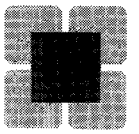

DONALD G. VIDT, MD, AND ALAN BAKST, PharmD, EDITORS

Adrenergic agents: clinical trials and experiences

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■ Beta-adrenergic blocking agents constitute first-line therapy for hypertension in many countries of the world. Comparative trials have been extensive in duration and have included large numbers of patients. Still, the desired cardioprotective effect of beta blockers has yet to be established. Their antiatherosclerotic effect has been noted in several animal experiments. Confirming evidence is needed before the clinical relevance of this effect can be evaluated, but these studies point to a potential therapeutic effect that may be immensely important in the future. Beta blockers can reverse left ventricular hypertrophy secondary to hypertension, but it remains to be shown that regression of left ventricular hypertrophy will reduce the associated risks.

□ INDEX TERMS: ADRENERGIC BETA RECEPTOR BLOCKADERS; HYPERTENSION □ CLEVE CLIN J MED 1992; 59:248–254

EFFECTIVE pharmacologic treatment of arterial hypertension has been possible for little more than three decades. In this brief period of time there have been several important therapeutic milestones. One of the latest and most important of these milestones was the development of adrenergic-blocking agents, which today constitute first-line therapy for hypertension in many countries of the world.

BACKGROUND

In 1948, Raymond P. Ahlquist postulated the existence of separate alpha and beta adrenoceptors.[1] This concept was later expanded by Lands et al to include a separation of beta-1, beta-2, and beta-3 adrenoceptors.[2]

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Therapeutic use of beta-adrenoceptor blocking agents was made possible by the innovative work of Sir James W. Black, for which he was awarded the Nobel prize in medicine in 1988. Also, clinical contributions by Prichard and his co-workers were invaluable for engendering the widespread general acceptance of beta-blocker therapy in hypertension that prevails today.

In 1958, the first pharmacologic means of blocking adrenergic receptors was provided by a dichloro analogue of isoproterenol[3]; this was rapidly followed by improved beta blockers such as pronethalol and propranolol. The first reports on the antihypertensive effect of beta blockers were published by Prichard's group in 1964.[4,5] These were soon confirmed by numerous studies.[6]

In the 1970s and 1980s, a multitude of therapeutic trials were conducted with beta blockers. These trials confirmed the early positive reports in every important regard, resulting in widespread clinical use of these agents. In most industrialized countries, beta blockers are now regarded as a first-line pharmacologic alternative for the treatment of hypertension. This view is

reflected in memoranda dating back several years from the World Health Organization/International Society of Hypertension[7] and the Joint National Committee in the United States.[8] More recent documents from these influential bodies confirmed the first-line therapeutic status of beta blockers.[9,10]

TABLE
PHARMACOLOGICAL PROFILES OF SOME BETA-ADRENOCEPTOR BLOCKING COMPOUNDS

Compound	β_1 blockade	β_2 blockade	MSA	β_1-ISA	β_2-ISA	Antihypertensive effect
Propranolol	+	+	+	–	–	+
Timolol	+	+	–	–	–	+
Oxprenolol	+	+	+	+	(+)	+
Pindolol	+	+	–	(+)	+	+
Atenolol	+	–	–	–	–	+
Practolol	+	–	+	+	–	+
Epanolol	+	–	+	–	?	+
ICI 118,551	–	+	?	–	–	–

MSA = membrane stabilizing activity; ISA = intrinsic sympathomimetic activity
Note: Selectivity for β_1 and β_2 adrenoceptors respectively is relative, depending on dosage and other factors

PHARMACOLOGY

By definition, beta blockers block beta-adrenergic receptors. Many drugs with this pharmacologic characteristic are currently available. Moreover, several beta blockers have ancillary properties that give them a special pharmacologic profile. This is particularly true of some of the newer agents in this large class of compounds. The *Table* illustrates the wide spectrum of actions obtainable with this class of drugs. Some agents have the same affinity for both beta-1 and beta-2 receptors and are usually termed "nonselective." Other agents have a higher affinity for either beta-1 or beta-2 receptors; these are termed "beta-1-selective" or "beta-2-selective," respectively. Some compounds exert an agonistic effect in addition to receptor blockade. This agonistic effect, intrinsic sympathomimetic activity (ISA), can be selective for beta-1 or beta-2 receptors. In addition, some beta blockers may have a quinidine-like or membrane-stabilizing activity.

