Drugs for the Heart

American Edition

DRUGS FOR THE HEART

AMERICAN EDITION

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Preface

Cardiovascular pharmacology is a very active scene. A plethora of new agents are now offered to the clinician—to say nothing of the new indications that are being found for old agents. Every agent seems to have several actions that are often apparently unconnected. Confusion is rife.

In this book, we hope to restore some order by examining six groups of drugs: beta-blockers, nitrates, calcium antagonists, antiarrhythmics, digitalis and sympathomimetics, and vasodilators. We will discuss what is known of their actions at both the cellular and the clinical levels. A knowledge of cellular mechanisms may help to avoid a serious hazard in polypharmacy. Information on clinical results will equally discourage adoption of the large number of drugs that should work but do not, or that have never been properly tested. We will speak often of "usual" or "average" or "maximum" doses, and some readers may protest that such terms are utterly not helpful. They are intended largely to allow some comparison of costs; it is not enough to know that one tablet is cheaper than another.

The ready availability of so many agents means that the physician has great power for poor as well as for good results. Not all cardiac illness steadily progresses. Some patients with angina spontaneously improve. Cardiac failure may be temporarily worsened by intercurrent illness while post-infarct arrhythmias come and go. We must constantly be asking ourselves whether the therapy can be simplified or stopped; and, conversely, whether the time has come for one of the more vigorous regimens described in these articles.

So, on to beta-blockers.

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Contents

Preface vii

Contributors ix

BETA-BLOCKING AGENTS
Lionel H. Opie, Edmund H. Sonnenblick, Norman M. Kaplan, and Udho Thadani 1

NITRATES
Lionel H. Opie and Udho Thadani 23

CALCIUM-ANTAGONISTS
Bramah N. Singh and Lionel H. Opie 39

ANTIARRHYTHMIC AGENTS
Bramah N. Singh, Lionel H. Opie, and Frank I. Marcus 65

DIGITALIS AND SYMPATHOMIMETIC STIMULANTS
Frank I. Marcus, Lionel H. Opie, and Edmund H. Sonnenblick 99

VASODILATING DRUGS
Lionel H. Opie and Donald C. Harrison 129

WHICH DRUG FOR WHICH DISEASE?
Bernard J. Gersh, Lionel H. Opie, and Norman M. Kaplan 153

Index 193

L. H. Opie, E. H. Sonnenblick
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1
Beta-Blocking Agents

The actions of catecholamines on the beta-adrenoceptors are antagonized by the "beta-blocking agents," because there is competitive inhibition. The effect of a given beta-blocking agent depends not only on the way it is absorbed, bound to plasma proteins, and metabolized, but also on the extent to which it inhibits the beta-receptor.

THE BETA-RECEPTOR

Our understanding of adrenergic effects is based on Ahlquist's original classification of adrenoceptors into alpha and beta types. The beta-receptors are further subdivided into the beta-one-receptors of heart muscle and the beta-two-receptors of bronchial and vascular smooth muscle; some metabolic beta-receptors cannot be easily classified. Situated on the cell membrane, the beta-receptor is closely coupled to the adenyl cyclase (adenylate cyclase) system (Fig. 1-1).

There are several receptor sites for adenyl cyclase: one for beta-agonists, one for glucagon, one for thyroid hormone, and one for histamine. Each agonist, acting on its receptor site, can activate adenyl cyclase to produce cyclic AMP from ATP. Cyclic AMP is the intracellular messenger of beta-stimulation; among its actions is the "opening" of calcium channels to promote a positive inotropic effect. In the sinus node the pacemaker current is increased (positive chronotropic effect).

