**SUMMARY** Adverse effects of \(\beta\)-adrenergic receptor blocking drugs can be divided into two categories: 1) those that result from known pharmacological consequences of \(\beta\)-adrenergic receptor blockade; and 2) other reactions that do not appear to result from \(\beta\)-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 \(\beta\)-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 \(\beta\)-blocker side effects. Side effects of the second category are rare. They include an unusual oculomucocutaneous reaction and the possibility of carcinogenesis. There are also many drugs that interact with \(\beta\)-blockers, which may increase toxicity. Finally, there are specific patient characteristics where one \(\beta\)-blocker may be more effective and safer than another.

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

**KEY WORDS** • \(\beta\)-adrenergic receptor blockers • drug interactions

**Adverse Effects of \(\beta\)-Blockers**

Comparing and tabulating adverse effects from different studies of \(\beta\)-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 \(\beta\)-blocker compounds appear similar. The side effect profiles of \(\beta\)-blockers are also remarkably close to those seen with concurrent placebo treatments, attesting to the remarkable safety margin of the \(\beta\)-blockers as a group.

The adverse effects of \(\beta\)-adrenergic receptor blockers can be divided into two categories: 1) those from known pharmacological consequences of \(\beta\)-adrenergic receptor blockade; and 2) other reactions that do not appear to result from \(\beta\)-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 \(\beta\)-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 \(\beta\)-blocking agents. The Boston Collaborative Drug Surveillance Program studied the effects of propranolol (nonselective, no partial agonism) in 800 hospitalized patients and of practolol (\(\beta\)-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 (\(\beta\)-selective, long-acting) treatment in patients with hypertension. The side effect profiles for pindolol (nonselective with partial agonism) and labetalol (nonselective, \(\alpha\)-blocker) have also been assessed in extensive clinical trials in hypertensive patients. The long-term \(\beta\)-blocker trials in thousands of myocardial infarct survivors have reported on the adverse reactions with different \(\beta\)-blocking compounds used in this clinical situation.

In the Boston Collaborative Surveillance Program,
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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(headache, dizziness, fatigue, tinnitus, blurring of vision, paraesthesias, 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-Weser with permission.

Propranolol 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.

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

Forrest 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%. The overall incidence of severe side effects was not much different from that seen with placebo treatment (Table 2). 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. 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. 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. In the Norwegian timolol study, 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). 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>Propranolol3</th>
<th>Sotalol14</th>
<th>Oxprenolol15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>4.1/3.6*</td>
<td>3.2/2.1</td>
<td>6.0/2.2</td>
<td>3.0/2.5</td>
<td>6.0/2.2</td>
<td>3.8/2.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.6/0.1</td>
<td>2.8/1.2</td>
<td>2.1/1.9</td>
<td>2.0/0.3</td>
<td>2.0/0.3</td>
<td>2.1/0.7</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>4.4/0.9</td>
<td>NA</td>
</tr>
<tr>
<td>Depression</td>
<td>0.2/0.3</td>
<td>NA</td>
<td>0.0/0.4</td>
<td>0.0/0.4</td>
<td>1.8/0.4</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>1.5/0.1</td>
<td>0.9/0.7</td>
<td>0.5/0.7</td>
<td>0.5/0.7</td>
</tr>
<tr>
<td>Pulmonary problems</td>
<td>NA</td>
<td>1.1/0.4</td>
<td>0.0/0.4</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 Friedman with permission.
like pindolol or oxprenolol, which have intrinsic symp-
pathomimetic activity. Compounds with intrinsic symp-
pathomimetic activity in dosages producing β-block-
dade, 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.27-29

Multiple double-blind randomized trials have con-
firmed the reality of a propranolol withdrawal reac-
tion.27-30 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.31,32
When the β-adrenergic receptor blocker is then with-
drawn, the increased β-receptor population readily re-
results in excessive β-receptor stimulation that will be
clinically important when the delivery and use of oxy-
gen is finely balanced, as occurs in ischemic heart
disease. Other suggested mechanisms for the with-
drawal reaction include heightened platelet aggregabil-
tion,27 an elevation in thyroid hormone activity,29 and an
increase in circulating catecholamines.34

As it seems possible that postadrenergic receptor
blockade sensitivity may be due to the generation of
additional β-adrenergic receptors, a β-adrenergic re-
ceptor blocking drug with some partial agonist activity
might provide enough receptor stimulation to prevent
the generation of additional β-adrenergic receptors.35
Studies with atenolol, metoprolol, pindolol, and pro-
pranolol in normal subjects and patients indicate that
administration of pindolol is not associated with in-
creased sensitivity to isoproterenol after pindolol is
stopped, in contrast to the other β-adrenergic receptor
blocking drugs that do not possess partial agonist activ-
ity.30,37 Despite this difference with pindolol, it is still
prudent to discontinue all β-blockers with caution in
patients with ischemic heart disease.38

