

Beta-blockers: ancillary properties important after all?

CLEOPHAS T.C., VAN DER MEULEN J.

Department of Medicine, Merwede Hospital, Dordrecht, Netherlands

Ancillary properties of beta-blockers include level of lipophilicity, intrinsic sympathicomimetic activity (ISA), high receptor affinity, selectivity, and vasodilatory property. So far compounds with different ancillary properties have been considered equally effective. Based on current literature it seems no longer appropriate that this be done so. A subgroup analysis of the HAPPHY hypertension trial found that the lipophilic compound, metoprolol, was more effective than the lipophobic, atenolol, in reducing the combined risks of cardiac failure, infarction, and cardiac death. This was confirmed by a meta-analysis of 69 secondary prevention trials myocardial infarction: the lipophilic compounds metoprolol and propranolol reduced the risk of cardiac death by 17 and 15% where as the lipophobic atenolol did so only by 5% (differences significant at $p < 0.0001$). The ancillary property intrinsic sympathicomimetic property (ISA) seems to contribute little to effectiveness in patients with hypertension or angina pectoris. However, ISA may benefit patients with hypoadrenergic orthostatic hypotension. Noncardioselective beta-blockers cause a

pressor effect due to increased alpha receptor-mediated vasoconstriction unopposed by beta-2 receptor-mediated vasodilation and are thus less effective for the treatment of hypertension than cardioselective compounds. The clinical relevance of this phenomenon has now been confirmed by a series of controlled clinical trials. In recent years beta-blockers with vasodilatory properties such as celiprolol, carvedilol, and nebivolol, have become available. Although long-term clinical experience with these compounds is largely missing there is a growing evidence to attest that these compounds provide additional benefits particularly in patients with increased afterload or cardiac failure. We conclude that based on theoretical arguments and surrogate measures in patients with hypertension, in addition to death rates in patients with myocardial infarction lipophilic cardioselective beta-blockers should be given preference.

Key words Beta-blockers, ancillary properties, lipophilicity, intrinsic sympathicomimetic property, receptor affinity, selectivity, vasodilatory property.

Introduction

In 1995 Morris Brown, a Cambridge-UK professor of clinical pharmacology, claimed in a BMJ editorial that beta-blockers were effective for the treatment of angina pectoris and hypertension, that the type of beta-blocker, however, was of no clinical relevance (1). This editorial was written in reply to a publication of our group in *Circulation* entitled: "Paradoxical pressor effects of non-selective beta-blockers" (2). In a letter to the editor discussion a few weeks later the chair Brown withdrew his former statement and admitted that beta-1 selective are more effective for hypertension and that non-selective are so for angina pectoris (3).

Because of their excellent record of effectiveness and safety, beta-blockers have become one of the commonly prescribed classes of drugs to be used in the treatment of hypertension and angina pectoris, for the prevention of recurrent angina pectoris, and possibly also in specific cases of cardiac failure. The most important ancillary properties of beta-blockers include: 1. Lipophilicity. 2. Intrinsic sympathicomimetic activity (ISA). 3. High receptor affinity. 4. Selectivity 5. Vasodilatory property.

The current paper gives an overview of the most important ancillary properties of beta-blockers, and studies the literature to find out whether they are clinically relevant, and if so to what extent.

Lipophilicity

Is the difference in lipophilicity/hydrophilicity clinically relevant? Apart from differences in kinetics

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may give rise to sleepiness and dreams), a question of major importance is whether it is associated with differences in clinical effectiveness. In 1987 the HAPPHY hypertension trial compared beta-blockers to diuretics (4). In a subgroup analysis the lipophilic beta-blocker, metoprolol, was more effective than the hydrophilic, atenolol. However, since this was a subgroup analysis, the finding was rightly criticized. In the past year Soriano et al. performed a meta-analysis involving no less than 69 secondary prevention trials myocardial infarction (5) and, surprisingly, the best performance was displayed by the lipophilic beta-blocker metoprolol: 17% overall risk reduction of myocardial infarction, compared to 15% with the somewhat less lipophilic, propranolol, and only 5% with the hydrophilic, atenolol. The strong part of this investigation was that individual beta-blockers were compared with each other rather than selective versus non-selective ones, a common procedure till then. In doing the latter one finds 10% risk reduction with selective versus 15% with non-selective, and loses sight of the advantage of metoprolol since metoprolol and atenolol together are less effective than propranolol separately. Considering this analysis we now have to accept that the medical community has been wrong to assume that non-selective compounds would be

more effective to cardiac patients. Actually, lipophilic agents appear to be more so.

