ACE Inhibitors & Angiotensin Receptor Blockers

This handout contains a written transcript of the narration in the online presentation. Please review the online presentation for additional material including interactive multimedia content, illustrations, practice questions, references, and audio.

You can access the online presentation at: www.apexanesthesia.com

Case Study

Chip is a 52-year-old male with a history of primary hypertension and asthma. He takes lisinopril daily, but his last dose was 24 hours ago. He also takes albuterol as needed. Today, Chip presents for a laparoscopic cholecystectomy. Following induction with propofol, fentanyl, and cisatracurium, his blood pressure declines to 60/40. His hypotension is refractory to treatment with phenylephrine as well as ephedrine. The surgeon is agitated, because he’s unable to place the patient in reverse-Trendelenburg due to your concerns about hypotension. What are your next steps?

In this objective, we’re going to review the physiology of the renin-angiotensin system, and then we’ll explore the anesthetic implications for the patient on an ACE inhibitor or angiotensin receptor blocker.

Renin-Angiotensin Aldosterone System

Blood pressure is regulated by 3 systems: the sympathetic nervous system, the renin-angiotensin aldosterone system, and the vasopressin system. Understanding how these systems operate in health and disease is quintessential to understanding the pharmacologic management of hypertension. In this video, we’re going to cover the renin angiotensin aldosterone system, otherwise known as RAS.

Let’s begin in the kidney, where the juxtaglomerular apparatus in the distal tubule is a key monitor of renal perfusion and solute concentration. In the setting of reduced renal perfusion, the juxtaglomerular cells secrete renin into the systemic circulation, and this enzyme is going to initiate a cascade of events aimed at restoring systemic blood pressure. Some conditions that increase renin output from the juxtaglomerular cells include beta-1 stimulation, hypovolemia, and hyponatremia as sensed by the tubuloglomerular feedback mechanism.

Next, let’s shift our attention to the liver, where a proenzyme called angiotensinogen is produced. This inactive protein travels into the circulation, and in the presence of renin, angiotensinogen is hydrolyzed to angiotensin one. When angiotensin one passes through the lungs, an enzyme expressed by the pulmonary endothelium named angiotensin converting enzyme converts angiotensin one to angiotensin two. Angiotensin two is a highly active protein that produces a variety of physiologic effects designed to restore systemic blood pressure.

First, angiotensin two is among the most powerful vasoconstrictors in the body, increasing arterial and venous tone. Second, in the zona glomerulosa of the adrenal cortex, angiotensin two stimulates aldosterone synthesis, and when aldosterone travels to the distal tubule and collecting ducts in the kidney, it facilitates sodium and water reabsorption as well as potassium and hydrogen excretion. Increased extracellular fluid volume increases cardiac output and blood pressure. Third, angiotensin two contributes to sympathetic nervous system activation by increasing catecholamine output from the adrenal medulla. Forth, it helps to increase antidiuretic hormone output from the posterior pituitary gland, and fifth it contributes to the thirst mechanism. The physiologic effect of angiotensin two is terminated by angiotensinase in the plasma. To bring us full circle, the restoration of blood pressure produces a negative feedback mechanism that reduces renin release.

Evolving evidence sheds new light on this classic physiology. For example, the discovery of angiotensin converting enzyme-2,
angiotensin 1-7, and the MAS receptor suggest the existence of an alternate RAS pathway that produces vasodilation as well as anti-thrombotic, anti-proliferative, and anti-inflammatory effects. Click the link at the end of this video to learn more.

Pharmacology Review

ACE inhibitors and angiotensin receptor blockers are indicated in the treatment of hypertension (where they are most useful when the etiology is increased renin release), post-myocardial infarction (where they help prevent pathologic ventricular remodeling), and congestive heart failure.

Although both drug classes target the renin-angiotensin aldosterone pathway, their differing side effect profiles can be attributed to where they act in this pathway. ACE inhibitors produce their antihypertensive effects by blocking the enzyme that converts angiotensin I to angiotensin II, while angiotensin receptor blockers antagonize the angiotensin II receptor. By inhibiting the ACE enzyme, ACE inhibitors reduce bradykinin clearance, which explains their airway side effects including cough, allergy-like symptoms, angioedema, and bronchospasm. Since angiotensin receptor blockers don’t impact ACE activity, they don’t produce these side effects.

