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THE POSITION OF BOPINDOLOL

A NEW β-BLOCKER

EDITED BY

P. A. VAN ZWIETEN

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Preface

The management of essential hypertension with β-adrenoceptor blocking drugs has been widely applied and in the majority of cases satisfactory control without unacceptable side-effects is achieved. The number of compounds continues to increase, although at a slower pace than previously. β_1-Selectivity, intrinsic sympathomimetic activity (ISA) and duration of action are the most relevant ancillary properties of individual β-blockers. β-Blockers with several combinations of these ancillary properties have become available over the years. In the treatment of hypertension a once daily dosage of drug is recognized more and more as a useful property which improves compliance. For this reason the tendency to develop long-acting β-blockers, as antihypertensives and also in the long-term treatment of angina pectoris, is understandable. Bopindolol is an example of a potent and unusually long-acting β-adrenoceptor blocking agent. These properties of the new compound are not only interesting for theoretical reasons, but also potentially useful to the drug's application as an antihypertensive.

On 23 May, 1986, a Round Table Conference by experts in the field was devoted to the profile of bopindolol compared with that of established β-blockers. The most important aspects of the field were covered, included both fundamental and clinical aspects.

A fairly complete and up to date survey has been obtained, as can be seen from this publication. It is my pleasure as a chairman of the conference and as editor of the publication to acknowledge the gratitude of the participants to Sandoz-Nederland (Uden). The company provided generous hospitality, leaving the scientific responsibility, however, entirely to the chairman and speakers.

P. A. van Zwieten

Contents

Different properties of β-adrenoceptor blockers: characteristics of bopindolol

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Summary

A survey is given of the principle of β-adrenoceptor blockade and its sequelae. β_1-Adrenoceptor selectivity, intrinsic sympathomimetic activity (ISA) and membrane stabilization are ancillary properties of certain β-blockers. The basic aspects and relevance of these properties are explained. Furthermore, a survey is given of the most important therapeutic applications of β-adrenoceptor blockers, as well as the backgrounds of their side-effects, contraindications and interactions with other drugs. Finally, a brief characterization is given of the newly introduced β-adrenoceptor blocking agent bopindolol.

Introduction

In the adrenergic nervous system, noradrenaline is the dominant neurotransmitter, whereas adrenaline is, at least quantitatively, of lesser importance. The adrenoceptors in this system are divided into the α and β subtypes, according to the receptor demand of these receptor subtypes. α-Adrenoceptor subtypes are present at both pre- and postsynaptic locations. At presynaptic sites mainly α_2-adrenoceptors are found; postsynaptic α-adrenoceptors are known to comprise both α_1- and α_2-adrenoceptor subtypes. It should be emphasized that the terms α_1 and α_2 refer to the receptor demand, whereas the expressions pre- and postsynaptic reflect the position with respect to the synapse. Postsynaptic α_1- and α_2-adrenoceptors both induce vasoconstriction when stimulated by their respective agonists (1).

β-Adrenoceptors are also subdivided into pre- and postsynaptic subtypes. The excitation of presynaptic (prejunctional) β-adrenoceptors facilitates the release of endogenous noradrenaline, whereas their blockade inhibits the mobilization of

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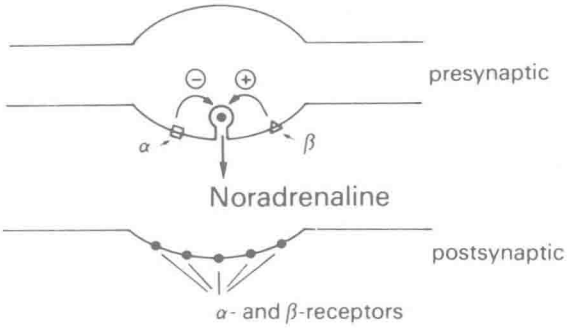

