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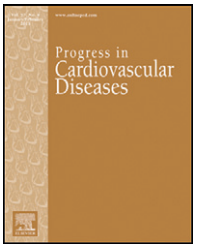

Beta-Adrenergic Receptor Blockers in Hypertension: Alive and Well

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ABSTRACT

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

The antihypertensive (HTN) effect of beta-adrenergic receptor blockers (β-blockers) was first documented by Pritchard and Gillam over a half century ago.[1,2] Propranolol was the first β-blocker approved as an oral antiHTN 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 HTN emergencies and in an oral form for HTN urgencies.[3,5]

To date, 14 β-blockers have received Federal Drug Administration approval for oral use in patients having systemic hypertension (HTN; Table 1). Sustained-release formulations of metoprolol, propranolol, and carvedilol have allowed these short-acting β-blockers to be used once daily in HTN.

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 2).[3]

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Abbreviations and Acronyms

ACEI = angiotensin converting enzyme inhibitors

ARB = angiotensin receptor blocker

β-Blockers = beta adrenergic receptor blocker

BP = blood pressure

CCB = calcium channel blocker

CV = cardiovascular

DM = diabetes mellitus

HF = heart failure

HTN = hypertension or hypertensive

IHD = ischemic heart disease

ISA = intrinsic sympathomimetic activity

LV = left ventricular

MI = myocardial infarction

MSA = membrane-stabilizing activity

Clinical experiences

Chronic BP lowering effects

In usually prescribed dosages, β-blockers have similar antiHTN efficacy,[6,7] however the findings of some meta-analyses have demonstrated that β-blockers may have less protective effects on cardiovascular(CV) and cerebrovascular endpoints than other antiHTN drugs, especially when used in the elderly.[8–15] There are also data to suggest that some β-blockers may have less effects on central aortic BP than other antiHTN drug classes.[16] However, β-blockers remain appropriate treatments for HTN patients with concomitant ischemic heart disease (IHD), angina pectoris, postmyocardial infarction (MI), left ventricular (LV) dysfunction with heart failure (HF), obstructive cardiomyopathy, arrhythmias, aortic dissection, and hyperkinetic circulations (tachycardia, HTN, anxiety).[17–20]

True dose equivalence among the various β-blockers has not been established, in part because few head-to-head studies have been done with individual β-blockers. β-Blockers, alone and in combination with other antiHTNs, will reduce BP in patients with combined systolic and diastolic HTN, and in most patients with isolated systolic hypertension.[4] Uncommonly there is a paradoxical elevation of systolic BP during β-blockade in persons with severe aortic arteriosclerosis, presumably due to the increased cardiac 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] 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 IHD.[4] Therefore, when necessary, a step-wise reduction in dose is advised in all high-risk patients.[4]

HTN urgencies and emergencies

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

Combinations with other drugs

The antiHTN effect of a β-blocker is enhanced by the simultaneous administration of a diuretic.[3] The combination of a β-blocker with hydrochlorothiazide (HCTZ) doses as low as 6.25 mg has 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 channel blockers (CCBs).[4]

Patient subgroup responses

There are few predictors of response to a β-blocker, but β-blockers are useful in hyperkinetic forms of HTN 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, which include many African American patients with HTN.[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 antiHTN effect in African Americans, when used as a monotherapy, that differs from that observed with traditional β-blockers.[21] Elderly and diabetic patients respond in a fairly heterogeneous fashion to β-blocker monotherapy. Certain ß-blockers can be used with caution in pregnancy-related HTN.[22]

Heterogeneity among β-blockers

β-Blockers as a group have similar therapeutic effects, despite their structural differences.[3] Their varied aromatic ring structures (Fig 1) 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 antiHTN drugs, important differences in intrinsic chemical properties of β-blockers (Table 1) can translate into significant differences in their clinical 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.[23] 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

Table 1 – Pharmacodynamic properties 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

Adapted with permission from Frishman WH. *Clinical Pharmacology of the ß-Adrenoceptor Blocking Drugs*. 2nd ed. Norwalk, Conn: Appleton-Century-Crofts; 1984.
+ = 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 $[alpha]_1$-adrenergic blocking activity.
[c] Labetalol has additional $[alpha]_1$-adrenergic blocking activity and direct vasodilatory activity ($[beta]_2$-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.[3]

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 heart rate-driven forms of HTN.[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, and metoprolol and nebivolol inhibit cardiac β_1-receptors but have less influence on bronchial and vascular smooth muscles (Table 2). In higher doses (e.g. >50 mg/day 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]

Intrinsic sympathomimetic activity (ISA) or partial agonist activity

Certain β-blockers are partial agonists at β_1-adrenergic receptor sites, β_2-adrenergic receptor sites, or both.[24] 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 stress of exercise (Table 1).

