SUMMARY Adverse effects of β-adrenergic receptor blocking drugs can be divided into two categories: 1) those that result from known pharmacological consequences of β-adrenergic receptor blockade; and 2) other reactions that do not appear to result from β-adrenergic receptor blockade. Adverse effects of the first type include bronchospasm, heart failure, prolonged hypoglycemia, bradycardia, heart block, intermittent claudication, and Raynaud’s phenomenon. Neurological reactions include depression, fatigue, and nightmares. It is not yet proven whether the β₁-selective adrenergic blockers or those with partial agonist activity reduce the overall frequency of adverse reactions seen with propranolol. Patient age does not appear, in itself, to be associated with more β-blocker side effects. Side effects of the second category are rare. They include an unusual oculomucocutaneous reaction and the possibility of oncogenesis. There are also many drugs that interact with β-blockers, which may increase toxicity. Finally, there are specific patient characteristics where one β-blocker may be more effective and safer than another.

(Hypertension 11 [Suppl II]: II-21-II-29, 1988)

KEY WORDS • β-adrenergic receptor blockers • adverse effects • β-blocker toxicity

Adverse Effects of β-Blockers

Comparing and tabulating adverse effects from different studies of β-adrenergic blockers is particularly difficult because of a number of factors. These include the use of different definitions of side effects, the kinds of patients studied, and study design features. Methods of ascertainment and reporting adverse side effects also differ from study to study. Given these problems, the types and frequencies of adverse effects attributed to various β-blocker compounds appear similar. The side effect profiles of β-blockers are also remarkably close to those seen with concurrent placebo treatments, attesting to the remarkable safety margin of the β-blockers as a group.

The adverse effects of β-adrenergic receptor blockers can be divided into two categories: 1) those from known pharmacological consequences of β-adrenergic receptor blockade; and 2) other reactions that do not appear to result from β-adrenergic receptor blockade. Side effects of the first type are widespread because of the ubiquitous nature of the sympathetic nervous system in the control of physiological and metabolic function. They include asthma, heart failure, hypoglycemia, bradycardia, heart block, intermittent claudication, and Raynaud’s phenomenon. The incidence of these adverse effects varies with the β-blocker used. Side effects of the second category are rare. They include an unusual oculomucocutaneous reaction and the possibility of carcinogenesis.

Major Clinical Experiences

There have been extensive clinical studies designed to identify the nature and frequency of side effects with β-blocking agents. The Boston Collaborative Drug Surveillance Program studied the effects of propranolol (nonselective, no partial agonism) in 800 hospitalized patients and of practolol (β₁-selective with partial agonism) in 199 patients. Forrest reported on the adverse reaction seen with oxprenolol (nonselective with partial agonism) in 4400 patients receiving the drug for angina pectoris. Zacharias et al. reported on the side effects seen with long-term atenolol (β₁-selective, long-acting) treatment in patients with hypertension. The side effect profiles for pindolol (nonselective with partial agonism) and labetalol (nonselective, α-blocker) have also been assessed in extensive clinical trials in hypertensive patients. The long-term β-blocker trials in thousands of myocardial infarct survivors have reported on the adverse reactions with different β-blocking compounds used in this clinical situation.

In the Boston Collaborative Surveillance Program,
The frequency of side effects was independent of the dose used. Adverse reactions were seen more commonly among older patients.4

In patients with hypertension, the frequency of adverse reactions with atenolol were reported to be approximately 15% in a 4-year follow-up study.5 In an extensive literature survey in 15,753 patients receiving pindolol, a similar incidence of side effects was seen.16

The frequency of side effects reported in labetalol-atenolol and pindolol.10 extensive literature survey in 15,753 patients receiving

TABLE 1. Adverse Reactions to Propranolol Among 800
Hospitalized Medical Patients*