Intrinsic sympathicomimetic activity (ISA)

Is intrinsic sympathicomimetic activity a property of clinical relevance? Beta-blockers with ISA are partially blocker and partially agonist. Their effect on cardiac output is smaller, but so is their effect on peripheral resistance. Even though such hemodynamic effects are interesting by definition (6) clinical relevance has been very limited so far. ISA beneficial blockers seem to be beneficial in patients with hypo-adrenergic orthostatic hypotension (7). However, we are talking of an extremely rare clinical condition. Hyperadrenergic orthostatic hypotension, e.g., due to vasodilators and volume depletion and to vagal neuropathy with diabetic neuropathy, is a much more common condition. ISA blockers do not provide any benefit here (8).

Because of their partial beta-2 agonistic property, ISA blockers may be metabolically more neutral, an aspect which will be addressed in more detail in one of the next paragraphs.

Receptor affinity

Is the property especially-high receptor affinity clinically relevant? Timolol is in the dose-response curves 10 times more potent than metoprolol is. Of course high potency is relevant. However, it may at the same time give rise to certain hazards. Picture the reports on timolol eye-drops a few years ago, which elicited Brown to express: "One drop of timolol down the lacrimal duct can kill" (1). Some patients treated with timoptol eye-drops swallowed the compound and subsequently developed a fatal attack of bronchial asthma.

Selectivity

Is cardioselective versus non-selective property clinically relevant? Fundamentally, beta-1 activity is the capability of a beta-blocker to antagonize isoproterenol-induced tachycardia. Beta-2 activity is the capability to antagonize isoproterenol-induced bronchial constriction or peripheral vasoconstriction. The problems with beta-2 blockade follows immediately from these definitions. For non-selective beta-blockade otherwise called beta-1+2 blockade causes vasoconstriction, or, at least, reduces vasodilation of major resistance vessels. In addition, beta-1+2 blockade involves negative metabolic effects simply because they are predominantly beta-2 receptor mediated: it involves not only reduced capacity of glyconeogenesis through glycogenolysis in muscle cells and enhancement of insulin resistance, but also effects on plasma lipids and lipoproteins. Houston (9) pooled the data of 17 trials and demonstrated that during non-selective beta-blockade cholesterol (C) and LDL-cholesterol (LDL-

C) rose by 4%, while triglycerides (TG) rose by 25-50%. During selective beta-blockade C and LDL-C did not change, while TG rose by 15-26% only. Finally, beta-2 blockade gives rise to severe bronchial constriction particularly in patients with bronchial asthma. Our group has been rather active through the past 10 years in studying one particular problem with beta-2 blockade, namely the problem of paradoxical hypertension (10), and it is our firm belief it is a clinically relevant problem. It was first demonstrated in the early 80ths to occur during infusion of epinephrine after pretreatment with propranolol but not so after pretreatment with metoprolol. The phenomenon was tested by the group of Van Herwaarden (11) and somewhat later that of Houben (12), both from Nijmegen Netherlands, and was confirmed by groups from other institutions. In the meantime, patients with high levels of epinephrine, such as patients with phaeochromocytoma, had been recognized to present with the same phenomenon. According to the theory it was caused by alpha-receptor mediated vasoconstriction unopposed by beta-2-receptor mediated vasodilation, a mechanism through which vasopressor effects from non-selective beta-blockade may become disproportionately large. Within a short period of time this pressor effect was demonstrated during withdrawal of the alpha-2-receptor agonist clonidine, and also during the use of cocaine, nicotine, and caffeine all of which being compounds that increase circulating plasma epinephrine levels. It was also demonstrated in stress models such as mental arithmetic, isotonic and isometric exercise, as well as dynamic exercise etcetera (13). Finally, in randomized clinical trials of patients exposed to a lot of psychological stress, e.g., acute admission to hospital (14), acute surgery (15), and acute myocardial infarction (16). Under all of these circumstances paradoxical hypertension and pressor effects were observed during non-selective beta-blockade, but not so during selective beta-blockade.

