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# TEACHERS' TOPICS

## Antianginal Actions of Beta-Adrenoceptor Antagonists

Stephen T. O'Rourke, PhD

College of Pharmacy, North Dakota State University

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Angina pectoris is usually the first clinical sign of underlying myocardial ischemia, which results from an imbalance between oxygen supply and oxygen demand in the heart. This report describes the pharmacology of β-adrenoceptor antagonists as it relates to the treatment of angina. The β-adrenoceptor antagonists are widely used in long-term maintenance therapy to prevent acute ischemic episodes in patients with chronic stable angina. Beta-adrenoceptor antagonists competitively inhibit the binding of endogenous catecholamines to $\beta_1$-adrenoceptors in the heart. Their anti-ischemic effects are due primarily to a reduction in myocardial oxygen demand. By decreasing heart rate, myocardial contractility and afterload, β-adrenoceptor antagonists reduce myocardial workload and oxygen consumption at rest as well as during periods of exertion or stress. Predictable adverse effects include bradycardia and cardiac depression, both of which are a direct result of the blockade of cardiac $\beta_1$-adrenoceptors, but adverse effects related to the central nervous system (eg, lethargy, sleep disturbances, and depression) may also be bothersome to some patients. Beta-adrenoceptor antagonists must be used cautiously in patients with diabetes mellitus, peripheral vascular disease, heart failure, and asthma or other obstructive airway diseases. Beta-adrenoceptor antagonists may be used in combination with nitrates or calcium channel blockers, which takes advantage of the diverse mechanisms of action of drugs from each pharmacologic category. Moreover, concurrent use of β-adrenoceptor antagonists may alleviate the reflex tachycardia that sometimes occurs with other antianginal agents.

**Keywords:** angina, β-adrenoceptor antagonists, myocardial ischemia, pharmacology

### INTRODUCTION

*Cardiovascular Pharmacology* is taught during the spring semester of the second-professional year of the PharmD curriculum at North Dakota State University. The course is the fourth in a series of six 3-credit courses focusing on pharmacodynamics and applied therapeutics, and is offered concurrently with neuropharmacology. The topics covered in cardiovascular pharmacology rely heavily on material learned in previous coursework. Prior to enrolling in cardiovascular pharmacology, students have already completed courses in pathophysiology (2 semesters), biochemistry (2 semesters), immunology (1 semester), principles of pharmacology (1 semester), autonomic and endocrine pharmacology (1 semester), and pharmacokinetics (1 semester). Major topics covered include antianginal drugs, anticoagulants/thrombolytics, diuretics, antihypertensives, antihyperlipidemics, cardiotonic agents, and antiarrhythmics. This paper summarizes the general approach and content presented in teaching the pharmacology of β-adrenoceptor antagonists and their use in the treatment of ischemic heart disease. Key aspects of cardiovascular physiology and pathophysiology that are of importance to myocardial ischemia are reviewed in depth prior to discussing the β-adrenoceptor antagonists.

**Corresponding Author:** Dr. Stephen T. O'Rourke, Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND 58105. Tel: 701-231-7836. Fax: 701-231-7606. E-mail: stephen.orourke@ndsu.edu

### INSTRUCTIONAL METHODS AND OBJECTIVES

From 2004-2006, *Cardiovascular Pharmacology* met 3 times per week, with each class lasting for a period of 50 minutes. Class size usually ranged from 80 to 85 students. A lecture-based format using PowerPoint slides was generally used. Reading assignments were taken from a standard pharmacology textbook, as well as recent relevant journal articles, when appropriate. Handouts containing schematic diagrams of key points were distributed to the students, as needed, but students were expected to take detailed notes of their own during class. Questions were frequently raised by the instructor for the purpose of stimulating discussion in the classroom. Questions from students were encouraged and often served as the basis for additional discussion. Current pharmacology-related topics of interest were also incorporated into the lectures

and discussions, and sometimes included reports from the lay media or recent findings presented at national or international scientific conferences.