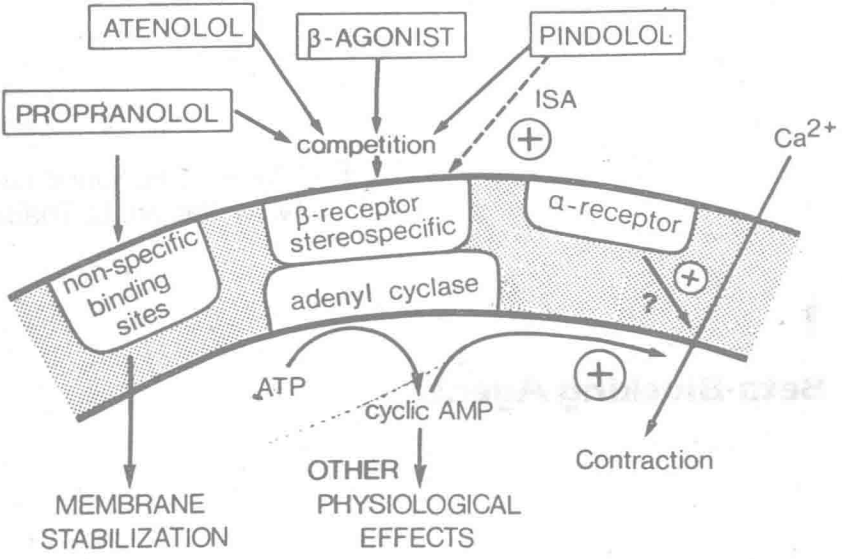

Fig. 1-1. Cardiac adrenergic receptors. Beta-agonists act on the stereospecific beta-receptor in the heart cell membrane. Beta-blockade by propranolol is partly a specific competitive antagonism and partly a non-specific binding (membrane stabilization). For ISA, see Figures 1-5 and 1-7. [Modified from Opie LH: Drugs and the Heart. I. Beta-blocking agents. Lancet, 1980, 1:693–698, by permission of The Lancet.]

THERAPEUTIC USES

Angina Pectoris and Myocardial Infarction

Beta-blockade reduces the oxygen demand of the heart in several ways (Fig. 1-2); notably, by reducing the double product (heart rate times blood pressure) and depressing contractility. By reducing the tachycardia of effort, beta-blockers may also increase the oxygen supply by prolonging diastolic coronary blood flow. The list of contraindications and side-effects is formidable (Table 1-1). The most important contraindication is asthma or a past history of asthma; several fatalities or near fatalities have been reported with noncardioselective agents, and even selective agents can only be given under supervision.

Angina Pectoris

All beta-blockers are usually effective in angina pectoris (Table 1-2), and the choice of drug matters little except that long-acting compounds need to be given only once daily.[1] But about 20 percent of pa-

