EDITORIALS

Discontinuation of Propranolol Therapy

Cause of Rebound Angina Pectoris and Acute Coronary Events

Sporadic reports have accumulated during the past several years pointing out the occurrence of acute myocardial infarction shortly after the abrupt discontinuation of propranolol therapy or therapy with other \( \beta \)-adrenergic blocking drugs in patients with coronary artery disease.\(^{1-4}\) These observations were emphasized to us when we noted three acute “propranolol withdrawal” events in a series of 21 patients participating in a double-blind evaluation of propranolol therapy compared to placebo.\(^5\) From these and published observations on this phenomenon, we have developed a number of impressions regarding “propranolol withdrawal” events.\(^6\)

First, the susceptible individual is generally one who, prior to propranolol therapy, has severe symptoms of coronary ischemia and has responded impressively to therapy. The total daily dose of propranolol for all reported cases of rebound events has been in excess of 120 mg per day, which is at the threshold level required for adequate \( \beta \)-adrenergic blockade and symptomatic relief of coronary artery disease. Within 12 to 24 hours after discontinuation of propranolol therapy, the susceptible patient observes a marked increase in the frequency, severity, and duration of anginal symptoms and, in particular, a recurrence of symptoms at mild levels of exertion or at rest which had in the past not produced angina. Some patients at this time may abruptly develop an acute myocardial infarction, while others may persist in a period of unstable angina which may be complicated by acute coronary insufficiency, frequent ventricular premature beats, myocardial infarction, or sudden death.\(^6\) In all reported patients in whom propranolol therapy was restarted, rebound angina was abolished.

Secondly, the onset of rebound anginal symptoms appears to correlate well with physiologic data demonstrating the disappearance rate of propranolol from myocardial tissues. Measurement of both myocardial propranolol levels\(^7\) and residual radioactivity from \(^{14}\)carbon-labeled propranolol\(^8\) has shown clearly that by 24 hours following discontinuation of the agent, neither residual propranolol nor its metabolites persist. Furthermore, there is no residual \( \beta \)-adrenergic blockade when isoproterenol is administered.

An important question has been raised as to whether these coronary events reflect a true rebound phenomena or whether they are the result of underlying progression of coronary disease which has been masked by long-term propranolol therapy. The fact that some of our patients had been receiving propranolol therapy for only six weeks and, after its discontinuance, had exhibited frequencies of anginal episodes which exceeded levels before propranolol therapy supports the hypothesis that a true rebound phenomenon exists.\(^6\)

Several alternative explanations can be suggested to explain the occurrence of “propranolol withdrawal” events. The possibility that an increase of circulating catecholamines occurs during propranolol therapy and might account for subsequent rebound has not been substantiated by direct measurements of urinary catecholamine excretion\(^9\) nor by plasma norepinephrine levels.\(^10\) Similarly, there is no evidence for denervation hypersensitivity to catecholamines resulting from long-term propranolol therapy. Other possible explanations for propranolol rebound include drug-induced modifications of the hemoglobin-oxygen dissociation curve and platelet aggregatability. Another explanation is that the circulatory readjustments due to \( \beta \)-adrenergic blockade result in increased ventricular volumes and wall stress.\(^11\) These cardiovascular adaptations to long-term propranolol therapy might be expected to persist beyond the period when \( \beta \)-blockade is disappearing and, thus, tend to increase myocardial oxygen demands concomitant with the return to unaltered heart rates and blood pressure.

The most significant consideration in discontinuing propranolol therapy relates to preparation for coronary arteriography and cardiac surgery. In our
opinion, it is best to discontinue propranolol therapy before left ventriculography, particularly in patients with prior myocardial infarction, because the drug’s negative inotropic effects may adversely affect the results of ventriculographic studies. In general, propranolol therapy need be discontinued only 24 to 48 hours before cardiac surgery. Previously expressed concerns that myocardial depression may persist up to 7 to 15 days after discontinuance of the drug have been shown to be unfounded by the aforementioned physiologic data. For many patients who exhibit unstable preoperative coronary symptoms (particularly those without evidence of prior severe myocardial damage) it is probably wisest to maintain the administration of propranolol therapy through the time of surgery. This may avoid precipitating a myocardial infarction before surgery and during induction of anesthesia, and may well assist in suppressing perioperative and postoperative ventricular arrhythmias.

The incidence of propranolol rebound in coronary events has been variously estimated to occur in 3 to 15 percent of risk events. We believe that propranolol administration for most patients can be terminated abruptly; however, patients must be alerted to the possibility of rebound angina, so that the drug can be immediately restarted. A gradual tapering of individual doses is suggested for patients who have exhibited an excellent therapeutic response to propranolol therapy and have had particularly severe coronary ischemic symptoms prior to therapy. Clearly, further investigative work in this area may permit a more definitive explanation of this interesting phenomenon.

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REFERENCES


The Story of Anatomically Corrected Malposition of the Great Arteries

Anatomically corrected malposition (ACM) is hardly a household word, even among pediatric cardiologists. Even though ACM can now be diagnosed accurately and corrected surgically, there is little doubt that many interested cardiologists, radiologists, and surgeons are still largely unfamiliar with these uncommon forms of congenital heart disease. This editorial will attempt to provide some perspective concerning these anomalies, plus a little background information relevant to the report of Zakshein and his colleagues that appears in this issue of Chest (see page 101).

First described by Théremin in 1895 (his case 47), this type of relationship between the great arteries and the ventricles was christened “anatomically corrected transposition” by Harris and Farber in 1939, these authors reporting no cases of their own, however. This term was intended to indicate that each of the abnormally located great arteries arose nonetheless above the anatomically correct ventricle—the abnormally located aorta above the anatomically left ventricle and the abnormally located pulmonary artery above the anatomically right ventricle (Fig 1).

Despite this conceptual crystallization by Harris and Farber, there remained considerable doubt concerning whether or not such malformations actually exist. Locht dismissed these anomalies as errors in observation. Geipel regarded them as inexplicable variations of nature. Van Mierop and Wiglesworth concluded that they were embryologically impossible and, hence, nonexistent, a view.