The only agent devoid of beta-1-blocking activity, ICI 118,551, is also the one compound that lacks antihypertensive action (*Table*).[11] Moreover, epanolol, which has both beta-1-blocking activity and marked beta-1-selective ISA, ameliorates or reduces antihypertensive activity.[12] Antihypertensive effects for all the other listed compounds are well established. This seems to indicate that blockade of beta-1 adrenoceptors is essential in the antihypertensive activity of beta blockers. However, other mechanisms may be important as well. Compounds with marked beta-2-selective ISA seem to reduce blood pressure mainly by reducing vascular resistance, in contrast to the action of beta blockers without ISA.[13] A review of beta blocker studies in black hypertensive patients shows that compounds with ISA produce a better antihypertensive response than beta-1-selective agents.[14]

EARLY STUDIES WITH BETA BLOCKERS

The first reports on the antihypertensive effects of beta blockers were open studies without placebo control. Two of these studies were in reference to the beta blocker pronethalol;[4,15] a third study used propranolol.[5] These studies demonstrated significant blood pressure reduction in most hypertensive patients. These results were soon confirmed by a number of other studies in which propranolol was used.[6]

A few of these early studies deserve a special comment. In 1966, Waal reported an antihypertensive effect in a study of the antiarrhythmic properties of propranolol. She also made the important prediction that propranolol might reduce mortality due to cardiac infarction in hypertensive patients.[16] Another important contribution in 1966 was made by Paterson and Dollery. In a crossover trial, they compared two dose levels of propranolol with hydrochlorothiazide and reported that the two modalities were equipotent in lowering blood pressure.[17] Also, Frohlich et al presented the first long-term follow-up of hemodynamic results from this type of therapy, reporting a significant antihypertensive effect with propranolol .[18]

Probably the most important trial in those early years was conducted by Prichard and Gillam in 1969 (*Figure 1*).[19] In a study comprising 109 patients treated with propranolol for up to 3.5 years, they achieved reduction of diastolic blood pressure to 100 mm Hg or lower in 92 patients with daily doses of propranolol ranging from 15 to 4,000 mg.[19] In a subgroup comprising 17 patients, a retrospective comparison of the antihypertensive efficacy of propranolol, guanethidine, bethanidine, and alpha-methyldopa showed that propranolol reduced blood pressure at least as well as the three other compounds. Moreover, a question-

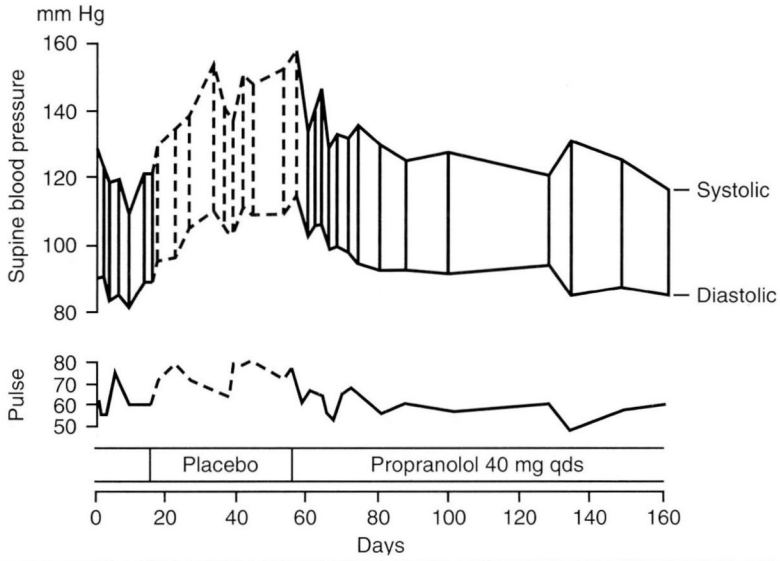

FIGURE 1. Blood pressure response to propranolol in one patient.[19]

naire-based inquiry showed that most patients preferred propranolol over their previous medication.

This large long-term study was important in promoting the widespread interest devoted to this therapeutic area in the following years. The result was a number of relatively large-scale studies[20,21,22] that, in principle, confirmed Prichard and Gillam's results (*Figure 2*). This early phase was followed by a period of large-scale intervention trials that used a beta blocker as one of the therapeutic modalities and studied the reduction in cardiovascular morbidity and mortality obtainable with antihypertensive therapy.

