The Uppers and Downers of Cardiac Pharmacology

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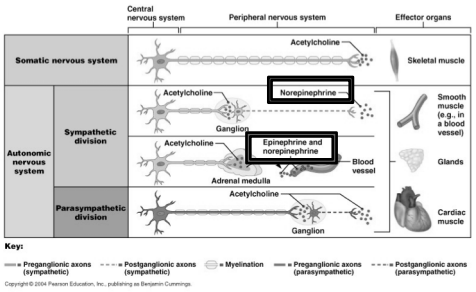


apbrwww5.apsu.edu

Alpha Receptors		Beta Receptors	
1. Vasoconstriction of a. Coronary arteries b. Veins 2. ↓motility of GIT smooth muscle cells			
α1 (postsynaptic)	**α2 (presynaptic)**	**β1 (postsynaptic)**	**β2 (postsynaptic)**
Gq protein coupled Activates **Phospholipase C** **PIP2 →IP3 + DAG**	**Gi protein** coupled Inhibits **Adenyl Cyclase** **ATP →X→cAMP**	**Gs protein** coupled Activates **Adenyl Cyclase** **ATP → cAMP**	
1. Vasoconstriction of blood vessels of a. Skin b. GIT c. Kidney d. Brain 2. Contraction of smooth muscles of a. Ureter b. Vas deferens c. Urethral spinchter d. Uterus e. Cilliary body (mydiarisis) 3. Glucose metabolism a. Gluconeogenesis b. Glucolysis	1. Glucose metabolism a. Inhibits insulin release b. Stimulates glucagon release 2. Contraction of anal spinchter 3. Inhibits release of Norepinephrine	1. The heart a. ↑heart rate (+ chronotropic) b. ↑impulse conduction (+dromotropic) c. ↑contraction (+ inotropic) d. ↑ejection fraction 2. ↑renin release by Juxtaglomerular cells 3. ↑hunger a. ↑ghrelin release by stomach	1. Smooth muscle relaxation of a. Bronchus b. Bronchioles c. Detrusor muscle d. Uterine muscle 2. Contraction of urethral spinchter 3. ↑renin release by Juxtaglomerular cells 4. Glucose metabolism a. Inhibits insulin release b. Stimulate i. Gluconeogenesis ii. Glucolysis 5. Lipolysis 6. Thickened salivary secretion

Generally speaking….

Sympathomimetics

- Any drug that acts on α, ß, or dopa receptors
- Positive inotropy, chronotropy, dromotropy
- Changes in vascular tone

Direct versus indirect agonists

- Indirect: displace catecholamines
- Indirect: decrease clearance of norepinephrine
  - Inhibit reuptake
  - Prevent metabolism (MAOI and COMT inhibitors)

Rational use of vasopressors and inotropes

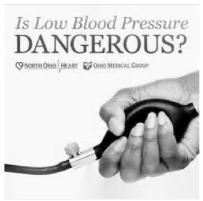
ONE DRUG, MANY RECEPTORS

DOSE-RESPONSE CURVE

DIRECT VERSUS REFLEXIVE ACTIVITY

Practical Issues

- Replete volume first
- Selection and titration
  - Choice should be made based on suspected underlying etiology of hypotension, shock, etc.
  - Titration to achieve end-organ perfusion
  - If first agent ineffective, add a second agent with a different mechanism of action
- Tachyphylaxis may occur
- Consider tissue levels with SQ administered medications, e.g. LMWH
- Frequent reevaluation



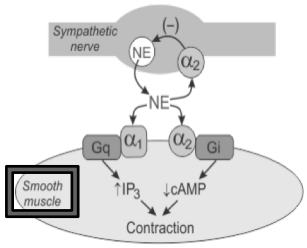
Vasopressors

Phenylephrine

Ephedrine

Norepinephrine

Vasopressin **



http://www.cvpharmacology.com/vasoconstrictor/alpha-agonist

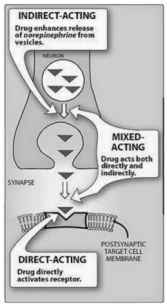
Alpha Receptor Agonists

Phenylephrine

- Direct-acting, relatively pure α1-agonist
- Metabolized by MAO not COMT
- Effects on coronary perfusion
  - During hypotension: will increase CBF without increase in CO
  - MVO_2 does not ↑↑ if hypertension is avoided
- No direct change in contractility, minimal direct changes in preload
- Disadvantages
  - May ↓ SV and ↑ PVR
  - May ↓↓ renal, peripheral, and mesenteric perfusion
  - RARELY may induce vasospasm: IMA, radial, gastroepiploic aa