Specific course objectives were listed in the syllabus and apply to each topic covered in the course. The primary learning objectives for students to achieve were: (1) know the important biochemical events initiated by the interaction of a drug with its biological receptor; (2) provide the mechanism(s) of action for the drugs included in each pharmacological category; (3) describe the pharmacological effect of each drug under both normal and pathological conditions; (4) know the important metabolic pathways and how metabolism affects the pharmacological actions of drugs from each category (formation of active metabolites, effects on duration of actions, drug-drug interactions, etc); and (5) describe the anticipated side effects, precautions and warnings, contraindications, and potential drug-drug interactions for each pharmacological category. Approximately 5 to 6 lectures were devoted to the pharmacologic management of angina. These included a brief review of cardiovascular physiology and pathophysiology relevant to myocardial ischemia, discussions of nitrovasodilators/nitric oxide, β-adrenoceptor antagonists, and calcium channel blockers, as well as new and/or future pharmacologic strategies (eg, ranolazine).

## Course Content

**Introduction.** Ischemic heart disease is the single leading cause of death among both men and women in the United States.[1] The first clinical sign of myocardial ischemia is usually angina pectoris, a term used to describe the strangling chest pain experienced by many patients with ischemic heart disease. Myocardial ischemia, or lack of oxygen, is caused by an imbalance between oxygen supply and oxygen demand in the heart. This imbalance is usually due to an inability to increase coronary blood flow in response to increased myocardial oxygen consumption.[2] The inability to increase coronary blood flow is often related to atherosclerosis of the large coronary arteries, which leads to a progressive narrowing of the blood vessel lumen and a reduction in coronary blood flow.[3] Coronary blood flow may also be restricted by either focal or generalized intense vasoconstriction (ie, vasospasm) in the major coronary arteries.[4] Antianginal drugs may effectively relieve or prevent acute ischemic episodes by increasing myocardial oxygen supply, decreasing myocardial oxygen demand, or both.

**Development of the β-Adrenoceptor Antagonists.** The discovery and development of the β-adrenoceptor antagonists represents one of the most significant advances in the history of cardiovascular pharmacology and therapeutics. Sir James Black is credited with leading the team that discovered the first clinically useful β-adrenoceptor antagonist, propranolol, which was developed specifically for the treatment of angina. Black proposed that pharmacologic blockade of cardiac β-adrenoceptors would reduce heart rate and myocardial oxygen demand and thereby prevent angina of effort associated with activation of the sympathetic nervous system (eg, exercise, emotional stress, anxiety).[5] This was a novel concept at that time (late 1950s, early 1960s) since the only effective antianginal drugs were the organic nitrates, such as nitroglycerin, whose therapeutic effects were attributed to vasodilation and increased coronary blood flow. Although there were no known β-adrenoceptor antagonists in existence, isoproterenol, a relatively pure β-adrenoceptor agonist that mimics the actions of norepinephrine and epinephrine on the heart, was available. Black reasoned that isoproterenol must possess the requisite structural characteristics necessary for interacting with cardiac β-adrenoceptors. Using isoproterenol as a starting point, he had his chemists synthesize numerous molecules that were chemical derivatives of the β-adrenoceptor agonist, ultimately leading to the discovery of propranolol. Black was awarded the Nobel Prize in 1988, in part, for his role in the discovery of propranolol and the approach that he used.

