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Cardiac Pharmacology: Clinical Applications

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Introduction

Cardiac pharmacology has traditionally been focused on the selection of agents designed to augment cardiac function. Increases in cardiac performance can occur as a result of increasing cardiac contractility (i.e. cardiac output), modifying after load (either pulmonary or systemic), and controlling heart rate and rhythm. Historically, positive inotropic drugs (PIDs) have served as the principal agents for increasing overall cardiac contractility and performance. The debate regarding the choice of the “ideal” inotropic agent (PID) has been going on for decades. Often the selection of which specific PID to administer is based on personal clinician preference rather than specific hemodynamic and/or pharmacologic indications. Earlier studies, focused in the area of cardiac surgery, identified both preoperative and intraoperative predictors which are associated for the need for inotropic (PID) support. However, a recent article has called in to question of the risk/benefit issues associated with the routine administration of PIDs, i.e., without a well defined or specific hemodynamic indication. In addition, genetic studies have already identified particular polymorphisms in patients undergoing CABG surgery that will affect the response to specific PID’s.

To optimize clinical benefits, it is imperative clinicians select cardiac pharmacological interventions based upon specific pathophysiological/disease processes, not as a matter of “routine”. Traditionally agents for the treatment of low output syndrome have been divided into drugs that work via increases in cAMP (either directly or indirectly) and those that work via alternative mechanisms. The magnitudes of agents that are used to treat low cardiac output syndrome in the perioperative period are the cAMP dependant agents. There are two main classes of these agents; the beta adrenergic receptor agents and the PDE inhibitors. Although comparisons among specific agents have failed to demonstrate any relevant differences in outcomes, studies have clearly demonstrated the advantage of using PDE-III agents in combination with catecholamine.

New agents have focused on non cAMP dependent mechanisms of action. Levosimendan is a calcium sensitizing agent which functions by binding Troponin C in a calcium dependent fashion. Levosimendan does not increase intracellular calcium as concentration, and therefore does not impair diastolic cardiac function. In addition, Levosimendan provides peripheral and coronary vasodilatation resulting in afterload reduction and improved coronary perfusion. The overall hemodynamic effects are an increase in contractility without a concomitant increase in myocardial O₂ consumption. As it is not a beta-adrenergic agent, its efficacy is not impacted by beta blockade. Unfortunately, the clinical reports of its effectiveness have been mixed. At the current time, its use is limited (in Europe) to patients with aortic decompensated heart failure, once any associated hypovolemia has been corrected.

Thyroid Hormone

Historically there has been a great deal of interest in the use of IV thyroid hormone (T3) for use as a positive inotropic agent in cardiac surgery. Multiple studies have demonstrated the presence of euthyroid “sick” syndrome associated with persistently reduced concentrations of T3 in blood following cardiac surgery (in both children and adults). In addition, data suggest that following ischemia and reperfusion injury, T3 increases inotropy faster than isoproterenol. However, randomized controlled clinical trials in patients following CABG, failed to demonstrate the efficacy of T3 in this population.

NATRIURETIC PEPTIDE

B-type natriuretic peptide (also called BNP and brain natriuretic peptide, because it was first isolated from pig brain) has recently received attention for the diagnosis and management of patients with cardiac dysfunction, particularly CHF. Endogenous BNP is synthesized predominantly in the heart, principally in the ventricles. The release of BNP occurs in response to increases in ventricular volume and/or wall stress (as seen in CHF or ischemia).

The precise mechanism mediating the biological actions of BNP are not completely understood, but it appears to be mediated by activating cyclic GMP (cGMP). However, some activities may be mediated by other

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pathways involving suppression of the renin angiotensin - aldosterone system, increasing the permeability of the vascular endothelium and/or inhibiting sympathetic neurotransmission in peripheral vasculature.

Laboratory and clinical studies have demonstrated the following hemodynamic effects associated with BNP infusion: vasodilatation (decreased right and left side filling pressures), decreased systemic vascular resistance (SVR) and increased cardiac index (CI). This increase in cardiac index is seen as a result of decreasing after load. There is no direct inotropic effect of BNP.

BNP has significant diuretic and natriuretic effects mediated by the inhibition of sodium transport in the collecting tubule as well as increasing glomerular filtration rate. In addition, there is inhibition of the renin-angiotensin-aldosterone system as a result of decreasing renin release from the macular densa, inhibiting aldosterone release for the zona glomerulosa and suppressing ACE activity. BNP also antagonizes the action of vasopressin subsequently inhibiting water transport in the collecting ducts.