Ephedrine

- Mixed-acting agent
  - Mild direct: Acts on α1, β1 and β2 receptors
  - Indirect: Enhanced release of NE to post-synaptic receptors
- Renal elimination (mostly unchanged)
- High-bioavailability and relatively long duration of action
- Some bronchodilation
- Less increase in SVR compared to phenylephrine
- Disadvantages
  - Reduced efficacy with depleted NE stores
  - Risk of malignant HTN with MAOIs
  - Tachyphylaxis
  - ↑HR



Ephedrine

- Clinical indications
  - Hypotension with low CO and HR
  - Treatment of sympathectomy
  - Temporary treatment of hypovolemia
  - Treat transient myocardial depression
- Caution
  - Patients on NDRIs and MAOIs
  - Cardiovascular disease, HOCM
  - Closed angle glaucoma
  - Hyperthyroidism

What about OB hypotension?

Vasopressors for the management of hypotension after spinal anesthesia for elective caesarean section. Systematic review and cumulative meta-analysis.

Veeser M[1], Hofmann T, Roth R, Klöhr S, Rossaint R, Heesen M.

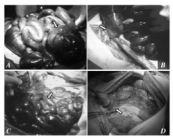
- Findings:
  - Decreased risk of fetal acidosis associated with phenylephrine use.

Acta Anaesthesiologica Scandinavica 2012

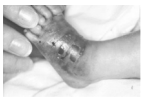
Norepinephrine

- Endogenous catecholamine
  - Primary physiologic post-ganglionic neurotransmitter
- Direct actions on α_1, α_2 and β_1 receptors
- Clinical offset: redistribution, neural uptake, and metabolism
- Advantages
  - Direct agonist
  - Equipotent to epinephrine on β_1 receptors
  - Redistributes BF to central organs
- May see an increase or decrease in BP depending on impact on SVR

Norepinephrine



- Disadvantages
  - Reduced organ perfusion
  - Myocardial ischemia
  - Pulmonary vasoconstriction
  - Arrhythmias
  - Skin necrosis with extravasation
- Clinical Considerations
  - Vasoplegia, septic shock, peripheral vascular collapse
  - Need for ↑BP with an ↑CO
  - ↓BP unresponsive to phenylephrine



Randomized Double-blinded Comparison of Norepinephrine and Phenylephrine for Maintenance of Blood Pressure during Spinal Anesthesia for Cesarean Delivery

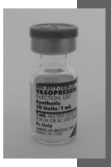
Ngan Kee, Warwick D. M.B.Ch.B., M.D., F.A.N.Z.C.A., F.H.K.A.M.; Lee, Shara W. Y. B.Sc.(Hons.), M.Sc., Ph.D.; Ng, Floria F. R.N., B.A.Sc.; Tan, Perpetua E. B.Sc., M.Phil.; Khaw, Kim S. M.B.B.S., M.D., F.R.C.A., F.H.K.A.M.

Conclusions: When given by computer-controlled infusion during spinal anesthesia for cesarean delivery, norepinephrine was effective for maintaining blood pressure and was associated with greater heart rate and cardiac output compared with phenylephrine. Further work would be of interest to confirm the safety and efficacy of norepinephrine as a vasopressor in obstetric patients.

Anesthesiology
Issue: Volume 122(4), April 2015, p 736–745

Vasopressin

- Direct acting on V_1 receptors
- Preferentially vasoconstricts peripheral, mesenteric as compared with coronary or renal
- Advantages
  - Independent of adrenoreceptors
  - Effective with vasoplegia unresponsive to usually mean
  - Restore coronary perfusion without ↑HR
    - ACLS: Removed to simplify the algorithm
- Disadvantages
  - Symptoms of ↓BF to mesentery, bronchoconstriction, etc.
  - Decrease hepatic BF (esp. if used with α_1 agonists)
  - Decreased platelet count
  - Lactic acidosis (controversial)