Vasodilatory property

In the past few years a new generation of beta-blockers, with vasodilatory properties, has entered the market. Carvedilol, a component of the former labetalol, is an alpha-1-selective alpha-blocker and non-selective beta-blocker. Nebivolol is an NO-donor and beta-1-selective beta-blocker. Celiprolol is beta-1 blocker and beta-2 agonist. These three compounds are interesting, particularly so to patients with increased afterload and/or compromised left ventricular performance because they are capable of reducing afterload. However, long-term experience with these compounds is largely missing. Carvedilol underwent some screening in patients with NYHA III heart failure, and appeared to be slightly beneficial

(17). Nebivolol is NO-donor and, therefore, contraindicated in post-myocardial-infarction-patients with symptoms of a stunned heart (18). Celiprolol is beta-2-agonist and was more effective than other beta-blockers in a study of patients with unstable angina pectoris from our group (13). Also, this compound may be metabolically more beneficial because of its beta-2 agonistic properties.

Discussion

The current paper reviews ancillary properties of beta-blockers and their clinical relevance. Additional ancillary properties include membrane-stabilizing property, otherwise called local-anesthetic property, and class III anti-arrhythmic effect. We should state here that the former phenomenon is, in fact, clinically irrelevant. So is class III anti-arrhythmic effect on kalium-channels. Although this property protects against ventricular arrhythmias, it pertains to one particular compound only, sotalol. Morris Brown who is obviously rather critical of our groups' standpoints, expressed in his BMJ article (1) that he did not consider the theoretical disadvantages of beta-2 blockade clinically important. In addition, he offered some arguments in favor of beta-2 blockade. First, norepinephrine has about the same 20 fold selectivity for beta-1 receptors (compared with beta-2 receptors) as an agonist as does atenolol as an antagonist, meaning that under most circumstances beta-1 blockade is protecting against a non-existent enemy of peripheral blockade of beta-2 blockade. Second, he considered negative metabolic effects of beta-2 blockade generally irrelevant, except perhaps for diabetics with seriously delayed hypoglycaemias and dyslipidemic patients with exceptionally high levels of cholesterol or triglycerides. Third, he argued that beta-2 blockade may offer important additional advantages: (1) also in the heart beta-2 receptors may be present to protect against arrhythmias (19); (2) beta-2 blockade may be helpful in preventing epinephrine-induced hypokaliemia (20); (3) the administration of selective beta-blockers caused a 5 fold upregulation of beta-2 receptors which in return may cause arrhythmias (21); (4) the beta-2 receptor gene is considered one of the candidate genes for essential hypertension, expression of this gene would be suppressed by beta-2 blockade (22). These arguments have been applied for many years to explain the presumably better effectiveness of non-selective beta-blockers in the secondary prevention trials. However, all of them have become less relevant now that the best protection seems to be given by lipophilic rather than non-selective beta-blockers. As we have seen in the past, e.g., in the CAST studies (23), theoretical arguments were defeated by clinical trial evidence. Our group