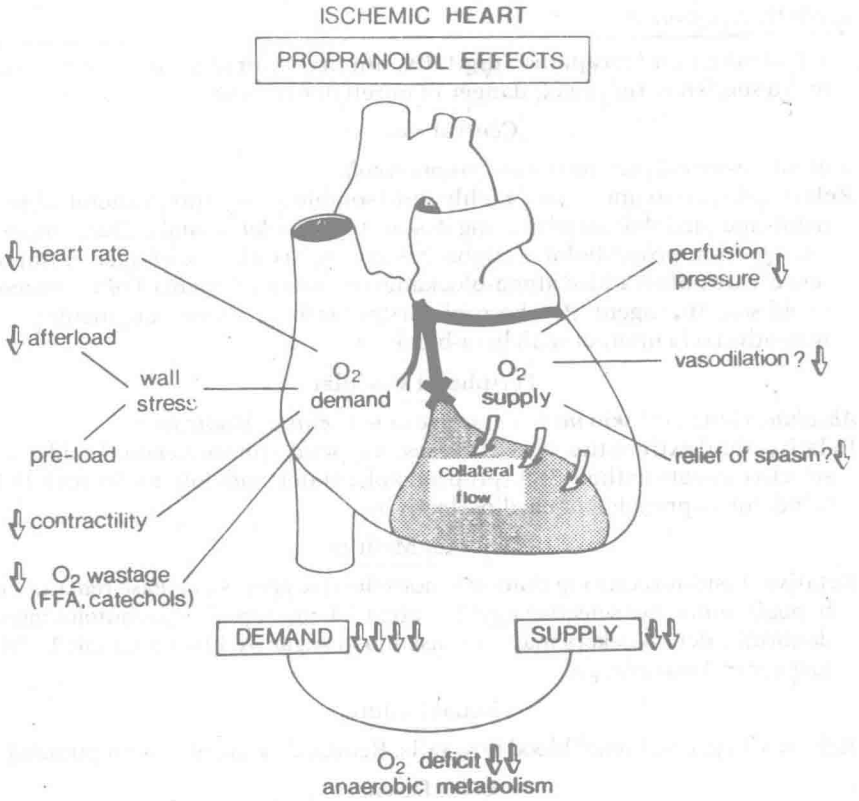

Fig. 1-2. Effects of beta-blockers on ischemic heart. Beta-blockers has a beneficial effect on the ischemic myocardium, unless the preload rises substantially as in left heart failure, by reducing oxygen demand. [Modified from Opie LH: Drugs and the Heart. I. Beta-blocking agents. Lancet, 1980, 1:693–698, by permission of The Lancet.]

Table 1-1
Beta-Blockade: Contraindications

Pulmonary
Absolute: Severe asthma or bronchospasm.
Relative: Mild asthma or bronchospasm or chronic airways disease. Use agents with cardioselectivity, plus beta$_2$-stimulants (by inhalation). High ISA also protects, but loss of sensitivity to beta$_2$-stimulation.
Cardiac
Absolute: Symptomatic bradycardia, low cardiac output, left ventricular failure (exception, some cardiomyopathies), high-degree heart block, acute myocardial infarction unless monitored.
Relative: Treated heart failure, cardiomegaly without clinical failure, Prinzmetal's angina (unopposed alpha-spasm), high doses of other agents depress-

(continued)

Table 1-1 (continued)

ing conduction (verapamil, digitalis, antiarrhythmic agents); in angina, avoid sudden withdrawal; danger in unreliable patient.

Central Nervous

Absolute: Severe depression (avoid propranolol).

Relative: Vivid dreams: avoid highly lipid soluble agents (propranolol, alprenolol) and pindolol; avoid evening dose or try atenolol. Visual hallucinations: change from propranolol. Fatigue (all agents; try change of agent). Impotence: rare unless added alpha-blockade (try change of agent). For migraine: avoid selective agent. Psychotropic drugs (with adrenergic augmentation) may adversely interact with beta-blockers.

Peripheral Vascular

Absolute: Gangrene, skin necrosis, severe or worsening claudication.

Relative: Cold extremities, absent pulses, Raynaud's phenomenon. Avoid nonselective agents without ISA (propranolol, sotalol, nadolol); prefer high ISA (pindolol, oxprenolol) or cardioselectivity.

Diabetes Mellitus

Relative: Insulin-requiring diabetes: nonselective agents decrease reaction to hypoglycemia; use selective agents—atenolol, metroprolol (acebutolol more doubtful). Beta-blockers may increase blood sugar by 1.0–1.5 mmole/L. Adjust control accordingly.

Renal Failure

Relative: In general renal blood flow falls. Reduce doses of all except pindolol.

Liver Disease

Relative: Avoid agents with high hepatic clearance (propranolol, alprenolol, oxprenolol, timolol, acebutolol, metoprolol). Prefer agents with low clearance (atenolol, nadolol, sotalol, or pindolol). If plasma proteins are low, reduce dose of highly bound agents.

Pregnancy Hypertension

Avoid unless treatment essential, but beta-blockers may be better than methyldopa. Avoid thiazide diuretics.

Surgical Operations

Beta-blockade may be maintained throughout, provided indication is not trivial; otherwise stop 24–48 hours beforehand. May protect against anasthetic arrythmias. Use atropine for bradycardia, beta-agonist for severe hypotension.

Age

Can use with care in elderly: Watch for increased side-effects and pharmacokinetic changes.

Modified from Opie LH : Drugs and the Heart. I. Beta-blocking agents. Lancet 1:693–698, 1980

ISA = Intrinsic sympathomimetic activity.