Table 2 – 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 (ISA drugs, α-β-blockers, potentiation of nitric oxide)
6. Reduction in vasomotor tone
7. Improvement in vascular compliance
8. Resetting of baroreceptor levels
9. Effects on prejunctional β-receptors: reduction in norepinephrine release
10. Attenuation of pressor response to catecholamines with exercise and stress

Modified from Frishman[3]

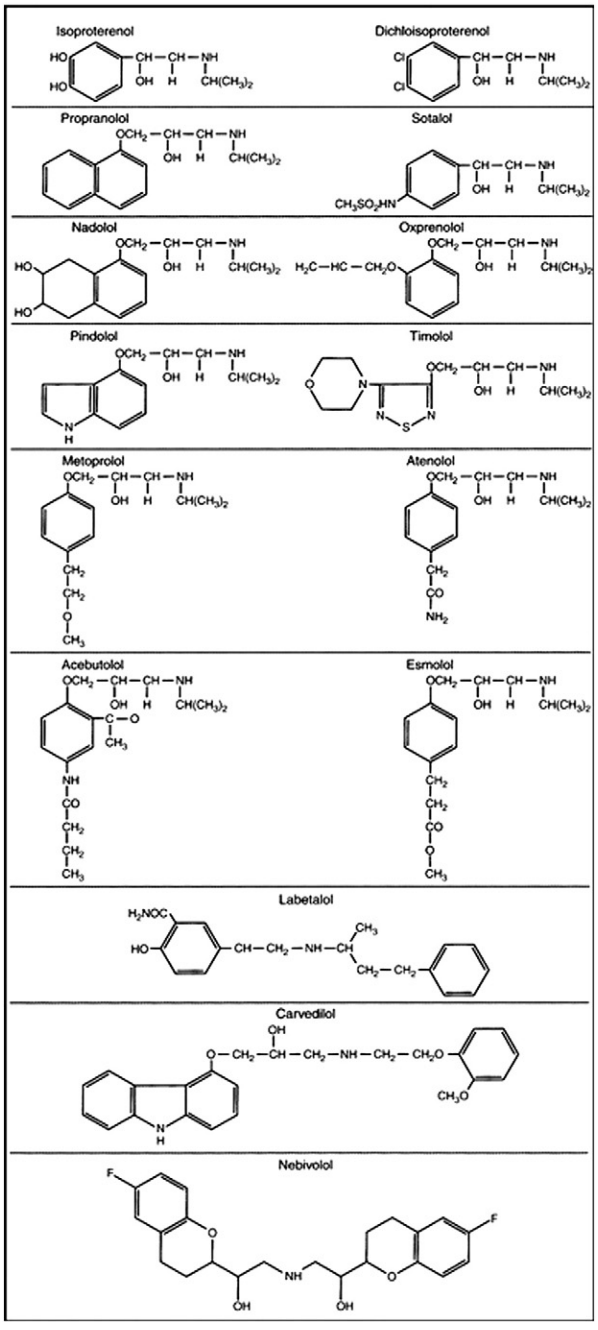

Fig 1 – Molecular structure of the β-adrenergic agonist isoproterenol and some β-adrenergic blocking drugs used to treat hypertension.

It is still being debated whether the presence of partial agonist activity in a β-blocker constitutes an overall advantage or disadvantage in cardiac therapy.[24]

Membrane-stabilizing activity (MSA)

At concentrations well above therapeutic levels, certain β-blockers have a quinidine-like or local anesthetic MSA (potentially anti-arrhythmic) on the cardiac action potential (Table 1).

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.[3,25] Like other β-blockers, they are useful in the treatment of patients with 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 in patients.