<table>
<thead>
<tr>
<th>Nature of reaction</th>
<th>Patients (n)</th>
<th>Adverse reactions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>5</td>
<td>0.6</td>
</tr>
<tr>
<td>Bradycardia and angina</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Subtotal</td>
<td>10</td>
<td>1.3</td>
</tr>
<tr>
<td>Non-life threatening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>17</td>
<td>2.1</td>
</tr>
<tr>
<td>Hypotension</td>
<td>16</td>
<td>2.0</td>
</tr>
<tr>
<td>Congestive heart failure or fluid retention</td>
<td>9</td>
<td>1.1</td>
</tr>
<tr>
<td>Gastrointestinal disturbances</td>
<td>9</td>
<td>1.1</td>
</tr>
<tr>
<td>CNS disturbances (headache, dizziness, fatigue, tinnitus, blurring of vision, paresthesias, depression)</td>
<td>9</td>
<td>1.1</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>Sensitivity reactions (rash, fever)</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>2:1 heart block</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Elevation in serum phenytoin level</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Subtotal</td>
<td>69</td>
<td>8.6</td>
</tr>
<tr>
<td>Total with adverse reactions</td>
<td>79</td>
<td>9.9</td>
</tr>
</tbody>
</table>

*With bradycardia in 3 cases and congestive heart failure in 1; with syncope in 5 cases.

Modified from Greenblatt and Koch-Weser4 with permission.

Labetalol was used for mixed clinical indications, and adverse reactions were reported in 79 patients (9.9%). These are summarized in Table 1. Ten adverse reactions were considered life threatening, and all appeared to result from impaired cardiac function. Of the 69 other reactions, 43 also involved interference with cardiac performance but were not deemed life threatening. The frequency of side effects was independent of the dose used. Adverse reactions were seen more commonly among older patients.4

In patients with hypertension, the frequency of adverse reactions with atenolol were reported to be approximately 15% in a 4-year follow-up study.6 In an extensive literature survey in 15,753 patients receiving pindolol, a similar incidence of side effects was seen.16

The frequency of side effects reported in labetalol-treated patients was similar to those described with atenolol and pindolol.10

Forrest7 reported a 13.7% incidence of side effects with oxprenolol in patients with angina pectoris. In 12 placebo-controlled long-term studies of patients surviving acute myocardial infarction, the incidence of side effects ranged from 7 to 20%.3,11-15 The overall incidence of severe side effects was not much different from that seen with placebo treatment (Table 2).3 The reason for discontinuing treatment because of side effects in the largest of these trials (β-Blocker Heart Attack Trial [BHAT]; β-Blocker Post-Infarction Trial) are shown in Table 3.

In the long-term postinfarction studies using propranolol (BHAT) and timolol, analyses were performed to assess the side effect profiles of β-blockers and placebo therapy in patients with regard to age.11-19 In these trials, all patients that were entered were believed to be good candidates for β-blocker therapy without contraindications to their use. In the BHAT, the percentages of patients with complaints were not significantly different in patients under 60 years of age from patients over 60 years of age.17 When assessing reasons for treatment discontinuation, the incidence of congestive heart failure was greater in the older age group; however, other adverse reactions were similar in older and younger patients.15 In the Norwegian timolol study,18 similar observations were made in patients under 65 years of age and in patients 65 or older. Overall, it would appear that the nature and frequency of side effects seen with β-blocker use in the elderly are similar to those seen with β-blocker use in younger patients.

Adverse Cardiac Effects Related to β-Adrenergic Receptor Blockade

Myocardial Infarction

There are several circumstances in which blockade of β-receptors may cause congestive heart failure: 1) in an enlarged heart with impaired myocardial function, where excessive sympathetic drive is essential to maintain the myocardium on a compensated Starling curve; and 2) when the left ventricular stroke volume is restricted and tachycardia is needed to maintain cardiac output. Considering the factors noted above, any β-blocking drug may be associated with the development of heart failure. Furthermore, it is possible that an important component of heart failure may be accounted for by increases in peripheral vascular resistance produced by nonselective agents (e.g., propranolol, timolol, and sotalol).20 It has been claimed that β-blockers with intrinsic sympathomimetic activity are better in preserving left ventricular function and less likely to pre-

