A Comparison of Beta-Blocking Agents

OF THE MANY beta-receptor blocking agents developed over the past two decades only one, dl-propranolol, has become generally available to American physicians. However, as experience accumulates regarding the safety and efficacy of other beta-blockers, it is likely that at least some of these drugs (many of which are widely used in Europe) will gain approval for use in the United States. Thus an understanding of the comparative properties of these drugs may well prove useful in selecting optimal patient therapy in the future.

Nearly all of the beta-blockers used clinically share with isoproterenol, the prototype beta-agonist, an isopropyl substituted amine group thought to produce a high affinity for the beta-receptor. They differ from isoproterenol in that each has a different aromatic moiety substituted for the catechol ring, the portion of the catecholamine molecule thought to relate most directly to beta-agonist activity. Thus beta-blockers are all able to combine reversibly with the beta-receptor site and, by a competitive action, exclude substances which might otherwise act as beta-agonists. The net effect of each drug depends not only on receptor site affinity and intensity of competition from beta-agonists, but also on the ability (or inability) of the blocker itself to stimulate the beta-receptor. A spectrum of betagonist activity exists for the beta-blockers ranging from propranolol, which is essentially devoid of stimulatory activity, to dichloroisoproterenol, which has appreciable agonist properties. Several drugs—alprenolol, 6, 7 practolol, 8-10 and oxprenolol 8, 11—occupy an intermediate position in that they have both potent blocking abilities and a weak agonist action. These drugs have been termed “competitive dualists.” 12

The physiologic consequences of administering beta-blocking agents depend heavily on the intensity of ambient beta-stimulation. In the presence of high levels of beta-stimulation all effective beta-blockers act directly to reduce contractility, decrease automaticity in the sinoauricular node and in subsidiary pacemaker tissue, and to reduce conduction velocity. These actions may be modified, of course, by reflex, autoregulatory, or other secondary influences. When beta-stimulation is minimal, the effects of a given concentration of a beta-blocker are correspondingly diminished. If competitive dualists are administered under these circumstances, they may actually result in an increase in beta-stimulation. For example, practolol and oxprenolol augment isometric contractile force and heart rate when given to dogs depleted of endogenous catecholamines by prior treatment with reserpine. This is not true of propranolol or sotalol. These considerations imply that studies of the inotropic or chronotropic influence of a beta-blocking agent must be interpreted in terms of the basal level of catecholamine stimulation of the study subject.

Responses to a beta-blocking agent may also vary depending upon the relative action of the drug on cardiac and noncardiac (arteriolar, bronchiolar, etc.) beta-receptors, i.e. its “cardioselectivity.” By blocking the vasodilator effects of circulating beta-agonists, propranolol may cause a net increase in peripheral vascular resistance, an effect not observed with the more cardioselective agent practolol even when this drug is given in a dose producing a similar degree of cardiac beta-receptor blockade.

Comparison of the beta-blocking activity of the various drugs under discussion is complicated by a lack of parallel behavior in dose-response curves. The relative potency of two physiologically similar drugs, in the simplest case, may be expressed by a single ratio, representing a constant displacement between two log dose-response curves. In this case, equivalent doses of two different drugs can be calculated by multiplying any given dose by a single, fixed number. Recent studies in our laboratory have shown that this situation may obtain when sotalol is compared with propranolol but not when the competitive dualist practolol is compared with propranolol. 9 The dose-response curve for practolol tends to plateau at larger doses. Thus, four times as much practolol duplicated the beta-blocking actions of 0.01 mg/kg propranolol, but 64 times as much practolol failed to match the effects of 0.04 mg/kg propranolol. The plateau in the dose-response curve for practolol may be due to a beta-agonist action of practolol at high concentrations. In practical terms, these findings suggest that very
large doses of practolol, and perhaps other competitive dualists, may fail to reach the high degree of reduction in beta-receptor activity readily attained by propranolol or sotalol.

In the choice of a beta-blocking agent, lack of side effects is naturally a prime consideration. The finding that pronethalol increases the frequency of thymic lymphosarcoma in a highly susceptible strain of mice has led to its disuse. Propranolol does not have an oncogenic influence. The question of oncogenic tendencies has been raised for other beta-blocking agents and is presently being investigated. To date, however, no clear evidence of an oncogenic property similar to that for pronethalol has been found for any other beta-blocker.

The physiologic process of beta-blockade may itself produce undesirable consequences. Bronchospasm and other sequelae of blocking noncardiac beta-receptors may be avoided by using practolol, a "cardioselective" blocking agent. This may represent a decisive advantage of practolol over propranolol in the treatment of asthmatic patients, in patients with pheochromocytoma, who may develop severe hypertension due to unopposed alpha-receptor-mediated vasoconstriction if beta-receptors of the arterial bed are blocked, and possibly in patients predisposed to hypoglycemia by hepatic insufficiency.

Inhibition of sympathetic stimulation to the myocardium with resultant depression of myocardial contractility is also an unwanted consequence of beta-blockade when this therapeutic maneuver is employed to attenuate increases in heart rate. Given the capacity to synthesize additional beta-blocking agents, it was hoped that drugs would be developed that selectively blocked beta-receptors influencing heart rate while sparing beta-receptors influencing contractility. Such selective action was initially believed to be inherent in the blocking properties of practolol and sotalol. Studies in our laboratory, however, indicate that neither practolol nor sotalol is more "chronoselective" than propranolol. When the secondary effects on cardiac performance of altering preload and afterload are excluded, it becomes apparent that the depression in contractile force associated with a given reduction in heart rate is the same for each drug. Thus it would appear that the cost, in terms of contractile depression, is the same for a given reduction in heart rate regardless of the particular beta-blocker employed.

In addition to their effects on the beta-receptor, racemic (dl) propranolol, alprenolol, and pronethalol exhibit quinidine-like "membrane-stabilizing" properties associated with nonspecific depression of myocardial contractility. However, the clinical significance of these studies remains uncertain since quinidine-like activity of the commonly used racemic mixtures has generally been observed at concentrations considerably in excess of those manifesting significant beta-blocking action. When usual therapeutic doses of dl-propranolol or other beta-blocking agents are administered to animals previously depleted of catecholamines to nullify the depressant effects of beta-blockade, there is no evidence of depression in contractility, heart rate, or A-V conduction. In the case of dl-propranolol, such depression is readily demonstrable, but only with doses above 0.64 mg/kg, an amount far greater than that ordinarily used clinically. Thus, in the therapeutic context, it seems likely that reductions in contractility and heart rate following the usual doses of propranolol and other beta-blocking agents are caused largely by withdrawal of sympathetic stimulation rather than by a primary depressant action.

In conclusion, some of the beta-blocking drugs not yet generally available in the United States may offer important advantages relative to the prototype beta-blocker, propranolol. Cardioselectivity is clearly advantageous in certain individuals sensitive to the effects of noncardiac beta-blockade. In addition, the competitive dualists might offer a greater range of safe dosage since their effects (good and bad) plateau at higher doses. Unfortunately, none of the drugs tested appears to offer chronoselective beta-blockade. This would imply that doses of beta-blocking agents sufficient to attenuate sympathetically mediated rises in heart rate all carry with them the risk of precipitating or exacerbating congestive heart failure, particularly in patients with impaired myocardial function.

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