Vasopressin

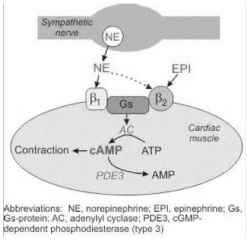
- Clinical considerations
  - Alternative to epinephrine
  - Vasoplegic syndromes
    - ACEI and ARB unresponsive to phenylephrine
    - Septic shock
  - Concomitant use with corticosteroids in septic shock
  - Adjunct to catecholamines in septic shock
- Dosing
  - Resuscitation dose 40 units
  - Infusion 4-6 units/hour
  - IVP 1-2 units

Vasopressin and Septic Shock Trial, VASST 2008 NEJM

Vasopressors for shock

- Gramper, et al (2016) Cochrane Collaboration Review
- Comparison of vasopressor regimens (all RCTs) using 6 different pressor regimens
- Findings:
  - Dopamine increases risk of arrhythmia compared with norepinephrine and might increase mortality.
  - No other differences were found between other regimens. Evidence was insufficient to prove that any of the pressors were superior in terms of mortality
  - Experience, physiologic effects, drug interactions, availability, and cost should be considered

Beta-agonists



Abbreviations: NE, norepinephrine; EPI, epinephrine; Gs, Gs-protein; AC, adenylyl cyclase; PDE3, cGMP-dependent phosphodiesterase (type 3)

	β1 Effects
HR	Increased
Contractility	Increased
Conduction	Increased
Automaticity	Increased
Risk of Arr.	increased

General Clinical Considerations

- What about ß2: bronchodilation and vasodilation
- Dopaminergic stimulation: renal and mesenteric vasodilation
- Effect of ventricular dysfunction in heart failure
  - Diastolic: ß1 enhances lusitropy = reduced LVEDP, LVEDV = improved filling, etc.
  - Systolic: ß1 enhances ejection = reduced LVESV = decreased heart size and MVO_2
- Variable impact on myocardial ischemia
  - Related to MVO_2, wall tension, complete ejection

Dopamine

- Endogenous catecholamine, precursor to NE/Epi
- Dose-responsive direct action with some indirect release of NE
- Clinical offset
  - redistribution, reuptake by nerve terminals, MAO and COMT
- Renal dose dopamine – controversial
  - Role of improved CO
  - Role of aldosterone inhibition

Dose (mcg/kg/min)	Receptor	Effects
1-3	DA_1	Increased renal and mesenteric blood flow
3-10	$ß_{1-2}$, DA_1	Increased HR, contractility, and CO Decreased SVR, PVR may initially rise from α-mediated vasoconstriction
>10	$ß_{1-2}$, DA_1, α	Increased SVR, PVR, HR, Arr. Decreased RBF Possible decreased CO

Epinephrine

- Endogenous catecholamine
- Clinical offset
  - Reuptake; MAO and COMT
- Bronchodilator, stabilizes mast cells

Dose mcg/kg/min	Receptors	SVR
0.01-0.03	B	May decrease
0.03-0.15	B and a	Variable
>0.15	A and B	Increased

- Direct agonist with dose dependent activation of α and ß receptors
  - Increased systolic blood pressure
    - Positive inotrope and chronotrope: $ß_1$ receptors
    - Vasoconstriction: $α_1$ receptors
  - Conversely, $α_2$ receptors agonism
    - Some vascular beds dilate = drop in total VR
      - Increased blood flow to skeletal muscles
    - Possible drop in DBP

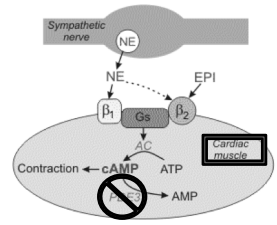
The role of adrenergic agents in goal-directed fluid therapy

Combination of fluid management using dynamic indicators and inotropes if patient is not fluid responsive

Inotropes that have used: low doses of dopexamine, dopamine, dobutamine, and epinephrine

Isoproterenol

- Extremely potent ß effects; very little/no α effects
  - Positive inotrope and chronotrope
  - Direct acting
- Rapid offset (half-life 2 minutes)
  - Metabolized by COMT and MAO
  - Some liver conjugation; 60% excreted unchanged by the kidneys
- Marked increase in CO associated with a fall in DBP, MAP, increase/decrease in SBP
  - Increased CO typically offsets vasodilation
  - Caution in patients with coronary artery disease
  - May shunt blood away from critical organs
  - Not a pressor!