TABLE 2. Percentage of Patients Who Stopped Taking Study β-Blockers in Various Long-Term Placebo-Controlled, Postinfarction Trials

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Practolol11</th>
<th>Timolol12</th>
<th>Metoprolol13</th>
<th>Propranolol1</th>
<th>Sotalol14</th>
<th>Oxprenolol15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>4.1/3.6*</td>
<td>2.9/2.1</td>
<td>0.6/1.0</td>
<td>4.0/3.5</td>
<td>2.6/3.8</td>
<td>1.8/1.2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0.6/0.1</td>
<td>2.8/1.2</td>
<td>4.2/1.9</td>
<td>1.2/0.3</td>
<td>2.1/0.7</td>
<td>0.3/0.2</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.5/0.1</td>
<td>3.9/0.2</td>
<td>2.6/0.7</td>
<td>0.7/0.3</td>
<td>4.4/0</td>
<td>NA</td>
</tr>
<tr>
<td>Depression</td>
<td>0.2/0.3</td>
<td>NA</td>
<td>0/0</td>
<td>0.4/0.4</td>
<td>0/0</td>
<td>1.8/0.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.3/0.1</td>
<td>0.4/0.1</td>
<td>0/0</td>
<td>1.5/1.0</td>
<td>0.9/0.7</td>
<td>0.5/0.7</td>
</tr>
<tr>
<td>Pulmonary problems</td>
<td>NA</td>
<td>1/1.0</td>
<td>0/0</td>
<td>0.9/0.7</td>
<td>0.5/0.2</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Treatment group/placebo group. NA = not available.

Modified from Friedman1 with permission.
like pindolol or oxprenolol, which have intrinsic sympathectomy. Compounds with intrinsic sympathomimetic activity are responsible for the increased sensitivity to isoproterenol after pindolol is administered. This increased sensitivity is due to a positive inotropic effect. The clinical significance of this effect in the intact organism is uncertain.

In patients with impaired myocardial function who require β-blocking drugs, digitalis and diuretics can precipitate heart failure, but there have been limited in vivo studies in humans to support this contention. In dog-transplanted, denervated heart preparations, β-blockers with intrinsic sympathomimetic activity have a positive rather than negative inotropic effect. The clinical significance of this effect in the intact organism is uncertain.

In patients with impaired myocardial function who require β-blocking agents, digitalis and diuretics can be used, preferably with drugs having intrinsic sympathomimetic activity or α-adrenergic blocking properties.

### Sinus Node Dysfunction and Atrioventricular Conduction Delay

Slowing of the resting heart rate is a normal response to treatment with β-blocking drugs with and without intrinsic sympathomimetic activity. Healthy individuals can sustain a heart rate of 40 to 50 without disability, unless there is clinical evidence of heart failure. Drugs with intrinsic sympathomimetic activity do not lower the resting heart rate to the same degree as propranolol; however, all β-blocking drugs are contraindicated (unless an artificial pacemaker is present) in patients with the "sick sinus syndrome." If there is a partial or complete atrioventricular conduction defect, use of a β-blocking drug may lead to a serious bradyarrhythmia. The risk of atrioventricular impairment is not the same with all β-blockers. Giudicelli and Lhoste showed that in dogs, β-blockade and not membrane stabilizing activity is responsible for atrioventricular conduction impairment. Compounds like pindolol or oxprenolol, which have intrinsic sympathomimetic activity in dosages producing β-blockade, do not impair atrioventricular conduction to the same extent as propranolol. The clinical significance of this electrophysiological difference among β-blockers in patients with atrioventricular conduction disease has not been determined.