Figure 1. α- and β-Adrenoceptors at pre- and postsynaptic sites. The stimulation of presynaptic α-adrenoceptors inhibits the release of noradrenaline from the varicosity where it is stored. However, stimulation of presynaptic β-receptors enhances the release of the neurotransmitter from the nerve ending. Conversely, the blockade of presynaptic β-receptors diminishes the release of noradrenaline. Once noradrenaline has been released, it travels through the synaptic cleft and reaches both α- and β-adrenoceptors at postsynaptic sites, thus causing physiological effects such as vasoconstriction or tachycardia.

endogenous noradrenaline (Fig. 1). β-Adrenoceptors are located, for instance, in the heart, the bronchi, and the gut, whereas various biochemical processes like the liberation of glucose from glycogen are also known to be mediated by β-receptors. At present, β-receptors are divided into β_1 and β_2 subtypes (2,3). The postsynaptic β_1-adrenoceptors are involved mainly in the regulation of cardiac function. Their stimulation causes an increase in cardiac frequency and contractility. Excitation of β_2-adrenoceptors by the appropriate agonists induces bronchodilatation, vasodilatation, and hyperglycaemia. The classic β-adrenoceptor agonists, such as, for instance, isoprenaline and orciprenaline, are non-selective; i.e., they stimulate β_1- and β_2-adrenoceptors equally well. Presynaptic β-adrenoceptors mainly belong to the β_2-subtype.

Selective β_2-adrenoceptor stimulants such as terbutaline and salbutamol influence predominantly the bronchi without causing excessive tachycardia. For this reason they are preferred as bronchospasmolytic agents over the non-selective $\beta_1 + \beta_2$-adrenoceptor agonists (isoprenaline, orciprenaline), which are known to provoke substantial complaints of tachycardia and palpitations.

More recently, dobutamine has been introduced as a rather selective β_1- adrenoceptor agonist, but it also possesses significant α_1-agonistic potency (4).

β-Sympatholytic drugs, β-adrenoceptor blocking agents

The β-adrenoceptor blocking agents possess substantial affinity for the receptors, so that the receptors are blocked and thus become inaccessible to agonists such as the endogenous neurotransmitters or the aforementioned synthetic β-sympathomimetic receptor agonists. The β-receptor agonists combine with the receptor, so that the drug-receptor complex is formed, without giving rise to receptor activation as observed for an agonistic compound (2).

The inaccessibility of the receptor for endogenous catecholamines (noradrenaline, adrenaline) considerably diminishes or even abolishes the influence of the sympathetic nervous system on various organs, although the sympathetic fibres are entirely intact.

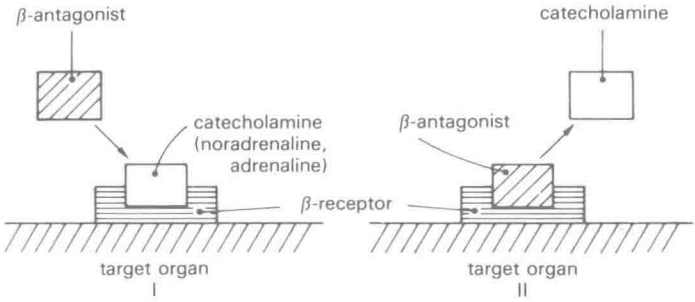

Figure 2. Principle of competitive antagonism at the level of β-adrenoceptors. An endogenous catecholamine (noradrenaline, adrenaline) combines with the receptor and causes a stimulus, leading to a physiological or pharmacological effect (e.g. tachycardia). A β-adrenoceptor blocking agent combines with the receptor without causing a stimulus. However, the receptor is blocked and therefore no longer accessible to endogenous catecholamines or external synthetic β-adrenoceptor agonists.

Competition exists between the neurotransmitter and the β-blocking agent for the β-adrenoceptor, thus justifying the application of the term competitive antagonism for the given situation (Fig. 2).

