β-Adrenergic Blockers

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Key Points and Practical Recommendations

- β-Blockers are appropriate treatment for patients with hypertension and those who have concomitant ischemic heart disease, heart failure, obstructive cardiomyopathy, or certain arrhythmias.
- β-Blockers can be used in combination with other antihypertensive drugs to achieve maximal blood pressure control. Labetalol can be used in hypertensive emergencies and urgencies.
- β-Blockers may be useful in patients having hyperkinetic circulation (palpitations, tachycardia, hypertension, and anxiety), migraine headache, and essential tremor.
- β-Blockers are highly heterogeneous with respect to various pharmacologic effects: degree of intrinsic sympathomimetic activity, membrane-stabilizing activity, β_1 selectivity, α_1-adrenergic–blocking effect, tissue solubility, routes of systemic elimination, potencies and duration of action, and specific effects may be important in the selection of a drug for clinical use.
- β-Blocker usage to reduce perioperative ischemia and cardiovascular complications may not benefit as many patients as was once hoped and may actually cause harm in some individuals. Currently the best evidence supports β-blocker use in two patient groups: patients undergoing vascular surgery with known ischemic heart disease or multiple risk factors for it and for patients already receiving β-blockers for known cardiovascular conditions. *J Clin Hypertens (Greenwich).* 2011;13:649–653. ©2011 Wiley Periodicals, Inc.

HISTORY OF USE

β-Blockers have been given many names in the literature (β-adrenergic–blocking agents, β-adrenergic antagonists, β-antagonists, β-adrenergic receptor antagonists). We have used the term β-blockers throughout our manuscript to avoid any confusion.

The antihypertensive effect of β-blockers was first documented by Pritchard almost half a century ago.[1,2] Propranolol was the first β-blocker approved as an oral antihypertensive agent. Propranolol was also used as an adjunct therapy to phentolamine, an α-adrenergic blocker, in the treatment of pheochromocytoma.[3,4] Ultimately, labetalol, a combined α/β-blocker, in its intravenous form, was demonstrated to be of clinical use in the treatment of hypertensive emergencies and in an oral form for hypertensive urgencies.[3,5]

To date, 14 β-blockers have received Food and Drug Administration (FDA) approval for oral use in patients with systemic hypertension (Table I). Sustained-release formulations of metoprolol, propranolol, and carvedilol have allowed these short-acting β-blockers to be used once daily in hypertension.

MECHANISM OF ACTION

There is no consensus as to the exact mechanism(s) by which β-blockers lower blood pressure (BP), and it is likely that multiple modes of action are involved (Table II).[3]

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CLINICAL EXPERIENCES

Chronic BP–Lowering Effects

In usually prescribed dosages, β-blockers have similar antihypertensive efficacy[3]; however, the findings of recent meta-analyses have demonstrated that β-blockers may have less-protective effects on cardiovascular and cerebrovascular end points than other antihypertensive drugs, especially in the elderly.[6–13] There are also data to suggest that some β-blockers may have lesser effects on central aortic pressure than other antihypertensive drug classes.[14] However, β-blockers remain appropriate treatments for hypertensive patients with concomitant ischemic heart disease, angina pectoris, post–myocardial infarction, left ventricular dysfunction with heart failure, obstructive cardiomyopathy, arrhythmias, aortic dissection, and hyperkinetic circulations (tachycardia, palpitations, hypertension, anxiety).[15,16]

True dose equivalence among the various β-blockers has not been established, in part because few head-to-head studies have been performed with individual β-blockers. β-Blockers, alone and in combination with other antihypertensives, will reduce BP in patients with combined systolic and diastolic hypertension and in most patients with isolated systolic hypertension. Uncommonly there is a paradoxical elevation of systolic pressure during β-blockade in persons with severe aortic arteriosclerosis, presumably due to the increased stroke volume caused by rate slowing in the setting of increased impedance.[4] Escalating doses of β-blockers and combined α/β-blockers can induce salt and water retention, requiring adjunctive diuretic therapy.[4]

TABLE I. Pharmacodynamic Effects of β-Adrenergic–Blocking Drugs Used in Hypertension

Drug	β_1-Blockade Potency Ratio (Propranolol=1.0)	Relative B_1 Selectivity	Intrinsic Sympathomimetic Activity
Acebutolol	0.3	+	+
Atenolol	1.0	++	0
Betaxolol	1.0	++	0
Bisoprolol[a]	10.0	++	0
Carteolol	10.0	0	+
Carvedilol[b]	10.0	0	0
Labetalol[c]	0.3	0	+?
Metoprolol	1.0	++	0
Nadolol	1.0	0	0
Nebivolol[d]	10.0	++	0
Penbutolol	1.0	0	+
Pindolol	6.0	0	++
Propranolol	1.0	0	0
Sotalol	0.3	0	0
Timolol	0.6	0	0

+ = modest effect; ++ = strong effect; 0 = no effect. [a]Bisoprolol is also approved as a first-line antihypertensive therapy in combination with a very low-dose diuretic. [b]Carvedilol has peripheral vasodilating activity and additional α_1-adrenergic–blocking activity. [c]Labetalol has additional α_1-adrenergic–blocking activity and direct vasodilatory activity (β_2-agonism); it is available for use in intravenous form for hypertensive emergencies. [d]Nebivolol can augment vascular nitric oxide release. Adapted with permission from Frishman.[42]

TABLE II. Proposed Mechanisms to Explain the Antihypertensive Actions of β-Blockers

1.	Reduction in heart rate and cardiac output
2.	Central nervous system inhibitor effect
3.	Inhibition of renin release
4.	Reduction in venous return and plasma volume
5.	Reduction in peripheral vascular resistance (intrinsic sympathomimetic activity drugs, α/β-blockers, potentiation of nitric oxide)
6.	Improvement in vascular compliance
7.	Resetting of baroreceptor levels
8.	Effects on prejunctional β-receptors: reduction in norepinephrine release
9.	Attenuation of pressor response to catecholamines with exercise and stress

Modified from Frishman.[43]

Abrupt discontinuation of a β-blocker, particularly when administered in high doses, may be followed by adrenergically mediated withdrawal symptoms and the appearance of angina pectoris in patients with coronary artery disease.[4] Therefore, when necessary, a step-wise reduction in dose is advised in all high-risk patients.[4]

Hypertensive Urgencies and Emergencies

The combined α/β-blocker labetalol is the only β-blocker indicated for parenteral management of hypertensive emergencies and for treatment of intraoperative and postoperative hypertension.[5] It can also be used in oral form to treat patients with hypertensive urgencies.[5]

Combinations With Other Drugs

The antihypertensive effect of a β-blocker is enhanced by the simultaneous administration of a diuretic.[3] The combination of a β-blocker with hydrochlorothiazide doses as low as 6.25 mg have been approved along with an atenolol/chlorthalidone combination. β-Blockers are also useful add-on therapy in the setting of vasodilator-related tachycardia, as may occur with hydralazine, minoxidil and dihydropyridine calcium entry blockers.[4]

Patient Subgroup Responses

There are few predictors of response to a β-blocker, but β-blockers are useful in hyperkinetic forms of hypertension as in individuals with a high cardiac awareness profile or somatic manifestations of anxiety, such as tremor, sweating, and tachycardia.[4] Although, there is a limited relationship between plasma renin activity and response to a β-blocker, certain patient subsets demonstrate lower response rates to β-blocker monotherapy, including low-renin, salt-sensitive individuals, such as many blacks with hypertension.[4] Racial differences in the BP response to traditional β-blockers are diminished when the drug is combined with a thiazide diuretic or a vasodilating β-blocker, such as labetalol, carvedilol, or nebivolol.[4] For example, nebivolol may have an antihypertensive effect in African Americans as monotherapy that differs from traditional β-blockers.[17] The elderly and diabetic populations respond in a fairly heterogeneous fashion to β-blocker monotherapy. Certain β-blockers can be used with caution in pregnancy-related hypertension.[18]

HETEROGENEITY AMONG β-BLOCKERS

β-Blockers as a group have similar therapeutic effects, despite their structural differences.[3] Their varied aromatic ring structures confer many pharmacokinetic differences, including completeness of gastrointestinal absorption, degree of first-pass hepatic metabolism, lipid solubility, protein binding, volume of distribution, penetration into the central nervous system, concentration in the myocardium, rate of hepatic biotransformation, pharmacologic activity of metabolites, and renal clearance.[3] The relevance of these variations depends on the clinical conditions present in the individual being treated. In contrast to other classes of antihypertensive drugs, important differences in intrinsic chemical properties of β-blockers (Table I) translate into significant clinical differences in effects.[3]

Solubility, Elimination, and Duration of Effects

The β-blockers can be divided into two broad categories by their solubilities, metabolism, and elimination routes.[19] Lipid-soluble agents are eliminated primarily by hepatic metabolism and tend to have relatively

short plasma half-lives with wider variations in plasma concentrations. Water-soluble agents that are eliminated unchanged by the kidney tend to have longer half-lives and more stable plasma concentrations.[3] Propranolol and metoprolol are both lipid-soluble, are almost completely absorbed by the small intestine, and are largely metabolized by the liver. They tend to have highly variable bioavailability and relatively short plasma half-lives. A lack of correlation between the duration of clinical pharmacologic effect and plasma half-life may explain why these drugs can be effective even when administered once or twice daily.[3] Differences do emerge when the duration of effect of individual β-blockers is compared.[3] Several β-blockers do not provide full 24-hour coverage and thus fail to be effective in blunting early morning rises in BP. Dose titration is effective in some patients, particularly in those with heart rate–driven forms of hypertension.[4]

Extended-Release Preparations

Extended-release formulations of carvedilol, metoprolol, and propranolol are available that allow once-daily dosing of these drugs.

β_1-Selectivity

When used in low doses, β_1-selective–blocking agents such as acebutolol, betaxolol, bisoprolol, esmolol, atenolol, metoprolol, and nebivolol inhibit cardiac β_1-receptors but have less influence on bronchial and vascular smooth muscles (Table I). In higher doses (eg, >50 mg/d of metoprolol), however, β_1-selective–blocking agents also block β_2-receptors.[3] Accordingly, β_1-selective agents may be marginally safer than nonselective agents in patients with reactive airway disease, but β_1-blockers may still aggravate bronchospasm in certain patients. A second theoretical advantage is that unlike nonselective β-blockers, β_1-selective blockers in low doses may not block the β_2-receptors that mediate dilatation of arterioles.[3]

ISA or Partial Agonist Activity

Certain β-blockers are partial agonists at β_1-adrenergic receptor sites, β_2-adrenergic receptor sites, or both.[20] This combined action manifests itself as a neutral effect on heart rate when the sympathetic nervous system is not activated (supine rest) and as a blunted increase in heart rate when the sympathetic system is activated during the stress of exercise (Table I).

It is still debated whether the presence of partial agonist activity in a β-blocker constitutes an overall advantage or disadvantage in cardiac therapy.[20]

Membrane-Stabilizing Activity

At concentrations well above therapeutic levels, certain β-blockers have a quinidine-like or local anesthetic membrane-stabilizing activity (potentially antiarrhythmic) on the cardiac action potential (Table I).

Combined α/β-Adrenergic–Blocking Activity

Carvedilol and labetalol are β-blockers with antagonistic properties at both α- and β-adrenergic receptors, with direct vasodilator activity.[3,21] Like other β-blockers, they are useful in the treatment of hypertension and angina pectoris. However, unlike most β-blocking drugs, the additional α-adrenergic–blocking actions of carvedilol and labetalol lead to a reduction in peripheral vascular resistance that acts to maintain higher levels of cardiac output.

Nitric Oxide–Releasing Activity

Nebivolol is a β_1-selective blocker that has additional vasodilator actions apparently related to an enhancement of nitric oxide activity.[22] Whether this additional property in a β-blocker confers greater benefits has not yet been determined.

OTHER APPLICATIONS

The therapeutic efficacy and safety of β-blockers have been well established after over 40 years of clinical experience in human beings. The clinical utility of β-blockers has been documented in patients with angina pectoris, cardiac arrhythmias, and congestive cardiomyopathy and for reducing the risk of mortality and possibly nonfatal reinfarction in survivors of acute myocardial infarction.[3,23] Of course, not all of the agents in the class of β-blockers have shown benefit in each of the clinical applications listed above. Most antihypertensive drugs, including β-blockers, can reduce left ventricular mass and wall thickness, although β-blockers have been found to be less effective in this regard than diuretics, angiotensin-converting enzyme inhibitors, calcium antagonist, and angiotensin receptor blockers.[4,24] β-Blockers may be useful as primary protection against cardiovascular morbidity and mortality in certain hypertensive patients. The drugs have also been found to be of use for a host of other cardiovascular and noncardiac disorders.[3,19,25]