Abbreviations: NE, norepinephrine; EPI, epinephrine; Gs, Gs-protein; AC, adenylyl cyclase; PDE3, cGMP-dependent phosphodiesterase (type 3)

PDE inhibitors

- Breakdown of cAMP by cAMP-dependent phosphodiesterase
- Type 3 isoenzyme targeted by current inotropic medications
- Type 5 uses for erectile dysfunction and pulmonary hypertension
- Nonselective: methylxanthines
- Decrease platelet aggregation by increasing platelet cAMP

http://cvpharmacology.com/vasodilator/PDEI

Milrinone

- PDE_3 inhibitor
- Potentiates cAMP
  - May also relax the LV by increasing Ca^{+2} uptake
- Long half life
- Excreted unchanged in urine; liver metabolism

	Effects
HR	Usually no change or slight increase
Contractility and CO	Increased
BP	Variable
Preload	Decreased
SVR and PVR	Decreased
MVO_2	Usually no change or slight increase

Milrinone

- Advantages
  - Favorable myocardial profile
    - Decrease preload and afterload
    - Minimal tachycardia
    - Less arrhythmogenesis
  - Retains efficacy when NE stores are depleted (chronic CHF)
  - No tachyphylaxis
- Disadvantages
  - Predictable hypotension with rapid IV bolus
- Dosing
  - Loading dose: 50 mcg/kg over 10 minutes
  - Infusion: 0.5 mcg/kg/min
- Indications
  - Low CO with high SVR and LVEDP
  - Bridge to transplant

Calcium

- Actions
  - Necessary for cardiac muscle contraction
- Uses
  - Reverses hypotension
    - Anesthetic induced
    - CCBs
    - Hypocalcemia
    - CPB
    - BBs
  - Hyperkalemic cardiotoxicity

	Effects
HR	No change or decrease
Contractility	Increased
BP	Increase
Preload	No change
SVR	Increase
CO	Variable

Glucagon

- Peptide hormone
  - Increases intracellular cAMP
- Clinical offset: redistribution and proteolysis
  - Duration of action: 20-30 minutes
- Side effects: headache, severe nausea, hyperglycemia and hypokalemia
- Dose: 1-5mg IV slowly
- Use
  - Treatment of beta-blockade overdose due to increase cAMP in the myocardium
  - Bypasses the inhibitory effect of beta-blockade

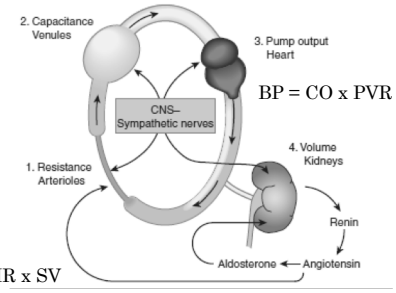
Vasodilators

Direct acting: Nitrates and Hydralazine

Calcium Channel Blockers: Dihydropyridines

Angiotension Receptor Antagonists

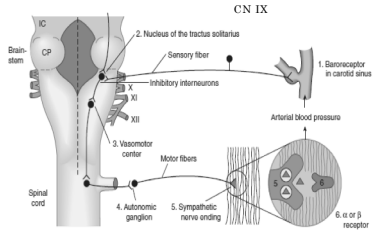
Anatomic Sites of Blood Pressure Control



BP = CO x PVR

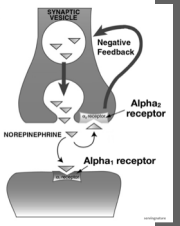
CO = HR x SV

SNS and PNS: Baroreceptors



Clonidine

- Stimulates α_2 receptors in CNS
  - Reduces sympathetic tone = decreased BP and H
  - Reduces plasma norepinephrine levels
- Ratio of α_2: α_1 220:1
- Lipid soluble – rapidly enters the brain
- Patch or oral options
  - Oral rapidly absorbed (peak levels 60-90 mins)
- Elimination half-life 9-12 hours
- Metabolized in the liver; renal excretion