Various properties of β-adrenoceptor blocking agents

All therapeutically applied β-adrenoceptor blocking agents are known to block β_1-adrenoceptors. Most therapeutic effects, but not all, are based on β_1-adrenoceptor blockade (see below). Various β-blockers are known to substantially block β_2-adrenoceptors as well. This is particularly the case for the so-called non-selective β-blockers. In most cases the β_2-adrenoceptor blockade causes side-effects. Only in a few cases, i.e., in the treatment of glaucoma and in certain forms of tremor, is β_2-blockade known to be the basis of the therapeutic effect. Bronchoconstriction and vasoconstriction are known to be induced by β_2-receptor blockade (2).

Apart from the blocking activity of β-sympatholytic agents, various compounds in this series possess other properties, such as membrane-stabilizing (local anaesthetic) potency and/or intrinsic sympathomimetic activity (ISA). These properties shall be dealt with separately below, together with the so-called cardioselectivity of β-adrenoceptor blocking agents, which is based on the preferential antagonistic activity of certain β-blockers for β_1-adrenoceptors.

Cardioselectivity of β-blockers

Since in the cardiovascular field all therapeutic effects of β-blockers are based on β_1-receptor blockade, whereas in most cases the blockade of β_2-receptors causes unpleasant and sometimes dangerous side-effects, a great effort has been invested in the development of β-receptor blocking drugs with a preferential affinity toward β_1-receptors. Some compounds with such a preferential affinity have indeed been developed. So far, however, the selectivity of this type of drug has remained limited. Even when the expression β_1-receptor selectivity might be acceptable, the term cardioselectivity is certainly not justified for the compounds available at present (5).

In spite of a preferential affinity for β_1-adrenoceptors, the β-sympatholytic compounds classified as cardioselective still display so much affinity for β_2-adrenoceptors that they are certainly not safe in patients suffering from obstructive airways diseases like bronchial asthma. Moreover, the bronchi have been demonstrated to contain a limited density of β_1-adrenoceptors. It should be recognized, however, that the severity of the impairment of ventilation is certainly less than that observed for non-selective $\beta_1 + \beta_2$-adrenoceptor blocking agents (5,6).

The expression cardioselective has been widely used; it would be preferable to classify the drugs involved as β_1-receptor selective. Well-known examples of rather selective β_1-adrenoceptor blocking agents (at least in low doses) are atenolol, metoprolol, practolol (virtually no more applied), and to a lesser degree acebutolol (see Table 1).

Table 1

Various β-adrenoceptor blocking agents and their differentiation with respect to membrane stabilization, β_1-selectivity, and intrinsic sympathomimetic activity (ISA).

Drug	β_1-selectivity	Membrane stabilization	ISA
Acebutolol	$\beta_1 > \beta_2$	−	+
Alprenolol	$\beta_1 + \beta_2$	±	+
Atenolol	$\beta_1 >> \beta_2$	−	−
Betaxolol	$\beta_1 >> \beta_2$	±	−
Bopindolol	$\beta_1 + \beta_2$	−	+
Metoprolol	$\beta_1 >> \beta_2$	−	−
Metipranolol	$\beta_1 + \beta_2$	−	−
Oxprenolol	$\beta_1 + \beta_2$	±	+ +
Penbutolol	$\beta_1 + \beta_2$	±	+
Pindolol	$\beta_1 + \beta_2$	−	+ + +
Practolol	$\beta_1 >> \beta_2$	−	+ +
Propranolol	$\beta_1 + \beta_2$	+	−
Sotalol	$\beta_1 + \beta_2$	−	−
Timolol	$\beta_1 + \beta_2$	−	−

$\beta_1 + \beta_2$: non-selective compound; $\beta_1 >> \beta_2$ β_1 selectivity.