Both drug classes reduce glomerular filtration rate, so they are contraindicated in the patient with renal artery stenosis. Aldosterone inhibition may promote hyperkalemia, which can increase serum potassium in patients with pre-existing renal impairment. Pregnancy is also a contraindication due to an increased risk of fetal complications (1). Perhaps most relevant to anesthetic practice, both drug classes can produce hypotension refractory to conventional treatment, and this topic will be explored in greater detail shortly.

Adverse Events

Central to providing the safest anesthetic experience, we must explore refractory hypotension that can occur in patients on ACE inhibitor or angiotensin receptor blocker therapy. Also, we’ll consider the current thinking on whether these drugs should be continued perioperatively and then discuss some issues yet to be resolved.

As we reviewed in the video, there are three systems that regulate blood pressure: the sympathetic nervous system, the renin-angiotensin aldosterone system, and the vasopressin system. It’s well recognized that anesthetic agents attenuate sympathetic activity, so there’s a greater reliance on the RAAS and the vasopressin systems to support blood pressure during general anesthesia. In the patient on an ACE inhibitor or angiotensin receptor blocker, the RAAS pathway is also attenuated, thus there is an even greater reliance on the vasopressin system. In some instances, this is not enough to maintain hemodynamic stability, and this helps to explain why vasoplegia (severe hypotension unresponsive to conventional therapy) is a feared complication in surgical patients who continue ACE inhibitor or angiotensin receptor blocker therapy preoperatively.

In the setting of vasoplegia, our usual first-line treatments whether it’s reducing anesthetic depth, a fluid challenge, phenylephrine, ephedrine, or epinephrine, may be ineffective. There is some evidence that a norepinephrine infusion can produce a hemodynamic benefit in this context.

In the event that our first-line options fail, familiarity with the use of second-line agents, such as vasopressin (or its analogue terlipressin) as well as methylene blue, is essential.

Vasopressin reverses hypotension by stimulating three vasopressin receptor subtypes: V1 (produces vasoconstriction), V2 (promotes anti-diuresis) and V3 (stimulates the release of cortisol, angiotensin, and natriuretic peptide) (1).

Methylene blue antagonizes the vasodilating effects of nitric oxide in the vascular smooth muscle.
Key side effects include increased pulmonary vascular resistance, coronary vasoconstriction, decreased cardiac output, dysrhythmias, and a reduction in mesenteric and renal blood flow (1).

Because it’s eliminated by the kidneys, methylene blue is contraindicated in patients with severe renal dysfunction. Additionally, it can produce methemoglobinemia in patients with glucose-6-dehydrogenase deficiency.

Methylene blue can precipitate life-threatening serotonin syndrome in patients taking serotonin reuptake inhibitors (2).

Due to its effect on the optical characteristics of hemoglobin, the pulse oximeter and cerebral oximeter may temporarily produce unreliable results following methylene blue administration.

The decision to withhold an antihypertensive agent prior to surgery can be guided by answering three key questions.

Is discontinuing the drug associated with a/an:
- Withdraw syndrome?
- Increased cardiovascular risk?
- Improvement in perioperative hemodynamics?

In the case of discontinuing ACE inhibitors and angiotensin receptor blockers, three recent trials revealing markedly different conclusions have fueled controversy about the best course of action (1-3). Additionally, if these drugs are held, it may be prudent to consider the drug’s specific pharmacokinetic profile when considering the timing of its discontinuation.

In 2017, a large, multinational prospective (though not randomized) trial concluded that withholding ACEIs and ARBs was strongly associated with a decrease in intraoperative hypotensive events, a decrease in postoperative vascular events, and a lower risk of death (1). While these findings greatly contradict the ACC/AHA guidelines that say that it’s reasonable to continue ACEI and ARB therapy preoperatively (2), it is clear that these drugs carry hazardous consequences in some. While we await randomized trials that will inform best-evidence recommendations about whether to continue or hold these drugs before surgery, we should proceed cautiously.

**Key Points**

Under general anesthesia, ACE inhibitors and angiotensin receptor blockers can produce a state of hypotension that is unresponsive to conventional first-line therapies.

Vasopressin and methylene blue are second-line treatments that can reverse vasoplegia.

The ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery states:
- It’s reasonable to continue ACE inhibitors and ARBs perioperatively.
- If these agents are held preoperatively, then it’s reasonable to resume them postoperatively.

While we await randomized trials that will inform best-evidence recommendations about whether to continue or hold these drugs before surgery, we should proceed cautiously.

**References**

Textbooks: These books are included on the CPC Exam Bibliography published by the NBCRNA


Articles:


