Beta Blockers

This handout contains a written transcription of the narration in the online presentation (video). Please review the online presentation for additional material including interactive multimedia content, audio, and practice quizzes.

Case Study

You're called to the emergency department to assist in the resuscitation of Barbra, a 62-year-old-female with a history of atrial fibrillation and depression. The nurse informs you that an empty bottle of propranolol was found at the patient's side when the first responders arrived at the scene. Her heart rate is 35 beats per minute, her blood pressure is 65/40 mmHg, and she's thus far been unresponsive to sympathomimetic therapy. Based on this information, you suspect beta blocker overdose. What is the gold standard treatment for this condition? What newer therapies have shown promise? In this objective, we're going to consider the physiology and pharmacology of the beta receptor, beta blocker overdose, and the current thinking in the use of beta blockade in surgical patients.

Beta Receptor Physiology

The beta receptor is a key component of the sympathetic nervous system, where receptor activation augments sympathetic activity and receptor inhibition reduces sympathetic activity. Beta receptors are classically divided into two subtypes: beta-1 and beta-2. The beta receptor is a G-protein coupled receptor. The receptor is activated when it binds with an agonist (also called a first messenger). Examples of beta agonists include epinephrine, norepinephrine, dobutamine, and isoproterenol.

The beta receptor is coupled to a G stimulatory protein, so beta receptor activation increases adenylate cyclase activity. In turn, adenylate cyclase facilitates the conversion of ATP to cyclic AMP. cAMP, the second messenger, is responsible for "turning on" a variety of protein kinases inside the cell that will ultimately instruct the cell to perform a specific function. It's important to note, however, that the function of the second messenger is specific to each cell type. Let's look at a few examples.

In the cardiac myocyte, cyclic AMP augments myocardial performance in several ways. First, it increases intracellular calcium which increases the force of contraction, otherwise known as inotropy. Second, cyclic AMP increases the rate of myocardial relaxation by accelerating the return of calcium to the sarcoplasmic reticulum — this is called lusitropy. By contrast, beta-2 stimulation of vascular smooth muscle produces a different cellular response, where cyclic AMP reduces the intracellular concentration of calcium. This produces vasodilation of the skeletal muscle vascular beds and reduces systemic vascular resistance. For completeness, we'll provide an exhaustive list of beta-1 and -2 receptor function at the end of this video.

For every ligand-receptor interaction, there must be an "off" switch. As we've seen, beta receptor stimulation increases cyclic AMP, so now we need a way for the cell to return to its baseline level of activity. Phosphodiesterase III metabolizes cyclic AMP to adenosine monophosphate. This "turns off" the protein kinases and the cell is no longer instructed to perform that specific function.

Here's a list of the most important beta-1 and -2 receptor functions in the body. It's important that you understand these, because a drug's specificity for each receptor subtype can be used to predict its function and side effects.

Here is a more inclusive list of beta-1 and -2 receptor function:

Beta-1 functions include:

- Heart: Increased heart rate, contractility, conduction velocity, and lusitropy
- Kidney: Renin release

Beta-2 functions include:

- Bronchial tree: Bronchodilation
- Coronary arteries: Vasodilation
- Skeletal muscle arteries: Vasodilation
- Pancreatic beta cells: Increase insulin release
- Liver: Increase serum glucose
- Uterus: Uterine relaxation
- Bladder: Relaxation of the detrusor muscle
- Eye: Ciliary muscle relaxation for accommodation
- Cell: Activate hydrogen/potassium pump to drive potassium into cells. This can produce hypokalemia.

Pharmacology Review: Part 1

Beta blockers are categorized as a function of the receptor subtypes for which they select. This includes drugs that select for the beta-1 receptor, non-selective agents that target both the beta-1 and -2 receptors, and those that are non-selective that also block the alpha-1 receptor. We can take advantage of receptor selectivity by choosing drugs that provide a desired clinical effect while minimizing side effects. Receptor selectivity tends to diminish in the setting of beta blocker overdose.

	β1	β1 + β2
(-) ISA	Atenolol Bisoprolol Esmolol Metoprolol	Propranolol Timolol Sotalol
(+) ISA	Acebutolol Celiprolol	Labetalol Oxprenolol Pindolol
α1 Block	0	Carvedilol Labetalol

Beta blockers are indicated for the treatment of hypertension, coronary artery disease, chronic congestive heart failure, dysrhythmias, and migraines. Long-term beta blocker therapy prolongs life in patients with coronary artery disease who've experience a previous myocardial infarction.

Abrupt withdraw of chronic beta blocker therapy can cause rebound hypertension and angina. Avoid beta blockers if the patient has severe bradycardia, second- or third-degree heart block, uncompensated congestive heart failure, and asthma.

Intrinsic sympathomimetic activity describes a drug with a partial agonist effect, while simultaneously blocking other agonists that have a higher affinity for the receptor. Beta blockers with ISA antagonize catecholamines at the beta receptor, yet they provide some degree of sympathetic activation while occupying the receptor. This was once believed to help maintain cardiac output or prevent bronchospasm, however more recent evidence questions whether beta blockers with ISA might be more harmful than those without.

Anesthetic agents may enhance the myocardial depressant effects of beta blockers. Beta blockers can mask the sympathetic effects of hypoglycemia, making this a challenging diagnosis in diabetics under general anesthesia.