Application of BNP (Nesiritide) in the clinical arena.

Nesiritide was initially approved for treatment of patients with decompensated heart failure (NYHA Class IV). Comparison studies, including the VAMC (vasodilation in the management of acute congestive heart failure) and PRECEDENT (prospective, randomized evaluation of cardiac ectopy with dobutamine or Nesiritide therapy) trials. In clinical studies, Nesiritide reduces symptoms of acute decomposition. HF similarly to NTG without developing acute tolerance. However the mortality rate at 6 months was greater in patients receiving Nesiritide than the NTG group. Recent data, suggest that Nesiritide may not affect a compelling safety advantage but may be associated with an increased incidence of adverse side effects, including renal failure and mortality.

BNP: Predictive value in a clinical setting

Studies in the cardiology literature demonstrate both a diagnostic and predictive value for BNP levels as it relates to the diagnosis of CHF. BNP has prognostic value in patients with heart failure and acute coronary syndromes. Recent studies have also shown that BNP levels are useful predictors of significant coronary events and death following percutaneous coronary intervention. The interest in using BNP to “signal” cardiac dysfunction has also been examined in patients undergoing coronary artery surgery. A study by Kerbaul et al (in patients undergoing off pump coronary artery surgery) revealed that pre-operative BNP levels were excellent predictors of postoperative outcomes. However, studies in patients with septic shock have failed to demonstrate an association between BNP levels and outcomes.

Dosing: BNP

The recommended dosing regimen for Nesiritide (in CHF) include 1) bolus loading dose of 2 mcg/kg administered over one minute followed by a fixed dose continuous infusion at a rate of 0.01 mcg/kg/min. Higher infusion rates *do not* appear to improve hemodynamics but may result in an increased incidence of hypotension. Dosage adjustments *are not* necessary in patients with renal dysfunction. The clearance is not significantly affected by factors such as; age, gender, race/ethnicity or endogenous BNP levels at baseline or the severity of heart failure at baseline.

NEWER APPROACHES FOR MANAGEMENT OF PULMONARY HYPERTENSION: INHALED PULMONARY VASODILATORS

Pharmacological Management of Pulmonary Hypertension

Pharmacological methods for the management of pulmonary hypertension are focused on the administration of pharmacological agents that demonstrate specificity for dilating the pulmonary vasculature (i.e. pulmonary versus systemic vasodilatation). The greatest benefit will be derived from those agents that exert the greatest possible effect on the pulmonary vascular bed while minimally affecting the systemic vasculature. To this end, the administration of agents that would maintain systemic arterial pressure but decrease RV after load is ideally suited. Reducing RV dilation and RV end-diastolic pressure is essential in avoiding a leftward shift in the intraventricular septum.

Traditionally, pulmonary vasodilatation is accomplished using intravenous agents. One of the primary limitations of this route of administration has been the negative effects of this route on intrapulmonary shunt and the systemic circulation (i.e., blood pressure). All of the intravenous agents while decreasing PVR are associated with a

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significant increase intrapulmonary shunt, and a worsening of an already existing hypoxemia. In addition, they produce hypotension. Newer agents delivered by inhalation offer the advantages of matching ventilation and perfusion and have little or no effects on systemic vascular resistance and therefore maintain blood pressure and oxygenation.

Inhaled Nitric Oxide (1st Inhaled Agents)

The clinical use of nitric oxide in pulmonary hypertension was first described in the early 1990s. Nitric oxide (NO) has evolved from a pollutant and toxic contaminant in nitrous oxide cylinders to a vitally important agent with a multitude of physiological mechanisms. NO is now known to control basal vascular tone, to constitute the common pathway of action of nitro-vasodilators, to interact with hypoxic pulmonary vasoconstriction, to inhibit platelet activation and aggregation, and to play a role in sepsis-induced myocardial dysfunction and vasodilation. Ventilation-perfusion matching in the lung is improved by auto-inhaled NO produced in the upper airways that selectively vasodilates vessels belonging to ventilated alveoli. NO is synthesized by the incorporation of molecular oxygen in the guanidine nitrogen of L-arginine. A family of enzymes, the nitric oxide synthases (NOS) and neuronal NOS catalyzes this reaction. When delivered as a gas, exogenous nitric oxide diffuses into the adjacent vascular smooth muscle where it activates guanylate cyclase. This leads to an increase in cyclic guanosine 3',5' monophosphate (cGMP) resulting in smooth muscle relaxation. NO rapidly binds to hemoglobin (after diffusing into the intravascular space) forming nitrosyhemoglobin, which is then rapidly oxidized to methemoglobin, which is extracted by the kidneys. Since all of the inhaled NO (iNO) is rendered inactive in the pulmonary circulation, the systemic effects, i.e. system vasodilation and subsequent hypotension are minimized. It is this rapid conversion of NO (yielding an inactive form) that impacts its specificity. Potential problems with the administration of iNO are an increased bleeding time, negative inotropic effects, and the formation of potentially toxic end products (e.g. nitrogen dioxide, methemoglobin and peroxynitrite).