Membrane stabilization (local anaesthetic activity)

Various β-adrenoceptor blocking agents are known to influence the cell membrane in an unspecific manner, besides the more or less specific blocking activity of the β-adrenoceptors. The direct effect on the cell membrane, classified as membrane-stabilizing, local anaesthetic, or quinidine-like activity, is known to reduce the membrane permeability for various ions, such as sodium, potassium, and calcium. These effects are unrelated to β-adrenoceptor blockade (7). Membrane stabilization as discussed above is very similar to local anaesthetic activity. As such it causes bradycardia and reduction of contractility and of the rate of atrioventricular (AV) conduction. Accordingly, the cardiac output is also reduced (8).

Membrane stabilization does not influence, in either the positive or negative sense, the therapeutic efficacy of β-receptor blockade. The drugs involved do not display substantial membrane-stabilizing activity. It has been argued that the membrane-stabilizing activity of β-blockers contributes to the antiarrhythmic potency of these drugs but this argument seems questionable (8).

Concerning the classical β-blocker propranolol it seems of interest to mention that both optical (stereo-)isomers of this compound display substantial and comparable membrane-stabilizing activity, whereas the β-adrenoceptor blocking potency remains limited to one of the two isomers, the other being devoid of such activity (2). Propranolol, alprenolol, and oxprenolol are well-known examples of β-blocking agents that possess membrane-stabilizing potency (see Table 1).

ISA

β-Adrenoceptor blocking agents will cause the formation of a drug-receptor complex with β-adrenoceptors; accordingly, all β-blockers are bound to possess affinity toward the β-receptor. Certain drugs, for instance, pindolol, oxprenolol, and alprenolol, not only display affinity toward the receptor, but also possess a mild degree of agonistic potency. Accordingly, the receptor is blocked and inaccessible to endogenous catecholamines (noradrenaline, adrenaline), whereas the β-blocker in question mildly stimulates the β-adrenoceptor. In molecular pharmacology, this phenomenon is characterized as partial agonism.

The various backgrounds of ISA have been dealt with in full detail by Ariëns (9). In Table 1 the various properties of currently available β-adrenoceptor blocking agents have been enumerated.

Therapeutic applications of β-adrenoceptor blocking agents

Cardiovascular disease

β-Adrenoceptor blocking agents have gained an important position as drugs of choice in the treatment of hypertension and angina pectoris. The treatment of tachyarrhythmia with β-blockers is a more refined and less generally applied application of these drugs. The antihypertensive potency of β-blockers has not as yet been satisfactorily explained. The following mechanisms have been put forward as a possible basis of the antihypertensive potency of β-blocking agents: reduction of cardiac output; a central mechanism; reduction of plasma renin activity; and blockade of presynaptic β_2-adrenoceptors (8,10). None of these mechanisms has proved to be satisfactory as an explanation of the antihypertensive effect of β-blocking agents. Neither is it possible to dismiss with certainty one or more of these mechanisms as being wholly incorrect. The antihypertensive effect of β-adrenoceptor blocking agents is based on the blockade of β_1-adrenoceptors. Cardioselectivity and membrane stabilization are of no consequence whatsoever with respect to the antihypertensive effect as such. Intrinsic sympathomimetic activity does not lead to a stronger or weaker antihypertensive effect. However, the haemodynamic profile of a β-blocker with ISA is different from that of a drug devoid of this property (11,12).

In the chronic treatment of classic exercise-induced angina pectoris with β-blocking agents, the reduced or abolished influence of endogenous catecholamines on the heart gives rise to a diminishment of myocardial oxygen consumption, thus improving the ratio of oxygen supply to demand, which is known to be disturbed in this disorder (13). In particular the reduction in cardiac frequency reduces oxygen consumption. β-Blockers are unsuitable for the interruption of an acute attack of angina, which

should preferentially be treated with nitroglycerin or isosorbine dinitrate. Prinzmetal angina, which is assumed to be due to coronary spasm, is, as a rule, unfavourably influenced by β-adrenoceptor blocking agents. This rare type of angina should preferentially be treated with a calcium entry blocker, such as nifedipine (14).

