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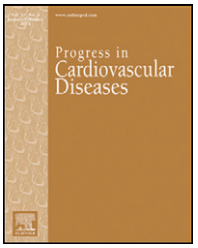

Beta-Adrenergic Receptor Blockers in Hypertension: Alive and Well

*William H. Frishman**

Department of Medicine, New York Medical College, Valhalla, NY
Westchester Medical Center Health Network, Valhalla, NY

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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]

Statement of Conflict of Interest: see page 251.

* William H. Frishman, MD, MACP, Chairman and Professor, Office of the Chairman, New York Medical College, 40 Sunshine Cottage Road, Valhalla, NY 10595-1524.
E-mail address: william_frishman@nymc.edu.

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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