#### β-Adrenergic Receptor Blocker Withdrawal

Following abrupt cessation of chronic β-blocker therapy, exacerbation of angina pectoris and, in some cases, acute myocardial infarction and death have been reported. Multiple double-blind randomized trials have confirmed the reality of a propranolol withdrawal reaction. The exact mechanism for the propranolol withdrawal reaction is unclear. There is some evidence that the withdrawal phenomenon may be due to the generation of additional β-adrenergic receptors during the period of β-adrenergic receptor blockade. When the β-adrenergic receptor blocker is then withdrawn, the increased β-receptor population readily results in excessive β-receptor stimulation that will be clinically important when the delivery and use of oxygen is finely balanced, as occurs in ischemic heart disease. Other suggested mechanisms for the withdrawal reaction include heightened platelet aggregability, an elevation in thyroid hormone activity, and an increase in circulating catecholamines.

As it seems possible that postadrenergic receptor blockade sensitivity may be due to the generation of additional β-adrenergic receptors, a β-adrenergic receptor blocking drug with some partial agonist activity might provide enough receptor stimulation to prevent the generation of additional β-adrenergic receptors. Studies with atenolol, metoprolol, pindolol, and propranolol in normal subjects and patients indicate that administration of pindolol is not associated with increased sensitivity to isoproterenol after pindolol is stopped, in contrast to the other β-adrenergic receptor blocking drugs that do not possess partial agonist activity. Despite this difference with pindolol, it is still prudent to discontinue all β-blockers with caution in patients with ischemic heart disease.

#### Adverse Noncardiac Side Effects Related to β-Adrenergic Receptor Blockade

**Effect on Ventilatory Function**

The bronchodilator effects of catecholamines on the bronchial β₂-adrenergic receptors (β₂) are inhibited by nonselective β-blockers (e.g., propranolol and nadolol). Comparative studies have shown, though, that β-blocking compounds with partial agonist activity, β₁-selectivity, and α-adrenergic blocking actions are less likely to increase airways resistance in asthmatics than propranolol. β₁-Selectivity, however, is not absolute and may be lost with high therapeutic doses as shown with atenolol and metoprolol. It is possible in asthma to use a β₂-selective agonist (such as albuterol) in certain patients with concomitant low-dose β₂-selective blocker treatment.
Peripheral Vascular Effects (Raynaud's Phenomenon)

Cold extremities and absent pulses have been reported to occur more frequently in patients receiving β-blockers for hypertension compared with treatment with methyldopa. Among the β-blockers, the incidence was highest with propranolol and lower with drugs having β1-selectivity or intrinsic sympathomimetic activity. In some instances, vascular compromise has been severe enough to cause cyanosis and impending gangrene. This is probably due to the reduction in cardiac output and blockade of β2-adrenergic receptor-mediated skeletal muscle vasodilation, resulting in unopposed α-adrenergic receptor vasoconstriction. β-blocking drugs with β1-selectivity or partial agonist activity will not affect peripheral vessels to the same degree as will propranolol.

Raynaud's phenomenon is one of the more common side effects of propranolol treatment. It is more troublesome with propranolol than practolol probably because of the β2-blocking properties of propranolol.

Patients with peripheral vascular disease who suffer from intermittent claudication often report worsening of the claudication when treated with β-blocking drugs. Whether drugs with β2-selectivity or partial agonist activity can protect against this adverse reaction has yet to be determined.

Hypoglycemia and Hyperglycemia

Several authors have described severe hypoglycemic reactions during therapy with β-adrenergic blocking drugs. Some of the patients affected were insulin-dependent diabetics, while others were non diabetic. Studies of resting normal volunteers have demonstrated that propranolol produces no alteration in blood glucose values, although the hyperglycemic response to exercise is blunted.