Nitrates: organ System Effects

- Vascular smooth muscle
  - Gradient of response
    - Veins vs. arteries
  - Role of atheromas in epicardial dilation
  - Increased venous capacitance/decreased preload
    - Risk of orthostatic hypotension
  - Baroreceptor and hormonal responses to ↓ arterial pressure
  - Redistribution of blood flow
  - Slight positive inotropic effect via nitric oxide
- Other smooth muscle groups
  - Minimal clinical effects due to brief duration of action
    - Erectile tissue
- Platelets
  - Increased in cGMP = decrease in platelet aggregation
- Other
  - *Nitrites* react to form methemoglobin
    - Not a big player with adults

Toxicity and Tolerance

Toxicity

Direct actions of vasodilation
- Headache, flushing, tachycardia, orthostatic hypotension

Contraindicated with increased ICP

Tolerance

Mechanisms not completely understood
- Reduced bioactivation +/- loss of soluble guanylate cyclase
- Systemic compensation

Variable tolerance depending on which nitrate is used
- Nitroprusside (SNP) not as affected

Nitroglycerin

- Direct acting vasodilator
  - activation of cGMP
- Clinical offset: redistribution, metabolism in smooth muscle and liver
- Advantages
  - Preload reduction
  - No metabolic toxicity
  - Effective for myocardial ischemia, CHF
  - Dilates pulmonary vascular bed
- Reflexive increases in HR and contractility
- Inhibits HPV (less than NTP)
- Methemoglobinemia
- Arteriolar effects (high doses up to 10 mcg/kg/min)
  - Decreased SVR = reduced wall stress and MVO_2
- Coronary artery
  - Relief of vasospasm
  - Redistribution of flow to ischemic areas
- Bolus dosing

Nitroprusside

- Direct acting
  - Dilates both venous and arterial but slightly more arterial at usual doses
- Clinical onset <1min.
- Longer half-life than NTG
- Bolus dosing: (careful!) 20 mcg
- Good for afterload reduction in all types of hypertension
- Blunts HPV
- Potential for steal with steal prone anatomy

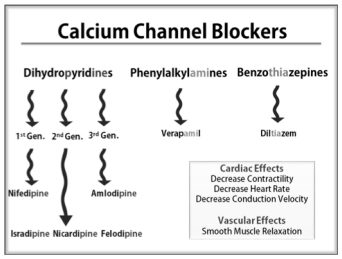
	Effects
HR	Increased (reflex)
Contractility	Increased (reflex)
BP	Decreased (dose dependent)
Preload	Decreased
SVR/PVR	Decreased (dose dependent)
CO	Variable

Cyanide toxicity

- NTP rapidly metabolized to cyanide
- Adults normally able to "detoxify" NTP
- Biggest issues with large, prolonged dosing; hepatic and renal disease
- Treatment
  - Stop the NTP
  - 100% O_2
  - Sodium thiosulfate (150 mg/kg over 15 minutes)
- Diagnosis
  - Challenging in anesthetized patients
  - Hypertension and metabolic acidosis (lactate >8)
    - Late signs: CV collapse with hypotension
  - Seizures/coma; mydriasis
  - Onset often preceded by tachyphylaxis
  - Elevated SVO_2

Hydralazine

- Dilates arterioles but not veins
  - May improve cardiac output, ICP, and RBF
  - Powerful sympathetic responses: tachycardia, increased contractility, increased RAAS
- Does not dilate epicardial arteries
- Risk of tachyphylaxis to antihypertensive effects
- May be used as combination therapy in severe HTN
- Dosage
  - 10-20 mg IVP every 4-6 hours
- Onset 5-20 mins. Peak 10-80 mins. Duration 1-4 hrs * may be difficult to titrate



Calcium Channel Blockers

Calcium Channel Blockers: Kinetics

- Act on L-type calcium channels
- Three chemically dissimilar types with varying actions on smooth muscle and cardiac conduction due to their different binding sites on the calcium channel
  - Dihydropyridines: smooth muscle
  - Benzothiazepine (diltiazem) and phenylalkylamine (verapamil)
- Orally active
- High first pass effect
- High plasma protein binding
- Extensive metabolism

Dihydropyridines

- Smooth muscle selective (for the most part)
- Amlodipine, Nicardipine, Nimodipine, Nifedipine, Clevidipine
- Issues with reflexive tachycardia, flushing, edema
  - Longer acting agents less issues with reflex tachycardia
- Caution
  - Careful in patients with pre-existing bradycardia, conduction defects, heart failure, especially the non-dihydropyridines
  - Avoid concomitant use with beta-blockers

