve CBF

QUESTIONS?