Three distinct subtypes of β-adrenoceptors, termed $\beta_1$, $\beta_2$, and $\beta_3$, have been identified.[6] With regard to the actions of epinephrine and norepinephrine in the cardiovascular system, increases in heart rate and force of contraction are mediated primarily via activation of $\beta_1$-adrenoceptors in the heart,[7] while vasodilation is mediated primarily by activation of $\beta_2$-adrenoceptors in vascular smooth muscle.[8] Propranolol is a competitive, reversible β-adrenoceptor antagonist that is equipotent at human $\beta_1$-adrenoceptors ($K_D$ = 3.6 nM) and $\beta_2$-adrenoceptors ($K_D$ = 1.1 nM).[9] Nevertheless, the beneficial antianginal effects of propranolol are believed to be due primarily to inhibition of cardiac $\beta_1$-adrenoceptors, while certain adverse effects and precautions (see below) involve inhibition of $\beta_2$-adrenoceptors in the vasculature and other organs.[10-12] This realization led to the development of β-adrenoceptor antagonists with greater selectivity for $\beta_1$-adrenoceptors, such as metoprolol and atenolol. Based on their $K_D$ values, metoprolol ($\beta_1$-adrenoceptor $K_D$ = 70-200 nM vs. $\beta_2$-adrenoceptor $K_D$ = 300-1200 nM) and atenolol ($\beta_1$-adrenoceptor $K_D$ = 0.6-1.5 μM vs. $\beta_2$-adrenoceptor $K_D$ = 3-9 μM) display approximately 4-6-fold greater selectivity for human $\beta_1$- vs. $\beta_2$-adrenoceptors.[9,13] Selectivity for $\beta_1$-adrenoceptors is referred to as ''cardioselectivity'', and represents an important pharmacologic property that can be used to distinguish

among β-adrenoceptor antagonists. Other pharmacologic properties that differentiate the β-adrenoceptor antagonists include intrinsic sympathomimetic activity (ie, partial agonist), membrane-stabilizing activity (ie, local anesthetic-like effects), and concomitant α-adrenoceptor blockade, though these properties are not required for efficacy in the treatment of angina.[14] Important pharmacokinetic differences include variations in lipid solubility, bioavailability, half-life and elimination (renal vs. hepatic).[12,15]

There are now more than a dozen β-adrenoceptor antagonists approved by the Food and Drug Administration for a variety of cardiovascular uses (eg, angina, hypertension, cardiac arrhythmias) and non-cardiovascular uses (eg, glaucoma, migraine). Four of these agents, including 2 nonselective antagonists (propranolol, nadolol) and 2 cardioselective antagonists (metoprolol, atenolol), are approved for the treatment of angina, although off-label use also occurs with others. All appear to be equally effective in treating patients with angina.[14,16] Selection of an appropriate agent for individual patients is based on pharmacokinetic and pharmacodynamic properties of the drugs, as well as the presence of coexisting medical conditions.

**Pharmacokinetic Properties and Dosage Forms.** Most β-adrenoceptor antagonists are well absorbed following oral administration, but many undergo first-pass hepatic metabolism; thus, the oral bioavailability of β-adrenoceptor antagonists is limited to varying degrees.[12,15,17,18] The oral bioavailability of propranolol is approximately 25%-30% on average, but it is dose-related and subject to considerable variation among individuals. Oral bioavailability of metoprolol (~50%) is also limited by first-pass metabolism. The elimination of propranolol and metoprolol may be decreased in the presence of liver disease or advanced age.[17] Nadolol and atenolol are hydrophilic and are incompletely absorbed following oral administration. Bioavailability of nadolol (~35) and atenolol (~40%) is little influenced by hepatic metabolism and both drugs are excreted essentially unchanged in the urine. These drugs show less interpatient variation in plasma levels than propranolol and metoprolol, but their elimination may be reduced by renal disease.[15] Half-lives range from about 4 hours for propranolol and metoprolol, to about 8 hours for atenolol, and up to 24 hours for nadolol. Extended release oral dosage forms are available for propranolol and metoprolol. Propranolol, metoprolol, and atenolol may also be administered by intravenous injection. The pharmacodynamic effects of the β-adrenoceptor antagonists often extend well beyond the time predicted by their half-lives.