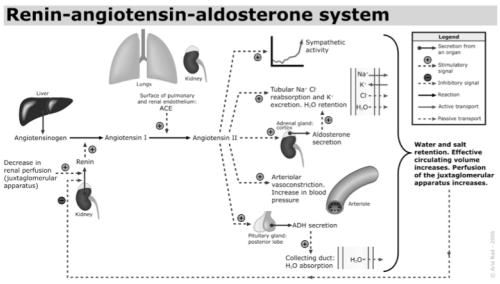
Clevidipine

- Dihydropyridine
  - Highly vascular selective
- Lack of effects on capacitance vessels
- Metabolized by plasma esterases
- Highly protein bound
- Half-life- 1-5 minutes
- IV only, lipid based emulsion
- Similar safety profiles to other vasodilators
- Reduces gastric emptying and will have reduced clearance in pts with pseudocholinesterase deficiency
- Increase hypotensive effects of anesthetics
- Dose
  - 1-2 mg/hr up to 4-6 mg/hr

CCB: organ systems effects

- Smooth muscle
  - Vascular most sensitive but will also see effects on bronchial, GI and uterine
  - Arterioles > veins
  - Useful in variant and effort angina
  - Differing effects on vascular beds
- Cardiac muscle
  - Decreased conduction through blocking slow Ca^{++} channels
  - Decreased excitation- contraction coupling
- Cerebral vasospasm
  - Nicardipine: greater affinity for cerebral vascular bed
- Other effects
  - Excessive inhibition
    - Serious cardiac depression
  - Orthostatic hypotension not a big issue
    - As compared with nitrates

ACE Antagonists



ACE Antagonists

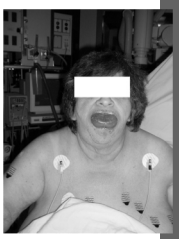
- All of the new agents are prodrugs
  - Not Captopril and Lisinopril
- Can used safely in ischemic heart disease (IHD)
- Commonly used in patients with renal disease
- Eliminated primarily in the kidneys (except lisinopril)
- Enalapril:
  - Parenteral use
    - Can be used for hypertensive emergencies
    - Dose 1.25 mg slow IVP every 6 hours
  - Excreted via kidney and GI tract
- Drug interactions
  - K^+-sparing diuretics
  - NSAIDS

Angiotensin Receptor Blockers (ARB)

- More selective blockers of ATII
- Potential for more complete inhibition of AT
- Less risk of cough and angioedema
- Hypotensive effects increase with diuretic use, vasodilators and anesthetic drugs
- NSAIDs and ASA decrease antihypertensive effects
- Interoperative hypotension treated with fluids and vasopressors, including vasopressin
- Risk of hyperkalemia with potassium-containing solutions (large volumes)
- Lisinopril and ARBs increase the muscle relaxant effects of depolarizing muscle agents (clinical significance?)

Adverse Effects of ACEI

- CNS: dizziness and fainting
- CV: first dose hypotension and tachycardia, angioedema. Hypotension more marked with hypovolemia
- Respiratory: dry cough
- GI: altered taste and weight loss
- Renal: ARF may occur in the setting of renal a. stenosis
- Other: hyperkalemia, neutropenia, agranulocytosis, impaired renal function, nephritic syndrome
- Lisinopril and ARBs increase the muscle relaxant effects of depolarizing muscle agents (clinical significance?)



Off-Label Use of Agents for Management of Serious or Life-threatening Angiotensin Converting Enzyme Inhibitor-Induced Angioedema.
Culley CM[1], DiBridge JN[2], Wilson GL Jr[3].

ACEI-IA is typically a self-limiting event. First-line therapies include ACEI discontinuation, observation, and supportive medications (eg, corticosteroids, antihistamines, and epinephrine). Symptom progression can be life-threatening and may require interventions such as tracheotomy and intubation. Off-label use of FFP and medications approved for hereditary angioedema have resulted in rapid resolution of symptoms and avoidance of intubation. Among these agents, icatibant has the most supporting evidence and has been incorporated into practice guidelines and algorithms as a second-line agent for serious life-threatening ACE-IA.