Table 1-2
Properties of Various Beta-Adrenoreceptor Antagonist Agents, Non-selective Versus Cardioselective

Generic Name	ISA	Plasma Half-Life (hours)	Usual Doses for Angina	Usual Doses as Sole Therapy for Mild/Moderate Hypertension	Arrhythmias: Slow IV Doses‡
Noncardioselective					
Propranolol (Inderal; Ayerst)	–	1–6	120–400 mg/day, 3–4 divided doses, but 80 mg twice daily usually adequate.[38] Start as for hypertension.	Start with 20–40 mg twice daily to avoid side-effects. Mean 160–320 mg/day (1–2 doses); less with diuretic.[17,44]	1–10 mg
Nadolol (Corgard; Squibb)	–	12–17	80–240 mg once/day; mean 100 mg[39]	40–320 mg/day; mean 120 mg/day; single dose.[45]	———
Timolol (Blocadren; Merck Sharp & Dohme)	–	4–5	15–45 mg, 3–4 divided doses	20–80 mg/day, 1–2 doses/day[48]	0.4–1.0 mg
Sotalol (not in United States)	–	15–17	240–480 mg/day	80–320 mg/day, single dose	10–20 mg
*Nonselective with ISA**					
Oxprenolol (Trasicor; CIBA-Geigy; not in United States)	++	2	Same as that of propranolol; mean 160 mg/day [1]	Same as for propranolol but higher; mean 240–480 mg/day, 2 doses/day[46]	1–12 mg

(continued)

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Table 1-2 (continued)

Generic Name	ISA	Plasma Half-Life (hours)	Usual Doses for Angina	Usual Doses as Sole Therapy for Mild/Moderate Hypertension	Arrhythmias: Slow IV Doses‡
Pindolol (Visken; Sandoz)	+ + +	4	2.5–7.5 mg three times daily[40]	10–30 mg/day, 1–2 doses[47]	0.4–2.0 mg
Nonselective with alpha-blocking activity					
Labetalol (not in United States)	–	3–4	Same as for hypertension	200–1200 mg/day in 2 doses; top dose 2400 mg/day[49]	IV for severe hypertension
Cardioselective					
Acebutolol† (not in United States)	+ +	about 3	200–600 mg thrice daily.[41] 1650 mg equals 220 mg propranolol.[40]	400–800 mg/day in 2 doses, can be given as single dose[50,51]	12.5–50.0 mg
Atenolol (Tenormin; Stuart)	–	6–9	100 mg once daily; 25 mg twice daily nearly as effective[42]	50–200 mg/day as single dose; usual dose 100 mg[51]	5–15 mg
Metoprolol (Lopressor; Geigy)	–	3	50–100 mg three times daily;[43] mean total 200 mg[1]	50–400 mg/day[43]; mean about 250 mg. With 300 mg, a single dose is adequate.[52]	5–15 mg

Data from references given in table. For additional information see also Opie LH: Drugs and the Heart. I. Beta-blocking agents. Lancet, 1980, 1:693–698.

*ISA = intrinsic sympathomimetic activity.

†Acetyl metabolite (diacetolol) is more important than parent compound during oral therapy; properties still under study.