The therapeutic effect of β-blockers in angina is probably based on β_1-adrenoceptor blockade only. Theoretically, all β-blockers developed so far would be useful as antianginal drugs, but not all of them have been studied systematically in this connection. No studies exist that would indicate that properties like β_1 selectivity, membrane stabilization, or ISA would be of particular benefit or disadvantage to the antianginal effect as such (13,15).

The antiarrhythmic effect of β-blockers in the usual doses is due only to their β-adrenoceptor blocking activity, because membrane stabilization occurs only at much higher doses. This indicates that β-adrenoceptor blocking agents can be applied in those conditions where enhanced sympathetic activity facilitates the occurrence of dysrhythmia, like anxiety, physical stress, general anaesthesia, and myocardial ischaemia. The rate of firing of the sinus node and also that of other cells in the heart showing spontaneous discharges is reduced by β-blockers. Therefore, atrial and ventricular dysrhythmias caused by abnormal automaticity can be treated with β-blockers. The increase in AV conduction time and the enhanced refractory period of the AV node by β-blockers explain the efficacy of these drugs in arrhythmias in which the AV node plays an important part (16).

So far, there are no indications that relevant differences exist between the various β-adrenoceptor blocking agents with respect to the treatment of cardiac arrhythmia. Obviously, properties like β_1-selectivity, membrane stabilization, and ISA are not of major importance for the antiarrhythmic activity of the β-adrenoceptor blockers.

More recently, β-blockers have proved to be of value in secondary prevention after myocardial infarction, with the aim to reduce the incidence of death and reinfarction. This protective effect has been demonstrated for timolol, metoprolol, propranolol, and sotalol (17–20). The only property common to these compounds is their ability to block β_1-adrenoceptors. As yet, no arguments have been introduced for the view that properties like β-selectivity and membrane stabilization are relevant for the cardioprotective effect.

For the sake of completeness, it should be mentioned that β-blockers may be of potential use in the following cardiovascular disorders: impending myocardial infarction; acute myocardial infarction, with the aim to reduce the size of the infarction; dissecting aortic aneurysm (maintenance therapy with a β-blocker after rapid lowering of blood pressure); asymmetric septum hypertrophy, through reduction of the gradient between the left ventricle and aorta, accompanied by a favourable influence on the induction of ventricular arrhythmia; and Fallot's tetralogy, owing to a reduction of spasm in the outflow tract of the right ventricle during a cyanotic spell. The detailed positions of the β-blockers in these conditions remain to be established. Moreover, no information exists with respect to a possible preference of particular properties of the β-blockers (selectivity, ISA) in these cardiological disorders.

Neurology and psychiatry

β-Adrenoceptor blocking drugs may be of use in the following situations (15): chronic migraine; anxiety combined with tachycardia; and certain forms of tremor. The treatment of migraine with β-blockers is empirical. So far, there is only a reasonable

degree of experience with propranolol. A β_2-effect appears to be involved. In the treatment of anxiety with a β-blocker, it seems likely, although not proven, that the inhibition of tachycardia by a peripheral effect disrupts a vicious cycle, thus diminishing the facilitative influence of palpitations on anxiety. However, a direct central effect of the β-blockers is difficult to rule out entirely. The antianxiety effect of the β-blockers is the basis of their application as a kind of doping in certain sports (target shooting, motor car racing). A systematic study of different β-blockers in these conditions has not yet been carried out (15).

The antitremor effect of β-blockers is due to the blockade of β_2-adrenoceptors located on skeletal muscle. The β_1-effect is probably not relevant to the antitremor effect. For this purpose, more or less selective β_2-adrenoceptor blocking agents are being developed at present by the pharmaceutical industry. ICI 118,551 (21) is an example of such a compound.