In humans, mobilization of muscle glycogen is a β-receptor-mediated function (β2-mediated), while mobilization of liver glycogen depends on α-receptor stimulation. As a result, β-receptor blocking drugs (especially nonselective β-blockers) may retard recovery from insulin-induced hypoglycemia. In humans, Abramson et al. showed that propranolol delayed the return of blood glucose values to normal after insulin-induced hypoglycemia. If liver glycogen is reduced by fasting or illness, the concomitant use of nonselective β-blocking drugs may further prolong recovery from hypoglycemia, since alternative stores cannot be mobilized. With propranolol, the normal hemodynamic response to hypoglycemia may be altered with an elevation of diastolic blood pressure due to an α-constrictive response to reflex increases in plasma catecholamines.

This enhancement of insulin-induced hypoglycemia and its hemodynamic consequences may be less with cardioselective agents (where there is no blocking effect on β2-receptors) and agents with intrinsic sympathomimetic activity (which may stimulate β2-receptors).

There is also marked diminution in the clinical manifestations of sympathetic discharge associated with hypoglycemia (tachycardia and tremor). These findings suggest that β-blockers interfere with compensatory responses to hypoglycemia and can mask certain warning signs of this conditions. Other hypoglycemic reactions, such as diaphoresis, are not affected by β-adrenergic blockade.

Central Nervous System Effects

Dreams, hallucinations, insomnia, and depression can occur during therapy with β-blockers. There are evidence of drug entry into the central nervous system (CNS) and are especially common with the highly lipid-soluble β-blockers (propranolol and metoprolol) that presumably penetrate the CNS better. It has been claimed that β-blockers with less lipid-solubility (atenolol and nadolol) will cause fewer CNS side effects. This claim is intriguing, but its validity must be corroborated with more extensive clinical experiences.

A recent retrospective study suggested that patients receiving β-adrenergic blockers had a higher incidence of depression requiring antidepressant medication than did patients not receiving the drug. There were many methodological problems in this study, and no firm conclusions about depression incidence can be made. Our group was unable to demonstrate the above observation in a large prospective study in patients over 80 years of age in which the prevalence and incidence of depression on propranolol was identical to that of patients not receiving β-blocker therapy. In this same study, patients on minor tranquilizers were much more prone to depression than patients on β-blockers.

Clinical pharmacological studies have generally supported the view that β-blockers do not have any marked sedative effects. No such action could be detected for propranolol, sotalol, oxprenolol, or atenolol.

Skeletal Muscle Effects

In vitro studies demonstrate that propranolol can produce neuromuscular blockade. The direct actions of epinephrine on skeletal muscle are mediated probably through β2-receptors, and tremor is the most common side effect of β2-stimulating drugs. Propranolol has been shown to attenuate the ankle jerk, and a prolonged curare-like effect has been described in one patient. Whether the cardioselective β-blockers have similar effects remains to be determined.

Muscle cramps can also occur with pindolol and have been described with practolol and propranolol. The etiology of this side effect is unknown.

Miscellaneous Side Effects

Diarrhea, nausea, gastric pain, constipation, and flatulence have been seen occasionally with all β-blockers (2–11% of patients). Patients on β-blockers who develop anaphylac-
tic shock may not respond to the usual doses of \(\beta\)-agonists.

Hematologic reactions are rare. Rare cases of purpura\(^1\) and agranulocytosis\(^2\) have been described with propranolol.

A devastating blood pressure rebound effect has been described in patients who discontinued clonidine while being treated with nonselective \(\beta\)-blocking agents. The mechanism for this may be related to an increase in circulating catecholamines and an increase in peripheral vascular resistance.\(^3,4\) Whether \(\beta\)_selective or partial agonist \(\beta\)-blockers have similar effects after clonidine withdrawal remains to be determined. It has not been a problem with labetalol.\(^5\)

Increases in patient weight may occur. Bengtsson\(^6\) noted an average 1-kg weight increment in patients taking alprenolol. A similar weight gain in patients has also been noted with propranolol,\(^7\) pindolol,\(^8,9\) and oxprenolol. The mechanism of this weight gain has not been elucidated. However, treatment with diuretic agents will commonly relieve it.