### 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 nado-
lo).39 Comparative studies have shown, though, that
β-blocking compounds with partial agonist activity,40
β₁-selectivity,41,42 and α-adrenergic blocking actions43
are less likely to increase airways resistance in asthma-
tics 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 β₁-selec-
tive blocker treatment.44 In general, all β-blockers

<table>
<thead>
<tr>
<th>TABLE 3. Percentage of Patients Withdrawn for Medical Reasons in β-Blocker Heart Attack Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effect</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Pulmonary problems</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
</tr>
<tr>
<td>New or extended myocardial infarction</td>
</tr>
<tr>
<td>Serious ventricular arrhythmia</td>
</tr>
<tr>
<td>Heart block</td>
</tr>
<tr>
<td>Syncpe</td>
</tr>
</tbody>
</table>
| Neurologicalntarget=1035 128323 Even with permission._

*Modified from β-Blocker Heart Attack Trial Research Group with permission.*
should be avoided in patients with bronchospastic disease.

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 β₂-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 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 condition. 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. These symptoms 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-
Hematologic reactions are rare. Rare cases of purpura and agranulocytosis 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. Whether $\beta_1$-selective or partial agonist $\beta$-blockers have similar effects after clonidine withdrawal remains to be determined. It has not been a problem with labetalol.

Increases in patient weight may occur. Bengtsson noted an average 1-kg weight increment in patients taking alprenolol. A similar weight gain in patients has also been noted with propranolol, pindolol, 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. In prospective clinical trials, patients receiving acebutolol had a dose-dependent increase in the development of positive antinuclear antibodies.

### 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>Monitor for hypertensive response; withdraw $\beta$-blocker before withdrawing clonidine</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; few patients show ill effects</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>Methylxanthines</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 methylxanthine and $\beta$-blockers</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Additive cardiac depressant effects</td>
<td>Administer i.v. phentytoin with great caution</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Additive cardiac depressant effects</td>
<td>Observe patient’s response; few patients show ill effects</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 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 panuus 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.

2) **Skin**: The skin changes usually begin with a pruritic rash involving the palms and the soles of the feet. Thickened plaques that resemble psoriasis may appear. Immunofluorescent studies have revealed granular deposits at the dermaelectodermal junction in some cases.

3) **Ear**: Deafness with serious otitis media has been reported in some patients receiving practolol.

**Sclerosing Peritonitis**

Thirty-three patients with this syndrome were included in Nichols' report. Patients may present with colicky abdominal pain or with an abdominal mass. This condition may progress in spite of withdrawal of the drug and may first develop up to a year after the discontinuation of practolol. The peritoneum becomes covered with a film of white fibrous tissue with thicker plaques. The natural history of this condition is unknown, and the diagnosis has usually been made at laparotomy or autopsy. Most patients appear to improve with time after cessation of treatment. The mean time to diagnosis of sclerosing peritonitis after starting practolol was 37 months.

As with sclerosing peritonitis, many of the other practolol reactions are reversible by withdrawal of the drug, together with treatment with topical corticosteroids, artificial tear solutions, antibiotic eye drops, and oral corticosteroids.

An important consideration is whether the practolol

**Table 5. Clinical Situations That Would Influence the Choice of a β-Blocking Drug**

<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. Substituté 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 tetalol (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>

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reaction is specific for practolol or is the direct and specific result of pharmacologically induced changes by β-blockade. There have been few convincing published reports of the oculomucocutaneous 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 β-blockers.

Carcinogenicity

Pronethanol, the first β-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 β-adrenergic receptor blocking drugs, were withdrawn from clinical trials because they caused mammary tumors in mice and rats at high doses. Other β-blockers, alpenrol, 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 β-adrenergic receptor antagonism rather than carcinogenicity by another mechanism. Against the β-blocker theory of carcinogenesis is the fact that many β-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 β-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 β-blockers with other pharmacological agents. The list of commonly used drugs with which β-blockers interact is extensive (Table 4). The majority of the reported interactions have been reported for propranolol, the best studied of the β-blockers, and may not apply to other drugs in this case.

How to Choose a β-Blocker

The various β-blocking compounds given in adequate dosage appear to have comparable, antihypertensive, antiarrhythmic, and antianginal effects. Therefore, the β-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).

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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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