Ophthalmology

Treatment of glaucoma simplex can be carried out with local application of timolol or other β-blocking drugs, provided that they are not local anaesthetic agents (15). The topical application of local anaesthetic agents to the eye, particularly for a prolonged period, inhibits the corneal reflex and hence may lead to irritation and infection. The lowering of ocular pressure by a β-adrenoceptor blocker is probably a β_2-effect (22). The blockade of β_2-adrenoceptors inhibits the production of ocular fluid, without greatly affecting its outflow. Timolol is the most important β-blocker so far marketed as eye drops for the treatment of glaucoma, but recently metipranolol has been introduced for the same purpose.

Endocrine disorders

β-Blockers can be of use in the non-surgical treatment of hyperthyroidism, particularly with respect to the treatment of cardiac arrhythmia in this condition, which is based on enhanced cardiac sensitivity for catecholamines. Also, in a thyrotoxic crisis (storm), β-adrenoceptor blocking drugs display beneficial effects. The interference of these drugs with the conversion of thyroxine into tri-iodothyronine has been discussed as a potential beneficial effect of β-adrenoceptor blocking agents in this condition (15). As a rule, the non-selective blocker propranolol is used for this purpose. The roles of β_1 selectivity, membrane stabilization, and ISA in this connection have not been studied systematically.

Side effects and contraindications; interactions with other drugs

Side-effects

Most of the side-effects of β-adrenoceptor blockers are due to the blockade of β_1- and/or β_2-adrenoceptors. Well-known side effects caused by the blockade of β-adrenoceptors include (7,8): obstructive airways disease (β_2); untreated congestive

heart failure (β_1); impaired AV conduction with bradycardia (β_1): reduced rate of sinus node firing with bradycardia (β_1); and hypoglycaemia ($\beta_2 > \beta_1$). The well-known complaint of cold extremities is due to vasoconstriction secondary to the blockade of vascular β_2-adrenoceptors, thus allowing unimpaired vasoconstriction induced by the stimulation of vascular α-adrenoceptors. The aforementioned indications concerning the receptor type involved would suggest that all typical cardiac side-effects (congestive heart failure, bradycardia, impaired AV conduction) are bound to occur for all β-blockers, irrespective of any β_1-selective potency or not. ISA might be of theoretical advantage with respect to the development of congestive heart failure and bradycardia, but in practice this advantage is marginal and probably not clinically relevant. It should be expected that β_1 selectivity would cause less obvious hypoglycaemia and less intense peripheral vasoconstriction. Indeed, it has been observed in clinical practice that these two types of side-effects are less severe for β_1-selective drugs than for the non-selective $\beta_1 + \beta_2$-receptor blocking agents. The influence of β-adrenoreceptor blocking agents with various properties on plasma glucose and lipids was discussed in some detail by Van Brummelen (23).

Similarly, it should be anticipated that β_1-selective drugs cause less severe bronchoconstriction than the non-selective drugs. This may be true in animal models and in hypertensive patients with a healthy airways system. However, in patients suffering from obstructive airways disease, the β_1-selective drugs can also cause bronchoconstriction and impaired ventilation, possibly because the selectivity of the so-called cardioselective drugs developed until now is limited, with some β_2-effect still being present. Moreover, bronchoconstriction may, to some degree, also be mediated by β_1-adrenoceptors and not exclusively by β_2-receptors (24). On the other hand, it was discussed recently by Van Herwaarden (24) that β-blockers with ISA cause somewhat less intense impairment of ventilation than do drugs devoid of this property.

The aforementioned side-effects, based on β_1- and/or β_2-receptor blockade, may also be observed with topical application of β-blockers to the eye in the treatment of glaucoma. In particular, bradycardia and bronchoconstriction should be anticipated. Hallucinations and vivid dreams have been observed as central nervous side-effects. An unspecific feeling of fatigue and reduced capability to exercise are more common side-effects that are at least partly based on central nervous mechanisms. These side-effects often become particularly noticeable to the patient when the treatment with the β-blocker is interrupted.