‡Only intravenous propranolol available in United States

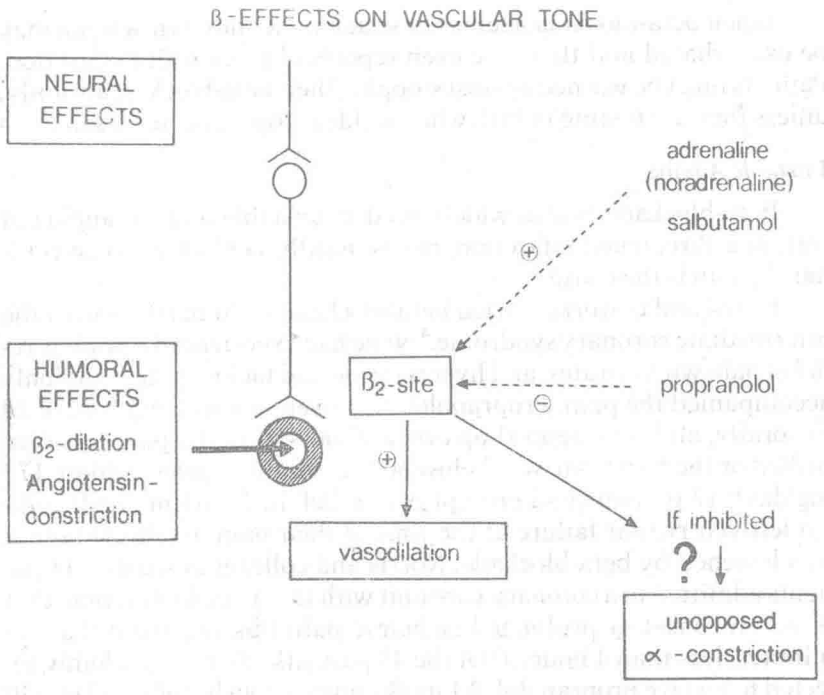

Fig. 1-3. Hypothetical effect of beta-blockade (propranolol) in allowing unopposed alpha-vasoconstriction. [Modified from Opie LH: Drugs and the Heart. I. Beta-blocking agents. Lancet, 1980, 1:693–698, by permission of The Lancet.]

tients do not respond to any beta-blocker. The reason for this possibly lies in unopposed alpha-vasoconstriction (Fig. 1-3), or sometimes the heart rate may already be low. Bradycardia and reduction of exercise-induced tachycardia are important determinants of the response to treatment, and the dose of beta-blocker is usually adjusted to secure a resting heart rate of 55–60 beats/minute, and more importantly, an exercise heart rate of less than 100–110 beats/minute. Lower resting rates may be acceptable, provided that heart block is avoided and symptoms are not provoked. Higher resting rates are found with drugs possessing intrinsic sympathomimetic activity (ISA), which are discussed later in this chapter. Beta-blocking drugs may be freely combined with nitrate vasodilators, which will increase the heart rate. Beta-blockade may also be combined with calcium antagonists, especially nifedipine.

In patients with angina pectoris who have abnormal left-ventricular function, beta-blockade decreases the incidence of angina, but may lessen exercise tolerance. Digitalization (and diuretics) can then prevent this deterioration in exercise tolerance and reverse the cardiac enlargement induced by beta-blockers.[2]

When beta-blocking agents are suddenly withdrawn, angina may be exacerbated and there are even reports of myocardial infarction. Patients must be warned against stopping their beta-blockers abruptly, unless they are resting in bed, when sudden stop seems to be safe.[3]

Unstable Angina

Beta-blockade is also widely used in unstable angina, angina at rest, and threatened infarction, but is usually ineffective when coronary spasm is the cause.

Fischl and coworkers tried beta-blockade in 20 patients with the intermediate coronary syndrome.[4] None had experienced complete relief of pain with nitrates, and hypertension and tachycardia commonly accompanied the pain. Propranolol was given in a starting dose of 20 mg orally, and was stepped-up every 4 hours until the pain was controlled or the heart rate was below 60 beats/minute (average dose 170 mg/day); 17 patients had prompt pain relief. In 7 patients with clinical left-ventricular failure at the time of their pain, the heart failure was lessened by beta-blockade. Norris and colleagues studied 43 patients admitted to a coronary-care unit with threatened infarction, that is, recent onset of prolonged ischemic pain (lasting more than 30 minutes, less than 4 hours.)[5] Of the 43 patients, 20 were randomly selected to receive propranolol, 0.1 mg/kg intravenously, followed by 320 mg orally over 27 hours, and these patients had fewer completed infarcts, as assessed by electrocardiogram (ECG) and serum–creatine-kinase levels, than did the controls. Excluded from this group had been any patients with a contraindication to beta-blockade, such as a history of cardiac failure or asthma, or a bradycardia of less than 60 beats/minute. A newer contraindication is peripheral vascular disease. Norris' patients may have been atypical, but this concept of early intervention in carefully monitored patients with myocardial infarction has much merit.