### Adverse Effects Unrelated to \(\beta\)-Adrenergic Receptor Blockade

\(\beta\)-Blockers have been associated with the development of antinuclear antibodies.\(^7\) In prospective clinical trials, patients receiving acebutolol had a dose-dependent increase in the development of positive

### Table 4. Drug Interactions That May Occur with \(\beta\)-Adrenoceptor Blocking Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Possible effects</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum hydroxide gel</td>
<td>Decreases (\beta)-blocker absorption and therapeutic effect</td>
<td>Avoid (\beta)-blocker and aluminum hydroxide combination</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>Mutual inhibition</td>
<td>Observe patient’s response</td>
</tr>
<tr>
<td>Antidiabetic agents</td>
<td>Enhanced hypoglycemia; hypertension</td>
<td>Monitor for altered diabetic response</td>
</tr>
<tr>
<td>Calcium channel inhibitors</td>
<td>Potentiation of bradycardia, myocardial depression, and hypotension</td>
<td>Avoid use, although few patients show ill effects</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Prolongs half-life of propranolol</td>
<td>Combination should be used with caution</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Hypertension during clonidine withdrawal</td>
<td>Observe patient’s response; few patients show ill effects</td>
</tr>
<tr>
<td>Digitalis glycosides</td>
<td>Potentiation of bradycardia</td>
<td>Observe patient’s response; interactions may benefit angina patients with abnormal ventricular function</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Hypertension; bradycardia</td>
<td>Administer epinephrine cautiously; cardio-selective (\beta)-blocker may be safer</td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>Excessive vasoconstriction</td>
<td>Observe patient’s response</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Inhibition of hyperglycemic effect</td>
<td>Monitor for reduced response</td>
</tr>
<tr>
<td>Halofenate</td>
<td>Reduced (\beta)-blocking activity; production of propranolol withdrawal rebound syndrome</td>
<td>Observe for impaired response to (\beta)-blockade</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Inhibition of antihypertensive response to (\beta)-blockade</td>
<td>Observe patient’s response</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Mutual inhibition</td>
<td>Avoid concurrent use of cardio-selective (\beta)-blocker</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Antagonism of levodopa’s hypertensive and positive inotropic effects</td>
<td>Monitor for altered response; interaction may have favorable results</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Propranolol pretreatment increases lidocaine blood levels and potential toxicity</td>
<td>Combination should be used with caution; use lower doses of lidocaine</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Hypertension during stress</td>
<td>Monitor for hypertensive episodes</td>
</tr>
<tr>
<td>Manoamine oxidase inhibitors</td>
<td>Uncertain, theoretical</td>
<td>Manufacturer of propranolol considers concurrent use contraindicated</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Additive hypotensive effects</td>
<td>Monitor for altered response, especially with high doses of phenothiazine</td>
</tr>
<tr>
<td>Phenylpropranolamine</td>
<td>Severe hypertensive reaction</td>
<td>Avoid use, especially in hypertension controlled by both methyldopa and (\beta)-blockers</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Additive cardiac depressant effects</td>
<td>Administer i.v. phenytoin with great caution</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Additive cardiac depressant effects</td>
<td>Observe patient’s response</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Excessive sympathetic blockade</td>
<td>Observe patient’s response</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Inhibits negative inotropic and chronotropic effects of (\beta)-blockers</td>
<td>Observe patient’s response</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>Enhanced neuromuscular blockade</td>
<td>Observe response in surgical patients, especially after high doses of propranolol</td>
</tr>
</tbody>
</table>

Modified from Hansten\(^9\) with permission.
antinuclear antibody titers, and the overall incidence was higher than that observed with propranolol. Symptoms (generally persistent arthralgias and myalgias) related to this abnormality were infrequent (less than 1% with both drugs). Symptoms and antinuclear antibody titers were reversible upon discontinuation of treatment.