COMPARATIVE TRIALS

The first prospective, controlled studies with beta blockers aiming at reducing cardiovascular morbidity and mortality were conducted in postinfarction patients, eg, the alprenolol study in Sweden, the practolol study in Great Britain, the timolol study in Norway, the Beta Blocker Heart Attack Trial in the United States, and the metoprolol study from Sweden. This area has been extensively reviewed,[23] and it is beyond the scope of this brief presentation to discuss this topic in detail. However, these studies clearly demonstrated that beta blockers given to patients who had suffered a myocardial infarction significantly reduced mortality and risk of reinfarction. These studies inspired a number of primary trials which studied the possible preventive effect of beta blockers against coronary heart disease when prescribed for the treatment of hypertension. Some of these studies will be discussed here.

The Australian therapeutic trial

Unlike the other large-scale studies listed below, the Australian therapeutic trial in mild hypertension[24] was not a strict trial of beta blockers in hypertension. However, a considerable number of patients received a beta blocker (mainly propranolol or pindolol) in the second therapeutic step if chlorothiazide alone had not been effective in lowering blood pressure. This was a single-blind study, with patients stratified by age and sex, and it was conducted in four hospitals and several community-based centers in Australia. Its main objective was to compare active treatment with placebo in patients with mild hypertension with regard to fatal and nonfatal outcomes. Altogether 3,427 men and women ages 30 to 69 with diastolic blood pressures from 95 to 110 mm Hg took part in this study.

After a mean follow-up of 4 years, mortality from all causes for beta-blocker-treated patients was 50 out of 1,721 (2.9%), vs 70 out of 1,706 (4.1%) for patients who had received placebo. The difference was statistically significant, mainly because of a two-thirds reduction in cardiovascular deaths. Nonfatal end points were also significantly reduced, and trial end points correlated well with the blood pressure levels achieved.[24]

International Prospective Primary Prevention Study

The International Prospective Primary Prevention Study in Hypertension compared cardiovascular morbidity and mortality in a prospective, randomized, double-blind trial comprising 6,357 men and women ages 40 to 64 with uncomplicated essential hypertension (diastolic blood pressures from 100 to 125 mm Hg).[25] The patients were randomized to two groups: one group received antihypertensive treatment that

included the beta blocker oxprenolol; the other received antihypertensive treatment with placebo in place of oxprenolol. Supplementary drug treatment was common in both treatment groups, the aim being to reduce diastolic blood pressure to 95 mm Hg or lower.

Based on more than 25,000 patient-years, the main findings of the study were that the beta-blocker-based group achieved significantly lower average blood pressures, earlier electrocardiographic normalization, less hypokalemia, and fewer withdrawals than the placebo group. However, cardiovascular outcomes were not significantly different between the two groups.[25]

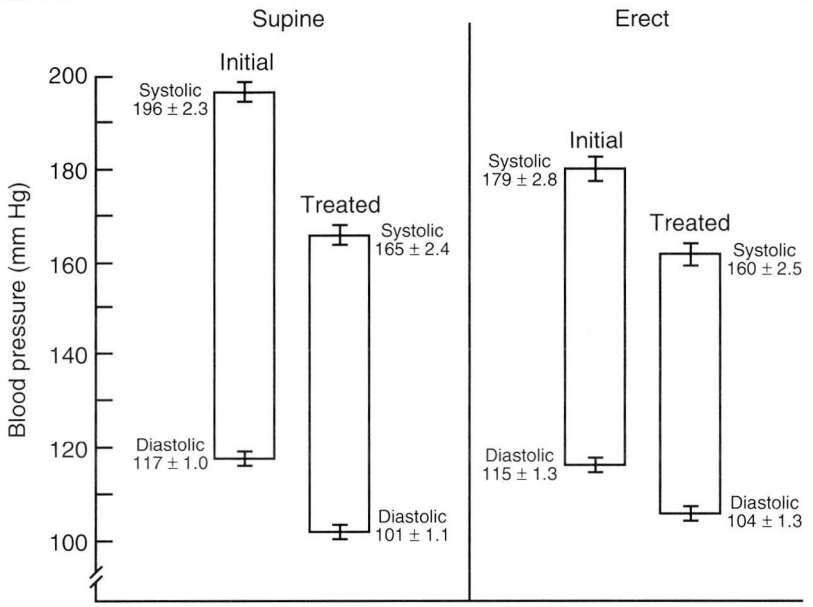

FIGURE 2. Effect of propranolol on blood pressure in 158 hypertensive patients.[21] Differences between initial and treated values are: supine systolic, 31 mm Hg; supine diastolic, 16 mm Hg; erect systolic, 19 mm Hg; and erect diastolic, 11 mm Hg. The *P* value for all differences was <.0005.