The widespread use of nitric oxide for pulmonary hypertension has been limited by its cost and the technological support required in delivering the drug safely. Alternative techniques designed to increase iNO availability in the pulmonary circulation are being sought in the form of Nitric Oxide donor agents such as:

Inhaled Sodium Nitroprusside and Inhaled Nitroglycerin

Inhaled Phosphodiesterase (PDE) Inhibitors (Inhaled and Oral)

The pulmonary vascular effect of the inhaled phosphodiesterase inhibitors has been investigated. Phosphodiesterase inhibitors work by blocking the hydrolysis of cyclic guanosine monophosphate (cGMP). Cyclic guanosine monophosphate is a biologic property of NO whose intracellular concentrations are increased with its use. Investigators have determined that these phosphodiesterase inhibitors not only augment the effect of combined iNO administration but also produced selective pulmonary vasodilation when given alone. PDE inhibitors of the type III (milrinone and amrinone) and type V (zaprinast, sildenafil and dipyridamole) have been studied. It has been reported that sildenafil administered alone (orally) or in combination with iNO has been useful in causing pulmonary and systemic vasodilatation and hence improved cardiac output in patients with pulmonary hypertension. Sildenafil may exert its effects via two independent mechanisms of action: Increased cGMP concentration and opening of potassium channels. In animal studies, aerosolized sildenafil and zaprinast demonstrated selective pulmonary vasodilation when given alone and augmented the effects of iNO when given in combination, interestingly; zaprinast lost some of its pulmonary selectivity at higher doses.

As Sildenafil is the only PDE V agent available for oral administration, it offers a unique therapeutic option. This agent has been used clinically in a variety of chronic settings including pregnancy complicated by PIH.

ARGININE VASOPRESSIN (AVP)

Arginine Vasopressin is an endogenous peptide synthesized exclusively in the hypothalamus and released from the posterior pituitary. Traditionally AVP release is stimulated by changes in vascular volume and vascular time. Vasopressin is bound by two distinct types of receptors: renal (V_2) and vasomotor (V_1).

Although under normal conditions AVP contributes little, if any to blood pressure maintenance, recent investigations have demonstrated the ability of AVP to be helpful in the management of certain refractory vasodilatory states. In a syndrome known as "vasodilatory shock" characterized by: catecholamine resistance, SVR



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≤ 650 dynes and blood pressure ≤ 65 mmHg. In these patients, with the diagnosis of vasodilatory shock, the infusion of AVP significantly improved hemodynamics and reduced the need for norepinephrine infusion.

Vasopressin has been used as a standard therapy for the management of diabetes incipitous. The syndrome of "vasodilatory" shock offer new opportunities for vasopressin use. This syndrome has been reported in patients: following CPB, with sepsis or those requiring the insertion of ventricular assist devices. A common theme in this "vasodilatory shock" state appears to be a relatively low level of circulating endogenous vasopressin. However, many clinicians are now routinely administering vasopressin for hypotension of unknown etiology. This is clear and concerning as in situations when the BP is low and both the cardiac index and resistance are higher, the administration of a potent vasopressor such as vasopressin will worsen overall cardiac performance. Vasopressin administration should be used (for hemodynamic purposes) in those patients manifesting the hemodynamic alterations associated with vasodilatory shock.

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What's New in Cardiac Pharmacology?
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Objectives – Upon completion of this lecture, participants will be able to:

1. Discuss the etiology of reduction in cardiac performance in the perioperative period.
2. Develop a treatment plan for patients requiring a positive inotropic agent
3. Discuss the role of atrial natriuretic peptides for diagnosis and treatment in selected clinical situations (CHF/cardiac surgery)
4. Appreciate the importance of pulmonary vasodilators in treatment of RV failure.
5. **Describe** the pharmacology and application of vasopressin for treatment of “vasodilatory shock”.

Disclosure

This speaker has indicated that he or she has no significant financial relationship with the manufacturer of a commercial product or provider of a commercial service that may be discussed in this presentation.