Oculomucocutaneous Syndrome

A characteristic, immune reaction, the oculomucocutaneous syndrome, affecting singly or in combination eyes, mucous and serous membranes, and the skin, often in association with a positive antinuclear factor, has been reported in patients treated with practolol and has led to the curtailment of its clinical use. Close attention has been focused on this syndrome because of fears that other β-adrenergic receptor blocking drugs may be associated with it. In 19 patients with such a reaction with practolol, the lesions healed after switching to atenolol treatment.

The main features in this syndrome in 439 patients reviewed by Nichols (see Conolly) were as follows:

1) Eye: A gritty feeling in the eye may occur that can progress to a panconjunctivitis; keratitis, and pannus formation. In Nichols' series, 18 patients manifested severe eye changes, 112 had corneal damage without loss of sight, and 146 had eye changes without corneal involvement. The average time to develop this syndrome was 23 months after initiating treatment.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Choice of β-blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma, chronic bronchitis with bronchospasm</td>
<td>Avoid all β-blockers if possible; however, small doses of β1-selective blockers (e.g., acebutolol, atenolol, metoprolol) can be used. β1-Selectivity is lost with higher doses. Drugs with partial agonist activity (e.g., pindolol, oxprenolol) and labetalol with α-adrenergic blocking properties can also be used.</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Drugs with partial agonist activity and labetalol might have an advantage, although β-blockers are usually contraindicated.</td>
</tr>
<tr>
<td>Angina</td>
<td>In patients with angina at low heart rates, drugs with partial agonist activity probably contraindicated. Patients with angina at high heart rates but who have resting bradycardia, might benefit from a drug with partial agonist activity. In vasospastic angina, labetalol may be useful; other β-blockers should be used with caution.</td>
</tr>
<tr>
<td>Atrioventricular conduction defects</td>
<td>β-Blockers generally contraindicated, but drugs with partial agonist activity and labetalol can be tried with caution.</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>β-Blockers with partial agonist activity and labetalol have less pulse slowing effect and are preferable.</td>
</tr>
<tr>
<td>Raynaud's phenomenon, intermittent claudication, cold extremities</td>
<td>β1-Selective blocking agents, labetalol, and those with partial agonist activity might have an advantage.</td>
</tr>
<tr>
<td>Depression</td>
<td>Avoid propranolol. Substitute a β-blocker with partial agonist activity or low lipid solubility.</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>β1-Selective agents and partial agonist drugs are preferable.</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>All agents will control symptoms, but agents without partial agonist activity are preferred.</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Avoid all β-blockers unless an α-blocker is given. Labetalol may be used as a treatment of choice.</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Use reduced doses of compounds largely eliminated by renal mechanisms (nadolol, sotalol, atenolol) and those drugs whose bioavailability is increased in uremia (propranolol, alprenolol). Also consider possible accumulation of active metabolites (alprenolol, propranolol).</td>
</tr>
<tr>
<td>Insulin and sulphonylurea use</td>
<td>Danger of hypoglycemia but is possibly reduced using drugs with β1-selectivity.</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Avoid topical (and other nonselective β-blockers). Severe rebound effect with clonidine withdrawal.</td>
</tr>
<tr>
<td>Oculomucocutaneous syndrome</td>
<td>Stop drug. Substitute any other β-blocker.</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Avoid nonselective β-blockers; use agents with partial agonism, β1-selectivity or labetalol.</td>
</tr>
</tbody>
</table>

Modified from Frishman with permission.
reaction is specific for practolol or is the direct and specific result of pharmacologically induced changes by \( \beta \)-blockade. There have been few convincing published reports of the occlusalunicotananeous reaction with oxprenolol and propranolol. In view of the extensive clinical use of both oxprenolol and propranolol, these reactions, even if drug induced, are exceedingly rare. There is need, however, for vigilance during therapy with the newer \( \beta \)-blockers.

Carcinogenicity

Propranolol, the first \( \beta \)-adrenergic receptor blocking drug to achieve widespread use, was withdrawn by its manufacturer because it caused thymic tumors and lymphosarcomata in mice, although it did not do so in rats or dogs. The doses used to produce these tumors were 10 times the maximum therapeutic concentration.