summarized in a recent Circulation (2) paper the disadvantages of non-selective versus selective beta-blockers and concluded that selective beta-blockers qualified better than non-selective for the treatment of hypertension. This conclusion was rejected by the comment from Cambridge-UK which literally stated: "Beta-1 selectivity rarely matters in clinical practice despite the hype". In a letter to the editor discussion in the BMJ a few weeks later (3) Brown withdrew his former statement: "Based on theoretical arguments and surrogate measures I tend to use low doses of the most beta-1 selective lipophilic agent, bisoprolol, for hypertension and the highest affinity non-selective agent, timolol, for ischemic heart disease". As far as our group is concerned, lipophilicity is fine, beta-1 selectivity is fine, high affinity offers better potency, so that is generally no problem either. However, there is now evidence that the ancillary property non-selectivity does not benefit the heart. Beta-blockers are often being compared to other classes of drugs as currently available for the treatment of hypertension and angina pectoris. Important physiological effects of different classes of drugs are: stimulation of the renin-angiotensin system (RAS) and the sympathetic nervous system (SNS), inhibition of the parasympathetic nervous system (PSNS) as well as endothelium-dependent mechanisms. These mechanisms are frequently activated by antihypertensive drugs, and, subsequently antagonize the blood pressure lowering effects of antihypertensive drugs. In contrast to most other classes beta-blockers do not stimulate the RAS, and inhibit effects of the SNS. The reverse is true for diuretics and calcium channel blockers, namely stimulation of the RAS and the SNS. Beta-blockers would, therefore, have to be theoretically more effective. This very conclusion, however, is not being confirmed by randomized controlled clinical trials. EWPHE (24), SHEP (25), and MRC ELDERLY (26) showed that diuretics performed well, and definitely better than placebo. Of four trials comparing beta-blockers with diuretics (4, 26-28) two showed that diuretics performed better than beta-blockers (MRC MILD and MRC ELDERLY) while the other two showed no differences (HAPPHY and IPPPSH). PRAISE, DEFIANT, CRIS, STONE, SYST-EUR (29-33) showed that calcium channel blockers performed better than placebo. Mega-trials like ALLHAT, NIFGITS, HOT, STOP, PRESERVE, PROGRESS (34-39) have not yet been completed but may soon show similar trends. Arguments in defense of the somewhat poor results of beta-blockers in hypertension trials are the following. First, trials involved largely heterogeneous populations. E.g., SHEP (25) and SYST-EUR (33) tested systolic hypertension in elderly persons, a population tending towards increased afterload and increased circulating

volumes. This particular population would theoretically benefit from volume reduction, whereas younger subjects with essential hypertension often have a high SNS activity, sooner or later accompanied by increased RAS activity. Especially, the latter group would better benefit from beta-blockers or ACE-inhibitors. Second, ACE-inhibitors and calcium channel blockers are metabolically rather neutral, whereas diuretics and beta-blockers, particularly non-selective, do have somewhat negative metabolic effects. Third, proliferative effects have been considered. A stimulated SNS and RAS enhance the mRNA expression of proto-oncogenes that subsequently induce growth hormones to produce proliferative cardiovascular effects (40). ACE-inhibitors and beta-blockers counteract this cascade, while calcium channel blockers and diuretics have an indirect stimulatory effect. Fourth, ACE-inhibitors and calcium channel blockers reduce blood pressure not only during the daytime when it is high but also during the nighttime when it is not so, whereas beta-blockers produce their main effects during the daytime, when SNS is high, only (41). Nighttime hypotension in patients with chronic hypertension may precipitate ischemic heart disease and a significant fall in cerebral blood flow (42). Fifth, patients already scheduled on beta-blockers because of angina pectoris or prevention myocardial infarction, will ethically be considered uneligible for a hypertension trial. Obviously, those categories of patients that would benefit most from beta-blocker treatment are systematically excluded from these trials. This mechanism of negative selection jeopardizes beta-blocker research.

Conclusions

Lipophilicity is relevant. Cardioselectivity is relevant. Membrane-stabilizing property and ISA are largely clinically irrelevant, as well as class III antiarrhythmic effect, except for sotalol. High receptor affinity is, of course, clinically relevant, but it is at the same time hazardous because of enhanced pharmacodynamic effects. Vasodilatory effect may be clinically relevant, although similar effect could be obtained by the addition of a vasodilator to a non-vasodilator beta-blocker. The best choice for the treatment of hypertension seems a cardioselective compound, for the treatment of coronary artery disease it is a lipophilic compound. It follows that a compound providing both lipophilic and cardioselective property like metoprolol seems a safe choice for any indication. Whether a cardioselective beta-blocker with vasodilatory property like celiprolol is an even better choice, future research will have to tell us. Unfortunately, beta-blocker research is currently somewhat in jeopardy.

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Correspondence to:

Dr. Ton J. Cleophas

Dept. Medicine, Merwede Hospital

306, 3300 AH Dordrecht, NETHERLAND