Editorial: 
Propranolol Withdrawal Syndrome — Why?

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FEW WHO HAVE WITNESSED the propranolol withdrawal phenomenon would deny its existence. The syndrome, which comprises the development of ventricular arrhythmias, severe angina, myocardial infarction and even death soon after sudden cessation of propranolol therapy, was first described in a series of case reports.1-3 Perhaps the most convincing evidence was obtained by Miller et al.,4 who noted a 50% incidence of the withdrawal syndrome after cross-over to placebo during a double-blind trial of propranolol in the treatment of angina pectoris. While this dramatic result was convincing evidence of the syndrome, it clearly over-estimated its true incidence, which is probably about 5%. It is also generally agreed that the problems of propranolol withdrawal occur more often in patients who maintain normal activity than those in the hospital. For example, Shiroff et al.5 could find evidence of the phenomenon in only one of 55 patients hospitalized before cardiac catheterization. The time at which adverse events occur seems to vary widely, from one to 14,5-6 or even 21 days.7 This would seem to represent a balance between the time taken for the drug to dissipate and the onset of the precipitating event. Although propranolol has a relatively short half-life (about 3-6 hours in patients with normal liver function), its duration of action depends just as much on the initial plasma concentrations,8 with higher levels associated with more prolonged action. With the usual doses of about 160-320 mg daily, negligible drug levels are seen between 16-48 hours after sudden withdrawal.9,10 Thereafter, the time at which the withdrawal syndrome occurs depends on the mechanism responsible and on the nature of the precipitating event. While reactivation of the beta-adrenergic nervous system is clearly involved, it is not clear why this causes tachycardia and tremulousness, or why it precipitates arrhythmias and coronary events.

One of the earliest suggestions was that the disease process had progressed, or that the patients continued to attempt the more strenuous activity that propranolol treatment had allowed. Disease progression seems less likely to account for the syndrome observed in patients after only six weeks of treatment given in the controlled trials,3,4 but increased activity could well account for the great incidence or severity in ambulant compared with hospitalized patients. The area of greatest interest has been whether there is a true rebound "hyperadrenergic" state, and, if so, of what? Because propranolol alters so many body functions, several alternatives have been proposed. The most obvious is that there exists a true hypersensitivity of the beta receptor to adrenergic stimuli. The one positive study of Boudoulas et al.11 showed a significant rebound increase in resting heart rate, pulse pressure, and shortening of electromechanical systole (QS1) produced by isoproterenol in normal volunteers. These changes occurred 24-36 hours after sudden withdrawal of only 48 hours of treatment with 160 mg daily. A preliminary report of supersensitivity to isoproterenol has recently appeared.12 These data are consistent with emerging in vitro studies of beta receptors.13 Thus, it has been suggested that exposure to catecholamines will reduce the number of beta receptors (measured as radio-ligand binding capacity) in several tissues. It might then be anticipated that receptor blockade and/or reduced catecholamine release might prevent this decrease, or even cause an increase in receptor number.

Although this theory is an attractive one, negative reports do exist, including the animal study by Myers and Horwitz in this issue of Circulation. These workers have failed to show increased sensitivity to epinephrine or isoproterenol in dogs. In view of the fact that the most obvious changes shown by Boudoulas et al.13 in man occurred at 36 and 48 hours, it is unfortunate that Myers and Horwitz performed no measurements between 24 and 72 hours postwithdrawal. This highlights the problems of investigating a transient phenomenon with variable timing. Patano and Lee4 also failed to show any changes in systolic time intervals of normal subjects studied at rest. This may simply reflect the importance of a sympathetic stimulus in eliciting supersensitivity.

Several other actions of propranolol have been implicated. For example, Frishman et al.15 have found that the platelets of patients with angina are hyperaggregable in response to epinephrine and thrombin. During propranolol therapy, platelet sensitivity to these agents decreases, and at 48 hours after cessation of therapy, hyperaggregability returns. In six of 10 patients the platelets were more sensitive to the aggregating agents than during control. Thus, while these studies are suggestive, they are not yet definitive regarding rebound. The fact that aggregating platelets produce a prostaglandin, thromboxane A2, which constricts coronary arteries,16 is another intriguing potential mechanism. Although as yet untested, rebound from other actions of the drug in suppressing plasma renin activity,17 shifting the oxygen dissociation curve to the right,18 and the possible inhibition of the deiodination of thyroxine to triiodothyronine19 may well be involved. Alteration in the activity of the sympathetic system is another candidate. Buhler et al.,20 21 have shown that after acute
I.V. administration, propranolol elevates serum norepinephrine as part of the sympathetic response which maintains blood pressure in the face of reduced cardiac output, but that with continued therapy in hypertensives, levels fell only in those whose blood pressure became controlled, though the changes were not great. It would seem that the effects of propranolol on serum norepinephrine are both time-dependent and variable. Urinary vanillylmandelic acid excretion was unchanged during the withdrawal phase of the Patano and Lee study. Presently, then, we are left with several potential mechanisms and a somewhat conflicting literature which suggests a multifactorial mechanism.

The existence of the withdrawal syndrome has raised several practical issues, in particular the need to routinely withdraw propranolol before open heart surgery. Although an initial report suggested that the negative inotropic effects of the drug may last for weeks, this has not been substantiated. and most experts agree that the drug need not be stopped before surgery. Indeed, it has been suggested that continued treatment may be beneficial. It is also generally agreed that, if the drug must be stopped, the dose should be tapered over a period of four to seven days, but the benefits of this approach have not been directly tested. Although serious withdrawal syndromes have been noted, usually in patients with severe angina who have benefited dramatically from therapy, these recommendations are advised for the other indications of the drug. If it is necessary to suddenly stop the drug, this should be done under close supervision, and therapy should be reinstituted if signs of withdrawal occur.

In summary, we believe that the propranolol withdrawal syndrome is real but rare, and its mechanism is undefined.

References
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