Prinzmetal's Variant Angina

In Prinzmetal's variant angina, which is caused by spontaneous coronary vasospasm, beta-blockade is ineffective and may even be harmful, possibly because of unopposed alpha-tone in the large coronary arteries (Fig. 1-3). Similar arguments favor the use of calcium antagonists (Chapter 3) in angina at rest with short-lived attacks of chest pain; in this case propranolol is ineffective.[6] The apparent contradiction between the latter study and that of Fischl,[4] both dealing with angina at rest, may be explained as follows. First, Fischl's patients probably did not have prominent vasospasm because the pain did not fully respond to nitrates; second, the attacks of pain were long

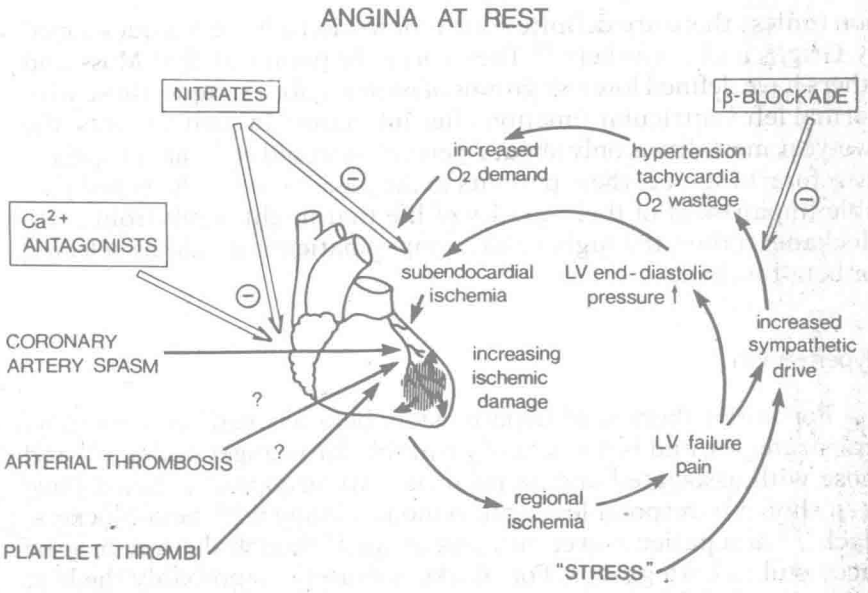

Fig. 1-4. Hypothetical mechanisms for angina at rest. The origin of this condition is partially related to coronary artery spasm. Once ischemia is established, vicious circle-mechanisms may activate the sympathetic nervous system.

enough to cause a secondary tachycardia and hypertension, which propranolol could inhibit (Fig. 1-4).

Acute Myocardial Infarction

In acute myocardial infarction, beta-blockade remains an investigational procedure, because the resultant depression of contractility, heart rate, and conduction is unpredictable. Increasing reports nevertheless indicate various benefits of early intravenous beta-blockade, including a reduction of ventricular arrhythmias. When a patient already on beta-blockade has a myocardial infarction, the treatment should probably be continued unless cardiac output is low or the heart rate is very slow, because of the risks of withdrawal rebound.

In the postinfarct phase, several beta-blocking agents have been shown to reduce the risk of sudden death in the 12 months following infarction[7,8]; one study suggests prolonged protection for years.[9] The value of chronic beta-blockade in protection against reinfarction is still under evaluation, although it has been established in the timolol trial, and when the results of all trials are combined.[8]

The wisdom of giving beta-blockade to all patients after infarc-

tion (unless there are definite contraindications) has been questioned by Griggs and coworkers.[10] They correctly point out that Moss and others have defined low risk groups of patients, for example, those with normal left ventricular function after infarction. In such patients, the two-year mortality is only about 2 percent. It would seen inappropriate, therefore, to subject these patients to the possible side-effects and possible impairment of their quality of life that might result from beta-blockade; rather, the higher risk group of patients should be selected for beta-blockade.

Hypertension

For initial therapy of hypertension, beta-blockade is one of several strategies, and is particularly suitable for younger patients[11] and those with associated angina pectoris. Two groups of patients have been shown to respond less well to monotherapy with beta-blockers; blacks,[12] and patients over 60 years of age,[11] though therapy may be successful in both groups. For blacks, a diuretic is probably the best choice; for the elderly, prazosin or small doses of a direct vasodilator may be preferable. Recent European work suggests the use of a calcium antagonist (Chapter 3). In the elderly, the diminished baroreceptor response of age dampens the degree of reflex sympathetic stimulation, which accompanies vasodilator therapy when given to younger patients without adrenergic inhibition.