β-Blockers will reduce perioperative ischemia, and studies published in the 1990s suggested that their routine administration before surgery provided protection against perioperative cardiovascular complications.[26–28] Based on these early studies, several national organizations endorsed the perioperative use of β-blockers as a best practice in certain patients.[29–31] However, more recent evidence has been accumulating to suggest that routine use of β-blockers may not benefit as many patients as was once hoped and may actually cause harm in some individuals.[32,33] The benefit of β-blockers may be only present in high-risk cardiac patients undergoing high-risk surgery. Currently the best evidence supports their use in two patient groups: patients undergoing vascular surgery who have known ischemic heart disease or multiple risk factors for it and patients who are already receiving β-blockers for cardiovascular conditions.[26–28,30,31]

ADVERSE EFFECTS AND CONTRAINDICATIONS

Most β-blockers, at least in the usual antihypertensive dose range, should not be used in patients with asthma, reactive airway disease, acute decompensated congestive heart failure with systolic dysfunction, heart block (greater than first degree), and sick sinus syndrome.[3] β-blockers have been documented to increase the risk of new-onset diabetes[34] and this risk increases with duration of therapy.[35] These drugs should be used with caution in insulin-dependent diabetes, because they may worsen glucose intolerance, mask the symptoms of hypoglycemia, prolong recovery from hypoglycemia, or increase the magnitude of the hypertensive response to hypoglycemia. There is probably a shorter recovery period from hypoglycemia with β_1-selective adrenergic blockers. β-Blockers should not be discontinued abruptly in patients with known ischemic heart disease. If a patient has serious contraindications to β-blockers, unacceptable side effects or persistent angina, calcium antagonists should be administered. Long-acting dihydropyridine and nondihydropyridine agents are generally as effective as β-blockers in relieving angina. β-Blockers may increase levels of plasma triglycerides and reduce those of high-density lipoprotein cholesterol.[3] β-Blockers with intrinsic sympathomimetic activity (ISA) and/or α-blocking vasodilator activity have little or no adverse effect on plasma lipids.[3]

The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI), a study comparing the effects of carvedilol vs metoprolol tartrate on glycemic and metabolic control in participants with hypertension and diabetes already receiving renin-angiotensin system blockade, demonstrated that carvedilol improved insulin sensitivity and glycemic control and reduced progression to microalbuminuria with equivalent BP lowering.[36] Based on this study, it appears that the pharmacologic differences among the β-blockers can affect the clinical utility of these agents in hypertensive patients with diabetes. Of note, weight gain was less with carvedilol than with metoprolol in GEMINI.[37]

DRUG-DRUG INTERACTIONS

There are special considerations when β-blockers are combined with other drugs.[38] Combinations of diltiazem or verapamil with β-blockers may have additional depressant effects on the sinoatrial and atrioventricular nodes and may also promote negative inotropy. Addition of H_2-blocking agents to the combination of verapamil and β-blockers can also lead to myocardial depression. Combinations of β-blockers and reserpine may cause marked bradycardia and syncope. Combination with phenylpropanolamine, pseudoephedrine, ephedrine, and epinephrine can cause elevations in BP due to unopposed α receptor–induced vasoconstriction.

CONTROVERSIES

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) has recommended β-blockers as potential first-line treatment for hypertension. These recommendations were based on the reduction of morbidity and mortality in large clinical trials, but most of the benefit related to secondary cardiovascular protection (in established disease) rather than primary prevention of events.[39] The most recent European guidelines[40] state that large-scale meta-analyses of available trial data confirm that diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers do not differ significantly in their ability to lower BP and to exert cardiovascular protection both in elderly and younger patients. The apparent lack of β-blocker benefit in primary prevention, especially reducing strokes in the elderly, has been attributed to atenolol and is probably not generalizable to all β-blockers. In this regard, almost all clinical trials have employed atenolol, once daily, which is a significant problem in study design because the half-life of the drug is only 6 to 9 hours. In contrast to ischemic heart disease and heart failure where heart rate reduction by β-blockade diminishes the risk, heart rate in hypertension reduction with β-blockers may increase cardiovascular mortality and other outcomes.[41]

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