Pharmacology Review: Part 2

Non-selective beta-blockers increase airway resistance, and many clinicians avoid beta blockade in the patient with asthma or COPD. The risk of pulmonary impairment vs. the benefit of cardiac protection has been debated, and further research is needed in this area.

Non-selective beta blockers reduce the efficacy of beta agonists in the patient who is actively wheezing.

Propranolol reduces liver blood flow, which can slow the metabolism of amide local anesthetics. This can increase the plasma concentration of the local anesthetic.

Atenolol relies on the kidneys as its primary route of elimination. It can accumulate in the patient with renal failure.

Esmolol is the only beta blocker that is metabolized by red blood cell esterases, and this accounts for a very short half-life of 9 min. Esmolol is typically used for heart rate control that is easy to titrate.

Labetalol has a beta to alpha block ratio of 7:1. This makes it attractive for treatment of hypertensive emergencies (decreased inotropy + systemic vasodilation → decreased blood pressure).

Beta Blocker Overdose

Beta blocker overdose is characterized by a profound myocardial depression. The clinical presentation may include bradycardia, dysrhythmias, hypotension, and decreased cardiac output that can progress to cardiogenic shock. Restoring hemodynamic stability is the mainstay of treatment; however, conventional therapy often fails to produce acceptable results. To date, there are no universally agreed upon treatment guidelines for beta blocker overdose.

Glucagon

Considered by many as the gold standard treatment for beta blocker overdose, glucagon improves heart rate and myocardial contractility independent of autonomic function. Said another way, even though the beta receptor is inhibited by the beta blocker, glucagon is able to increase adenylate cyclase activity without first stimulating the beta receptor. The dose range is 1 to 10 mg IV followed by a continuous infusion of 5 mg/hr. Key side effects of glucagon include nausea, vomiting, and hyperglycemia.

Sympathomimetics

Beta antagonism is competitive in nature, so a catecholamine may be administered to compete with the beta antagonist. The relative balance between the concentration of beta blocker and catecholamine will greatly influence the efficacy of the catecholamine. Atropine, vasopressin, PDE inhibitors, calcium, and cardiac pacing may be considered for hemodynamic support.

Emerging Therapies

Several case reports detail some exciting developments in the treatment of beta blocker overdose. Commonly used for local anesthetic toxicity, intravenous lipid emulsion has been used to successfully treat beta blocker overdose. The lipid emulsion acts as a lipid sink inside the vasculature, which captures the beta blocker in the plasma, rendering it unable to inhibit beta receptors throughout the body. High-dose insulin with dextrose supplementation to maintain euglycemia is believed to provide hemodynamic support through insulin's positive inotropic effects. Additionally, it increases glucose delivery to a stressed myocardium as well as improves microcirculatory flow. Venoarterial extracorporeal membrane oxygenation has been used to restore and then maintain perfusion until the beta blocker has been cleared from the body.

The Problem with POISE

Many view beta blocker therapy as a cornerstone of perioperative management in patients with suspect cardiovascular health, and the literature is replete with high-quality trials demonstrating a reduction in cardiac risk when beta blockers are administered to this population.

The POISE trial was a randomized controlled study of noncardiac surgical patients with, or at risk of, atherosclerotic disease. The researchers investigated the association between perioperative beta blockade and cardiac outcomes including myocardial infarction, cardiac arrest, and cardiac death. Although a reduced risk of myocardial infarction was observed, there was a problem. When compared to placebo, patients who received extended-release metoprolol experienced a higher incidence of stroke and mortality. A possible explanation for this finding was that the dose of metoprolol did not reflect common practice; it was too high. Consequently, this may have adversely affected the

patients' ability to self-resuscitate. This controversy gave way to newer guidelines warning that the routine use of high-dose beta blocker therapy without careful titration may be harmful. As with virtually every drug we administer, titration to effect is a guiding principle of evidence-based care.

Current Guidelines & Emerging Evidence

A patient on chronic beta blocker therapy should continue therapy throughout the perioperative period. We strongly recommend that you review the following guidelines:

- The Surgical Care Improvement Protocol (SCIP) states that a patient on chronic beta blocker therapy must receive a beta blocker within 24 hours of surgical incision. Additionally, beta blocker therapy for in-patients should be continued throughout hospitalization.
- The ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery provides guidance on which patients should receive perioperative beta blockade.
- A recent meta-analysis concluded that variable clinical responses to beta blockers are likely due to differing patient characteristics as well as the unique pharmacologic properties of these drugs. For example, the authors suggested that bisoprolol and atenolol may be safer than metoprolol because of the latter's extensive and highly variable metabolism by the cytochrome P450 system.
- In an analysis of the electronic medical records of nearly 35,000 cardiac surgical patients, researchers compared patients who were and those who were not taking a beta blocker preoperatively. Interestingly, they found that preoperative beta blocker use was not associated with a significant decrease in 30-day negative outcomes (inclusive of stroke, myocardial ischemia, need for prolonged ventilation, and death) [4].

Key Points

Here are some key points for your practice:

- The routine use of beta blockers should be questioned, and the decision to use one should be determined by the patient's specific risk-benefit ratio. The most current ACC/AHA guidelines provide guidance for this decision.
- Beta blockers differ in their pharmacokinetic and pharmacodynamic effects, and appropriate drug selection should be based on these unique characteristics.
- There are pharmacogenetic factors operative in patients that may play out in a complex and difficult to predict manner.
- Perioperative beta blockers should be titrated to clinical effect.