The Medical Research Council Trial

The Medical Research Council Trial was a single-blind, prospective, stratified, randomized, placebo-controlled study. Its aim was to investigate whether drug treatment of mild hypertension would reduce cardiovascular morbidity and mortality. The study took place in the United Kingdom in general practice settings. More than 17,000 men and women ages 35 to 69 with mild hypertension (diastolic blood pressures from 90 to 109 mm Hg) took part. Active treatment consisted of bendroflumethiazide in a rather high dose (10 mg daily), or propranolol. If blood pressure was not controlled by the first-step treatment, either methyldopa or guanethidine was added to the randomized treatment.[26]

After an average follow-up period of 5.5 years leading to the accumulation of more than 85,000 patient-years, mortality from all causes was 248 out of 8,700 patients (2.8%) on active treatment, vs 253 out of 8,654 patients (2.9%) on placebo.[26] The number of strokes was reduced in patients on active treatment, but the two groups did not differ in the rate of coronary events. More importantly, there were no significant differences between the thiazide and beta-blocker-treated groups that would have suggested a "cardioprotective" action of the beta blocker.[26]

The HAPPHY trial

The objective of the Heart Attack Primary Preventive Hypertension trial was to determine whether beta blockers were more effective than thiazide diuretics in preventing morbidity and mortality associated with coronary heart disease in patients with mild to moderate hypertension. This was an open randomized study without a placebo-control group in which 6,569 men ages 40 to 64 with diastolic blood pressures from 100 to 130 mm Hg were randomized to either beta-blocker treatment (mainly atenolol and metoprolol) or diuretics (mainly hydrochlorothiazide or bendroflumethiazide).[27]

Since there was no placebo group, this study was able to include patients with somewhat more severe hypertension (up to 130 mm Hg diastolic blood pressure). Moreover, since only men were recruited, a higher incidence of cardiovascular complications should have resulted than in the trials briefly reviewed above. However, at the end of the observation period,

mortality in the beta-blocker group was 96 out of 3,297 patients (2.9%), vs 101 out of 3,272 (3.0%) in the thiazide group. This difference was not statistically significant.[27]

The MAPHY study

The Primary Prevention Trial with Metoprolol in Hypertension (MAPHY) was an open, randomized trial that was part of the HAPPHY trial.[28] Its objective was to determine whether the beta blocker metoprolol was more effective than thiazide diuretic treatment (hydrochlorothiazide or bendroflumethiazide) in reducing cardiovascular morbidity and mortality in patients with mild to moderate hypertension. The 3,234 patients were men aged 40 to 64 with diastolic blood pressures from 100 to 130 mm Hg. Additional drugs were allowed in both the metoprolol and thiazide groups, provided that the initial allocation remained unchanged. Mortality was significantly lower for metoprolol-treated patients: after a median follow-up of 4.2 years, the mortality from all causes was 65 out of 1,609 (4.0%) in the metoprolol group, vs 83 out of 1,625 (5.1%) in the thiazide group.[28] One interpretation of these results has been that beta-blocker treatment conferred a cardioprotective effect. However, mortality in the thiazide group was unexpectedly high, which could fully explain the observed difference.

Significance of trial findings

These comparative trials were extensive in duration and included large numbers of patients. Still, the desired cardioprotective effect of beta blockers has not been established. There could be many explanations for this, the most obvious being that beta blockers do not have a primary preventive effect against coronary heart disease in addition to that seen with other antihypertensive drugs. However, results from secondary preventive trials in postinfarction patients certainly suggest that such an effect does exist.

Why is a primary preventive effect of beta blockers against coronary heart disease in hypertension so difficult to establish? The duration of treatment may have been too short in all of the studies reviewed above. Patients in the trials of beta blockers in hypertension have usually had mild degrees of hypertension; moreover, most studies have included women. Therefore, the failure to demonstrate a positive effect could be due to studying patients with very low risk profiles for too short a time. The notion that beta blockers have a specific cardioprotective effect when used in the treatment of hypertension is attractive, and to many people—including this author—it still appears to be a logical possibility.