**Hemodynamic Effects: Myocardial Oxygen Demand.** The fundamental approach to reducing myocardial ischemia, and hence relieving anginal pain, is to restore the proper balance between myocardial oxygen supply and oxygen demand.[3,11,18] Beta-adrenoceptor antagonists competitively inhibit the binding of endogenous catecholamines to $\beta_1$-adrenoceptors in the heart and most evidence strongly suggests that their anti-ischemic effects are due to cardiac depression.[5,10] Myocardial oxygen demand is determined in large part by heart rate and cardiac contractility. Increased heart rate and contractility result in increased myocardial oxygen consumption and, conversely, reductions in heart rate and contractility lead to a decrease in oxygen consumption. By inhibiting the actions of norepinephrine and epinephrine on the heart, the β-adrenoceptor antagonists reduce myocardial oxygen demand via a reduction in both heart rate and cardiac contractility and thereby attenuate the myocardial response to sympathetic nervous system stimulation that occurs, for example, with increased stress or exercise.[5,10] Though most β-adrenoceptor antagonists lower resting heart rate to some extent, the effect on exercise-induced tachycardia is much more pronounced. Thus, for a given degree of physical activity, myocardial oxygen consumption is diminished. It is important to note that the β-adrenoceptor antagonists do not change the point of imbalance between myocardial oxygen supply and consumption at which angina occurs; rather, they reduce the likelihood that this point is reached.

By mechanisms that remain poorly understood, β-adrenoceptor antagonists also decrease peripheral vascular resistance, which leads to a reduction in arterial blood pressure and afterload.[10,12] Reduced afterload results in decreased left ventricular wall tension, which is another major determinant of myocardial oxygen demand. This beneficial effect of the β-adrenoceptor antagonists may be partially offset, however, by an increase in left ventricular end-diastolic volume that occurs due to increased cardiac filling during diastole, but the net effect is to lessen oxygen demand.

**Hemodynamic Effects: Myocardial Oxygen Supply.** The heart is almost exclusively dependent on aerobic metabolism and an adequate supply of oxygen is critical to sustained cardiac activity.[5] Myocardial oxygen supply is a function of both oxygen delivery and oxygen extraction from the blood. Since oxygen extraction from coronary blood is near maximal at rest, there is little reserve to meet increased demand due to increased cardiac activity.[19] Thus, the most important determinant of myocardial oxygen supply is total coronary blood flow.

Since β-adrenoceptor antagonists are not coronary vasodilators, they have little propensity to increase coronary blood flow and myocardial oxygen supply. If anything, β-adrenoceptor antagonists may increase coronary

vascular resistance by inhibiting the $\beta_2$-adrenoceptor-mediated vasodilator effects of endogenous catecholamines and leaving $\alpha$-adrenoceptor-mediated vasoconstriction unopposed.[20,21] Thus, the anti-ischemic effects of the β-adrenoceptor antagonists are largely due to their ability to reduce myocardial workload and decrease oxygen consumption, rather than to improve myocardial oxygen supply.

**Adverse Effects and Precautions.** The β-adrenoceptor antagonists are generally well-tolerated, but they are not suitable for all patients. The most predictable adverse effects are bradycardia and cardiac depression, which are a direct result of blockade of cardiac $\beta_1$-adrenoceptors.[22] Therefore, adrenoceptor antagonists must be used cautiously in patients with myocardial dysfunction whose cardiac output is dependent on sympathetic drive. Adverse effects related to the central nervous system may be bothersome in some patients and include lethargy, sleep disturbances, and depression.[22]

If a β-adrenoceptor antagonist is to be used in ischemic patients also suffering from reactive airway disease, peripheral vascular disease, or diabetes mellitus, it is advisable to choose a $\beta_1$-selective antagonist.[23] Blockade of $\beta_2$-adrenoceptors in the airways of healthy individuals has little effect but may induce bronchospasm and cause worsening of symptoms in patients with asthma or other obstructive pulmonary disorders. Likewise, inhibition of vascular $\beta_2$-adrenoceptors in patients with peripheral vascular disease and other vasospastic disorders may lead to significant reductions in blood flow and tissue perfusion in affected areas. Nonselective β-adrenoceptor antagonists may delay recovery from hypoglycemia in patients with insulin-dependent diabetes. Not only do β-adrenoceptor antagonists block glycogenolysis, but they also impair perception of the symptoms of hypoglycemia, such as tachycardia, tremor, and nervousness, that are mediated by catecholamines. Although caution must be exercised, $\beta_1$-adrenoceptor antagonists are less likely to delay recovery from hypoglycemia.