Nitric oxide-releasing activity

Nebivolol is a β_1-selective blocker which has additional vasodilator actions apparently related to an enhancement of nitric oxide activity.[26] Whether this additional property in a β-blocker confers greater clinical benefits has not yet been determined.

Other applications

The therapeutic efficacy and safety of β-blockers have been well established after 50 years of clinical experience. Their clinical utility has been well documented in patients with angina pectoris, cardiac arrhythmias, aortic dissection, congestive cardiomyopathy, and for reducing the risk of mortality and possibly nonfatal reinfarction in survivors of acute MI.[27,28] 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 anti-HTN drugs, including β-blockers, can reduce LV mass and wall thickness, although β-blockers have been found to be less effective in this regard than diuretics, angiotensin converting enzyme inhibitors (ACEIs), CCBs and angiotensin receptor blockers (ARBs).[4,29] β-Blockers may be useful as a primary protection against CV morbidity and mortality in certain HTN patients. The drugs have also been found to be of use for a host of other CV and non-CV disorders.[3,30]

β-Blockers will reduce perioperative myocardial ischemia and studies published in the 1990s suggested that their routine administration before surgery provided protection against perioperative CV complications.[31–33] Based on these early studies, several national organizations endorsed the perioperative use of β-blockers as a best practice in certain patients.[34,36] 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.[36–38] The benefit of β-blockers may be only present in high-risk CV patients undergoing high-risk surgery. Currently the best evidence supports their use in two patient groups: patients undergoing vascular surgery who have known IHD or multiple risk factors for it, and for those patients who are already receiving β-blockers for CV conditions.[31–36]

Adverse effects and contraindications

Most β-blockers, at least in the usual antiHTN dose range, should not be used in patients with asthma, reactive airway disease, acute decompensated HF with systolic dysfunction, heart block (greater than first degree), and sick sinus syndrome.[3] However,

there are new data to suggest a mortality benefit with β-blocker use in patients having chronic obstructive pulmonary disease.[39] β-blockers have been documented to increase the risk of new onset diabetes mellitus (DM)[40] and this risk increases with the duration of therapy.[41] The drugs should be used with caution in insulin-dependent DM, because they may worsen glucose intolerance, mask the symptoms of hypoglycemia or prolong recovery from hypoglycemia, or increase the magnitude of the HTN 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 IHD. 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.[42] β-Blockers may increase levels of plasma triglycerides and reduce those of high density lipoprotein cholesterol.[3] β-blockers with ISA and/or α blocking-vasodilator activity have little or no adverse effect on plasma lipids.[3]

GEMINI, a study comparing the effects of carvedilol versus metoprolol tartrate on glycemic and metabolic control in participants with HTN and DM already receiving renin-angiotensin system blockade demonstrated that carvedilol improved insulin sensitivity and glycemic control and reduced progression to microalbuminuria and with equivalent BP lowering.[43] Based on this study, it appears that the pharmacological differences among the β-blockers can affect the clinical utility of these agents in HTN patients with DM. Of note, weight gain was less with carvedilol than with metoprolol in GEMINI.[44]

Drug–drug interactions

There are special considerations when β-blockers are combined with other drugs.[45] 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. The 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 Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure did not recommend β-blockers as a potential first-line treatment for HTN. They reasoned that benefits of β-blockade related to secondary CV protection (in established disease) rather than in the primary prevention of CV events.[46] However, the most recent European guidelines[7] state that large-scale meta-analyses of available trial data confirm that diuretics, β-blockers, ACEI, ARBs, and CCBs do not differ significantly in their ability to lower BP and to exert CV protection both in elderly and younger patients. The apparent lack of β-blocker benefit in primary prevention, especially in reducing strokes in the elderly, has been attributed to the use of atenolol, and is probably not generalizable to all β-blockers. In this regard, almost all clinical trials have employed atenolol, once daily, a significant problem in study design because the half-life of the drug is only 6–9 hours. In contrast to IHD and HF where heart rate reduction by β-blockade diminishes the mortality risk, in uncomplicated HTN,[47] heart rate reduction with β-blockers may cause less CV mortality benefit than with other anti-HTN drugs.[47,48,49]

Statement of conflict of interest

The author declares no conflict of interest.

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