ADDITIONAL FEATURES OF BETA-BLOCKER TREATMENT

Cardioprotection

Following the first reports of a secondary preventive effect of beta blockers in the treatment of postmyocardial infarction patients, several writers (including this author[29]) expressed the hope that beta blocker treatment in hypertensive patients would also have a primary preventive effect against coronary heart disease. However, many of the important intervention trials in this area have been negative in this respect—eg, the International Prospective Primary Prevention Study in Hypertension Study,[25] the Medical Research Council trial,[26] and the HAPPHY trial.[27] Claims of cardioprotection have been possible only in open studies without placebo control.[28,30] Therefore, it remains to be proven whether treatment of hypertension with beta blockers also provides the highly desirable primary preventive effect against coronary heart disease.

Antiatherosclerotic effects

Some newer aspects of beta-blocker treatment, in particular their antiatherosclerotic and cardioprotective effects in patients who have sustained traumatic brain injuries, have recently been reviewed.[31] The antiatherosclerotic effect of beta blockers has been noted in several animal experiments; the relevant papers were recently reviewed by Kaplan et al.[32] Kaplan and Clarkson and co-workers have studied the influence of psychosocial stress on coronary artery atherosclerosis in cholesterol-fed monkeys.[32] The authors point to a link between the sympathetic nervous system and atherosclerosis. They found that monkeys who were fed an atherogenic diet and who exhibited a rapid heart rate in response to stress had approximately twice the incidence of coronary atherosclerosis as animals with a slow heart-rate response.[32] Other investigators have observed that surgical removal of the sinoatrial node to reduce heart rate markedly diminished the risk of coronary atherosclerosis—independently of blood pressure, body weight, or serum lipoprotein fractions. Following these observations, it was logical, therefore, to study the effect of beta blockers. In two of three studies performed in monkeys, beta blocker treatment was found to have an antiatherosclerotic effect.[32]

Confirming evidence from other studies, particularly studies performed in people, are needed before the

clinical relevance of this effect can be evaluated. Still, these studies point to a potential therapeutic effect that may be immensely important in the future.

Reversal of structural cardiovascular changes

Structural cardiovascular changes, particularly left ventricular hypertrophy, constitute an independent risk for morbidity and mortality in hypertension. Reports from the Framingham study show that the presence of left ventricular hypertrophy indicated a worsening of prognosis comparable to that seen after a myocardial infarction, and that the risk for death, stroke, myocardial infarction, sudden death, and other cardiovascular complications is greatly increased.[33,34]

Thus, it seems highly desirable to be able to reverse hypertension-induced left ventricular hypertrophy. Beta blockers are among the classes of antihypertensive drugs shown to reverse left ventricular hypertrophy,[35] but it remains to be seen whether regression of left ventricular hypertrophy will reduce the associated risks.

Hypertrophic changes in the precapillary arterioles act as an amplifying mechanism by which any blood pressure-raising stimulus will be reinforced.[36] Complete reversal of structural arteriolar changes has not been described in adequately conducted clinical trials of antihypertensive treatment. Our group, having studied structural arteriolar changes using several different antihypertensive compounds and combinations, has come to the following conclusions: reversal of structural vascular changes in the precapillary vessels was not achieved with long-term antihypertensive treatment in blood vessels of the lower limb in man, but partial regression has been seen with some therapeutic modalities in the vascular beds of the forearm and the hand.[37] With single-drug treatment using a beta blocker, we have seen reversal of structural vascular changes only when nonselective beta blockade is accompanied by a marked beta-2-agonistic effect.[37]

CONCLUSION

Beta blockers have been used as first-line treatment for hypertension for two decades, and it appears that they will continue to play an important role for many years to come. Agents which combine beta-1-adrenoreceptor blocking activity with agonistic properties at the beta-2 receptor may have special advantages over other types of beta blockers. Their potential clinical benefits include lesser reductions in cardiac output and heart rate, and they may help diminish hypertension-induced structural arterial changes that are detrimental. Long-term beta blockade for treatment of hypertension may have a primary preventive effect against coronary artery disease, although this has yet to be demonstrated conclusively. Finally, the reversal of hypertension-induced hypertrophic cardiovascular changes is likely to become an important criterion for selection of antihypertensive therapy.

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