Ann Pharmacother. 2016 Jan;50(1):47-59. doi: 10.1177/1060028015607037. Epub 2015 Sep 28.

Perioperative management of patients treated with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers: a quality improvement audit

Vijay, Grover, Coulson, Myles (2016). Anesthesia and Intensive Care

No statistically significant difference between use of vasopressors, intraoperative fluid requirements, or lowest SBP between held and continued groups

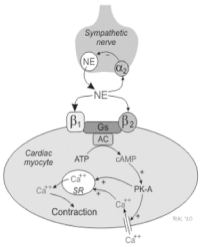
No adverse effects from holding ARB/ACEI either

Recommendations: patient specific decision-making

Withhold prior to major surgery/major fluid shifts, hypotension or large fluid requirements

βeta-Antagonists (Sympatholytic)

- Mechanism of Action
  - Negative inotropy
  - Decreased in activation of RAAS
  - Nonselective may oppose the vasodilating effects of ß2 agonists in some vascular beds
    - Brief effect
  - Prolonged use may decrease SVR through unknown mechanism



Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; AC, adenylyl cyclase; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum

http://www.cvpharmacology.com/cardioinhibitory/beta-blockers

Specifics of selected beta-antagonists

- Esmolol
  - Short acting due to esterase metabolism
  - Cardioselective ß1
- Metoprolol
  - Cardioselective ß1;
  - Enhances CNS depression of sedatives
  - May cause significant bradycardia if used during reversal
- Labetaolol
  - α_1 antagonism; non-selective ß antagonism
  - IV: ratio α_1:ß 1:7 (less significant ratio with PO)
  - Vasodilation and orthostatic hypotension
  - Limited effect on CO and coronary blood flow

Anesthesia Considerations

- Should not be abruptly stopped
  - Withdrawal Syndrome: tachycardia, hypertension, ischemia/infarction
- Continue up to surgery
- Increased cardiovascular effects
- May mask inadequate anesthesia, hypoglycemia
- Be aware of increased risk of bradycardia with reversal
- Adequate fluid admin may prevent postural hypotension
- Compensatory tachycardia with blood loss may be blunted

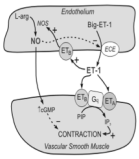
Controversy over perioperative beta blockade in noncardiac surgery

Two small randomized controlled trials published in 1996 and 1999 reported associations between perioperative ß-blockade and significant reductions in long-term and 30-day cardiac mortality, respectively. These 2 studies prompted guideline changes in 2002 encouraging perioperative ß-blockade in subsets of noncardiac surgery patients. However, subsequent trials failed to validate these results. In 2008, the first large randomized controlled trial on the topic was published and found an association between perioperative ß-blockade and an increase in perioperative mortality. Furthermore, in 2011, the lead author of the 1999 study was dismissed from his academic position for scientific misconduct, casting doubt on the validity of guidelines based on his work. Existing studies are highly heterogeneous, making comparisons difficult. Current literature does not support initiating perioperative ß-blockade in noncardiac surgery patients not already receiving these medications.

Durham and Mackey (2016) Journal of Clinical Therapeutics

Endothelin Receptor Antagonists

- Endothelin
  - 21-amino acid peptide produced by vascular endothelium
  - Potent vasoconstrictor
  - Receptor activation leads to formation of IP_3 – release of Ca++- increased smooth muscle contraction and vasoconstriction
  - Transient vasodilation with activation of ET_B without ET_A
- Bosentan (ET_B &ET_A)and Ambrisentan (ET_A)
  - Potential uses in hypertension, heart failure and pulmonary hypertension
  - Only approved for PAH



http://cvpharmacology.com/vasodilator/ETblockers

Combination agents

- Diuretics and potassium sparing diuretics
  - Reduces blood pressure without issues with hypokalemia and hypomagnesemia
- Beta blockers and diuretics
  - Counteracts the water retaining effects of BB
- ACEI and diuretics
  - Thiazide diuretics may induce the RAAS; ACEI counteract this effect
- ARB and diuretic
  - Similar to above but does not have the issue of coughing with ACEI
- CCB and ACEI
  - Affect possible end organ dysfunction: renal protective, reduction of LV mass, decrease mediators of vascular disease

Questions

CRNA in Training

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