Tolamolol and pamatolol, two cardioselective \( \beta \)-adrenergic receptor blocking drugs, were withdrawn from clinical trials because they caused mammary tumors in mice and rats at high doses. Other \( \beta \)-blockers, alprenolol, practolol, and timolol, have given some indication of tumorigenicity in rodents. The relevance of these findings to causation of tumors in humans is difficult to evaluate. The doses were high, and the relationship between malignant tumors in animals and humans is not defined. A disturbing aspect has been the suggestion that this might be a pharmacological property of \( \beta \)-adrenergic receptor antagonism rather than carcinogenicity by another mechanism. Against the \( \beta \)-blocker theory of carcinogenesis is the fact that many \( \beta \)-blocking drugs have successfully undergone stringent carcinogenicity testing in animals and have been used safely in humans.

Drug Interactions

The wide diversity of diseases for which \( \beta \)-blockers are employed raised the likelihood of their concurrent administration with other drugs. It is imperative, therefore, that familiarity be obtained regarding the interactions of \( \beta \)-blockers with other pharmacological agents. The list of commonly used drugs with which \( \beta \)-blockers interact is extensive (Table 4). The majority of the reported interactions have been reported for propranolol, the best studied of the \( \beta \)-blockers, and may not apply to other drugs in this case.

How to Choose a \( \beta \)-Blocker

The various \( \beta \)-blocking compounds given in adequate dosage appear to have comparable, antihypertensive, antiarrhythmic, and antianginal effects. Therefore, the \( \beta \)-blocking drug of choice in an individual patient is determined by the pharmacodynamic and pharmacokinetic differences between the drugs in conjunction with the other medical conditions the patient might have (Table 5).

References

1. Friedman LM. How do the various \( \beta \)-blockers compare in type, frequency, and severity of their adverse effects? Circulation 1983;67(suppl 1):1-9-1-90
23. Conolly ME, Kestin F, Dollery CT. The clinical pharmacol-
56. Bengtsson C. Comparison between alpranolol and chlorthali-
77. Seedat YK, Stewart-Wynne E. Clinical experiences with pin-
78. Waal-Manning HJ, Simpson FO. Pindolol: a comparison with
other anti-hypertensive drugs and a double-blind placebo trial.
79. Frishman W. Acebutolol: a new oral β-blocker for hyperten-
6:979–985
80. Wright P. Untoward effect associated with practolol adminis-
1:595–598
81. Waal-Manning H. Problems with practolol. Drugs 1975;
10:336–342
82. Felix RH, Ive FA, Dahl MCG. Cutaneous and ocular reactions
83. Windsor WP, Durrein F, Dyer NH. Fibrinous peritonitis: a
1975;2:435
85. Zacharias FJ. Cross-sensitivity between practolol and other β-
86. Holt PJA, Waddington E. Oculocutaneous reaction to oxpen-
87. Knapp MS, Gallaway HR, Clayden JR. Ocular reactions to
88. Cubey RB, Taylor SH. Ocular reaction to propranolol and
resolution on continued treatment with a different β-block-
89. Harty RP. Sclerosing peritonitis and propranolol. Arch Intern
Med 1978;138:1424–1426
1963;2:1266–1267
91. Status Report on Beta-Blockers. US Food and Drug Adminis-
Printing Office, 1978:13
92. Missri JC. How do β-blockers interact with other commonly
used drugs? Cardiovasc Med 1983;8:668–669
93. Hansten P. Drug interactions, 4th ed. Philadelphia: Lea and
Febiger, 1979:13–24
94. Frishman WH. The β-adrenoceptor blocking drugs. Int J
Cardiol 1982;2:165–178
Beta-adrenergic receptor blockers. Adverse effects and drug interactions.

W H Frishman

Hypertension. 1988;11:II21
doi: 10.1161/01.HYP.11.3_Pt_2.II21

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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