In patients with ischemic heart disease, abrupt discontinuation of β-adrenoceptor antagonists following chronic use is associated with a withdrawal syndrome. Exacerbations of angina, myocardial infarction, and increased risk of sudden death have been reported following abrupt cessation of β-adrenoceptor antagonists after long-term therapy;[24] therefore, patients should be warned against interruption or discontinuation of β-adrenoceptor antagonists without the advice of their physician. The mechanism underlying this phenomenon is not completely understood, but may involve increased sensitivity to β-adrenoceptor agonists and an upregulation in the number of β-adrenoceptors when the antagonist is abruptly withdrawn.[25,26] For example, after abrupt withdrawal of propranolol and metoprolol there is a rebound increase in resting heart rate as well as increased cardiac sensitivity to isoproterenol that persisted for at least 1 week.[26] These withdrawal phenomena could be attenuated by gradually decreasing the dose of the antagonist. Although optimal strategies for discontinuation of chronically administered β-adrenoceptor antagonists are not known, it is advisable to taper the dose gradually, limit the degree of exercise, and monitor the patient carefully.

**Clinical Use.** Beta-adrenoceptor antagonists are a mainstay in the treatment of chronic, stable angina.[2,10,11] While coronary blood flow (ie, oxygen supply) may be sufficient to meet myocardial oxygen requirements at rest in patients with fixed atherosclerotic lesions, the obstruction prevents blood flow from increasing during periods of increased oxygen demand. Under these conditions coronary blood flow is already at a maximal level in most patients, thus any increase in myocardial work can trigger an episode of acute angina. Precipitating factors include physical exertion, emotional stress or excitement, and temperature extremes. By decreasing heart rate, myocardial contractility, and afterload, β-adrenoceptor antagonists reduce myocardial workload and oxygen consumption at rest as well as during periods of exertion or stress. Oral β-adrenoceptor antagonists are widely used in long-term maintenance therapy to prevent acute ischemic episodes. Prophylactic use of these agents reduces the frequency and severity of acute anginal attacks. Because of their slow onset of action, oral β-adrenoceptor antagonists are not appropriate for terminating an acute attack of angina once it has begun; sublingual nitroglycerin is the agent most frequently used under these conditions. Several β-adrenoceptor antagonists, including propranolol, metoprolol, and atenolol, have cardioprotective effects and have been shown to decrease mortality after myocardial infarction.[27-30]

In patients with variant (Prinzmetal's) angina, the major underlying cause of angina is vasospasm of one or more coronary arteries.[31] Intense vasoconstriction decreases coronary blood flow, thereby reducing myocardial oxygen supply. Coronary vasospasm can occur in arteries with little or no atherosclerotic plaque and is not associated with an increase in myocardial oxygen demand.[4] Indeed, variant angina may strike at any time of the day or night, including during periods of rest or sleep. In contrast to stable angina, variant angina is most often the result of an abrupt decrease in myocardial oxygen supply (ie, coronary blood flow) rather than an increase in myocardial oxygen demand.[32] Unlike nitrates and calcium channel blockers, β-adrenoceptor antagonists do not directly dilate coronary arteries to increase coronary blood flow.

Moreover, blockade of vascular β-adrenoceptors inhibits the vasodilator actions of endogenous catecholamines and may exacerbate α-adrenoceptor-mediated vasoconstriction in coronary arteries.[20,21] Thus, β-adrenoceptor antagonists may worsen coronary vasospasm and are not indicated for treatment of vasospastic angina.