It remains unclear whether these central nervous system side-effects are related to either β_1- or β_2-receptor blockade or both. One would expect an obvious relationship with the ability of the drugs to penetrate the brain. However, in practice, the hydrophilic β-blockers, which less readily penetrate, also cause these central nervous system side-effects. Apart from the more or less specific side-effects discussed above, β-blockers can also cause less well-defined adverse reactions, like gastrointestinal discomfort and allergic reactions, which are probably not specifically related to β-receptor blockade. Allergic reactions are particularly observed around the eye when the drug is applied topically in the treatment of glaucoma. The deleterious oculo-mucocutaneous syndrome observed for practolol has not so far been reported for other β-blockers. This syndrome is unrelated to β-adrenoceptor blockade.

Contraindications

Obstructive airways disease is an obvious contraindication for β-adrenoceptor blockers. The β_1-selective drugs and those possessing ISA are probably less

dangerous but certainly not safe in these conditions. For details see Van Herwaarden (24).

Uncompensated congestive heart failure, bradycardia, and impaired AV conduction are also contraindications for β-adrenoceptor blockers. The problems are caused by β_1-adrenoceptor blockade. Accordingly, these contraindications hold for all β-blockers so far developed, properties like selectivity, ISA, and membrane stabilization being irrelevant. β-Blockers should be used reluctantly in patients with peripheral vascular disease leading to ischaemia, both in atherosclerotic disorders and in particular in conditions with a vasospastic component, such as Raynaud's phenomenon. The β_1-selective compounds are preferable in such a situation, since they cause less peripheral vasoconstriction than the non-selective drugs that also block β_2-adrenoceptors (7).

Interactions with other drugs

β-Blockers can be combined with various types of other drugs, usually without causing relevant interactions. However, problems may arise when β-adrenoceptor blocking agents are applied simultaneously with insulin and oral antidiabetics and calcium entry blockers.

β-Adrenoceptor blocking agents will enhance the hypoglycaemic effect induced by insulin and oral antidiabetics. The hypoglycaemia caused by β-blockers is mediated by a β_2-effect. For this reason it seems preferable that a diabetic patient, who is being treated with insulin or an oral antidiabetic agent and who requires a β-adrenoceptor blocker, receives a β_1-selective agent like atenolol or metoprolol instead of a non-selective agent that simultaneously blocks β_1-adrenoceptors. Other characteristics such as membrane stabilization and ISA are probably not relevant in this respect.

Calcium entry blockers of the verapamil type and β-adrenoceptor blocking agents both depress cardiac frequency, AV conduction, and contractility, although via different mechanisms. From a theoretical point of view, it would therefore seem unwise to combine both groups of drugs. However, an absolute contraindication for the combination of a β-blocker and a calcium entry blocker does not necessarily exist. Nifedipine and β-adrenoceptor blocking agents are frequently combined in the treatment of angina, and in the majority of patients this combination is effective and not problematic, although enhanced congestive heart failure caused by such a combination has been reported in a few cases (25).

Caution should be maintained, however, when verapamil and a β-blocker are applied simultaneously. In contrast to nifedipine, verapamil also has a depressant effect on cardiac contractility, heart rate and AV conduction. As such, there is an additive action in combination with a β-adrenoceptor blocking agent. The interaction between both drugs is probably most relevant when a patient who is regularly treated with an orally administered β-blocker is to receive an intravenous dose of verapamil. Combined oral treatment with both drugs in moderate doses does not, however, pose particular problems and even appears to be greatly beneficial in exercise-induced angina.

Finally, with respect to the combination of β-adrenoceptor blocking agents and other drugs, it should be mentioned that the withdrawal symptoms observed after abrupt cessation of treatment with clonidine are significantly enhanced by a β-adrenoceptor blocking agent. This interaction, which is rare, reflects the unopposed α-receptor stimulation brought about by the clonidine withdrawal phenomenon.