Dosage. Of younger patients with mild to moderate hypertension, 50 to 70 percent respond to "average" doses of beta-blockers,[12,13,14] but the optimal dose is hard to predict in the individual patient. It is best to start with a low dose to lessen the chances of initial fatigue, which is probably due to the fall in cardiac output. All patients should be closely observed in the early stages of treatment, both to assess side-effects and to gain the patient's confidence (thereby encouraging compliance). Though early uncontrolled observations suggested enhanced effects from higher doses, in careful dose-response studies with propranolol, little if any additional antihypertensive effect has been seen with doses above 80 mg/day, given either once or twice per day.[15,16,17] If the response to ordinary doses of beta-blocker is inadequate, the preferred action, therefore, is to add a diuretic and/or a vasodilator. Dose adjustment is more likely to be required with more lipid-soluble agents, which have a high "first-pass" liver metabolism that may result in active metabolites with properties different from those of the parent compound (4-hydroxypropranolol, acetyl metabolite of acebutolol); the rate of formation will depend on liver blood flow and function. Lipid-insoluble agents without hepatic metabolism include atenolol, sotalol, and nadolol (Fig. 1-5).

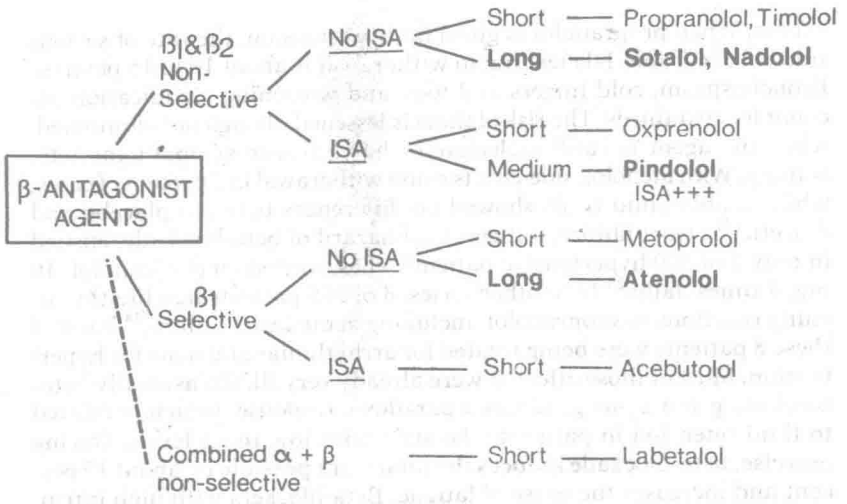

Fig. 1-5. Classification of some common beta-blocking agents. Heavy type represents long-acting agents. Intrinsic sympathomimetic activity is ISA; such beta-blocking agents not only inhibit beta-adrenergic activity but also have limited sympathomimetic activity. [Modified from Opie LH: Drugs and the Heart. I. Beta-blocking agents. Lancet, 1980, 1:693–698, by permission of The Lancet.]

Hepatic metabolism of metoprolol and other lipid-soluble beta-blockers varies with genetic polymorphism.[18]

Theoretically, the ideal beta-blocker for hypertension would be longacting, cardioselective, and usually effective in a standard dose; it would also have simple pharmacokinetics (no liver metabolism, little protein binding, no lipid solubility, and no active metabolites). Atenolol goes a long was to fulfilling these requirements, although lacking intrinsic sympathomimetic activity. In comparative studies, atenolol appears to provide some additional antihypertensive potency beyond that of other beta-blockers.[14,19,20] But in truth, there is so little to choose from between the various beta-blocking agents that many experts advise using "the drug you know," only changing if side-effects are expected or become troublesome.

Side-effects. In the ongoing, massive Medical Research Council trial, about 15 percent of patients given therapy with either thiazide diuretic (bendrofluazide, 5 mg twice a day), or propranolol (up to 320 mg/day) withdrew from treatment because of suspected adverse reactions in 5 years, compared to 5 percent of those on placebo.

Side-effects are probably more common with the noncardioselective

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