Beta-adrenoceptor antagonists may reduce the risk of progression to acute myocardial infarction in patients with unstable angina.[33] The pathophysiology of this condition is often complex and may involve several underlying factors superimposed upon one another, including rupture of atherosclerotic plaques and thrombus formation, constriction of coronary arteries, and increased myocardial oxygen demand.[34] In these patients, the beneficial effects of the β-adrenoceptor antagonists are likely due to a reduction in myocardial oxygen consumption.[35-37] If coronary vasospasm is the major underlying problem, nitrates or calcium channel blockers would be more effective and β-adrenoceptor antagonists should be used with caution.

Combination therapy with drugs from different pharmacologic classes is often used in the long-term management of patients with angina. This strategy takes advantage of the diverse mechanisms of action of drugs from each category and offers several potential benefits.[18,38-40] When used concurrently, β-adrenoceptor antagonists can inhibit the baroreceptor-mediated reflex tachycardia and positive inotropic effects that may sometimes occur with organic nitrates. Alternatively, organic nitrates increase venous capacitance and can thereby offset β-adrenoceptor antagonist-mediated increases in left ventricular end-diastolic volume. Moreover, organic nitrates are coronary vasodilators and, as such, may prevent the increase in coronary vasomotor tone that may potentially result from blockade of vascular β-adrenoceptors.[20,21] Dihydropyridine calcium channel blockers are also potent coronary vasodilators and provide similar advantages with regard to coronary vascular resistance in patients treated simultaneously with β-adrenoceptor antagonists. As with nitrates, dihydropyridines may also cause reflex tachycardia that can be alleviated by β-adrenoceptor antagonists. Concurrent use of β-adrenoceptor antagonists with the non-dihydropyridine calcium channel blockers, verapamil and diltiazem, is much more limited due to the potential for severe cardiac depression and must be used with great caution. In the long-term management of ischemic heart disease, β-adrenoceptor antagonists, with their antianginal effects, may also be combined with vasculoprotective drugs such as anti-platelet agents (aspirin, clopidogrel), angiotensin-converting enzyme inhibitors, and HMG-CoA reductase inhibitors to reduce the risk of ischemic vascular events.[3,10]

## ASSESSMENT

Student learning was assessed by 4 written examinations that typically contained a combination of multiple-choice, short answer, and essay questions. Student self-perception of their mastery of the course material was assessed using a Student Rating of Instruction evaluation form. When asked to ''please rate your understanding of the course content,'' the average score reported by the respondents during the past 3 years (2004-2006) was 4.55 on a 5-point scale, where 5 = very good and 1 = very poor. Indeed, 97% of the students rated their understanding as ''good'' or ''very good'' (highest rating) and 100% rated their understanding as ''average'' or better. These perceptions are in agreement with actual student achievement of the course objectives during this period (2004-6), as measured by student performance on examination of the material covered, in which 97% of the students achieved a passing score of at least 70%.

## SUMMARY

Beta-adrenoceptor antagonists are widely used in the treatment of angina pectoris and ischemic heart disease. These agents competitively inhibit the binding of endogenous catecholamines to $\beta_1$-adrenoceptors in the heart. Their anti-ischemic effects are due primarily to a reduction in heart rate and cardiac contractility during periods of exertion or stress, which decreases myocardial oxygen demand. Bradycardia and cardiac depression, which are a direct result of blockade of cardiac $\beta_1$-adrenoceptors, are predictable adverse effects, but lethargy, sleep disturbances, and depression may also be bothersome in some patients. Beta-adrenoceptor antagonists must be used cautiously in patients with certain co-existing conditions (eg, diabetes mellitus, peripheral vascular disease, heart failure, and obstructive airway disease). The β-adrenoceptor antagonists are often used in conjunction with other antianginal drugs (eg, nitrates and calcium channel blockers), and may also be used along with vasculoprotective therapies (eg, anti-platelet agents, angiotensin converting enzyme inhibitors, HMG-CoA reductase inhibitors) in order to reduce the risk of ischemic vascular events. Most pharmacists will encounter patients with ischemic heart disease in their professional practices; thus, it is incumbent upon pharmacy students to gain a working knowledge of the pharmacology of the beta-adrenoceptor antagonists and how these concepts apply to the anti-anginal actions of these agents.

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