The Cardiovascular and Renal Advisory Panel of the FDA met January 27-28, 1998, to discuss (1) evaluation and use of intravenous inotropic agents in patients with heart failure; (2) liver function test abnormalities with a new AT1 receptor blocker, tasosartan; and (3) the use of the platelet IIb/IIIa receptor blocker eptifibatide in syndromes of acute cardiac ischemia.

Intravenous Inotropic Agents for Heart Failure

Intravenous drugs for the treatment of heart failure historically have been approved after demonstration of acute dose-dependent hemodynamic effects in patients with heart failure. Recently, however, there appears to have been a marked increase in the intermittent or continuous use of intravenous inotropic agents for longer periods than originally anticipated, often without monitoring of cardiac rhythm. This practice has become prevalent despite recent trials with oral inotropic agents that have shown adverse effects on mortality and morbidity during long-term treatment and preclinical data presented to the committee that raised the possibility that intermittent exposure to intravenously administered positive inotropic agents may accelerate myocardial cell death. The committee therefore voted unanimously that short-term use of intravenous inotropic agents for decompensated heart failure should be approved if an improvement in symptoms, renal function, and/or hemodynamics (including patients after bypass surgery) can be shown. However, for prolonged intermittent or continuous intravenous use, an improvement in survival and symptoms should be demonstrated in a placebo-controlled trial. The committee unanimously recommended that labeling of intravenous positive inotropic agents be revised to reflect the following: (1) that these drugs are indicated for patients who are hospitalized with acutely decompensated heart failure, (2) that there is no experience in controlled trials with continuous infusions for periods >24 to 48 hours, (3) that there is no evidence that these drugs are effective or safe in patients with heart failure if used intermittently or continuously as a short-term or long-term management strategy, (4) that long-term oral use of these drugs has been associated with an increased risk of hospitalization and death, and (5) that there is no evidence that long-term use of these drugs given intravenously does not carry a similar risk.

Tasosartan and Abnormal Liver Function Tests

Tasosartan is an AT1 receptor blocker with a slowly eliminated active metabolite. Its antihypertensive efficacy seems to be similar to that of irbesartan, losartan, and valsartan. In the tasosartan database, however, values of AST or ALT twice the upper limit of normal were seen in 16 of 950 patients (1.7% versus 1.2% in placebo) and 8 times the upper limit of normal in 4 of 950 (0.4% versus 0%). Some patients with abnormal values were continued on therapy, and in some, values decreased or returned to normal. Drug rechallenge reproduced abnormal values in 6 of 6 patients. The committee heard evidence indicating that elevated transaminases may not correlate well with actual liver damage, and clinically apparent liver disease (defined as serum bilirubin value >2.5 mg% or prolonged prothrombin time) was not seen in the tasosartan database. A review of the New Drug Application databases for losartan and valsartan suggested an incidence of abnormal transaminases of 0.4% to 2.1%, comparable to incidence with the respective placebos. In these databases, however, liver function was assessed monthly, whereas it was assessed weekly with tasosartan. Moreover, the committee heard evidence from the FDA that postmarketing surveillance has identified 13 possible cases of serious liver disease (including 2 fatalities) in association with marketed AT1 receptor blockers. The committee unanimously agreed that the higher incidence of abnormal transaminases with tasosartan could well be attributed to the increased frequency of the determinations compared with other AT1 receptor blockers. The drug was recommended for approval with labeling that would specify the incidence of abnormal liver function tests with this and similar agents.

Eptifibatide (Integrilin)

An application to market eptifibatide, an inhibitor of the platelet IIb/IIIa receptor that prevents platelet aggregation via a mechanism different from that of aspirin, had been previously reviewed and not recommended by the committee. That decision was reached in part because only a single trial (with borderline statistical significance) was presented, whereas the usual standard is 2 efficacy trials. Moreover, in that trial (IMPACT II), only a low-dose regimen and not a high-dose regimen was shown to be effective. The results of IMPACT II were again presented briefly. The patients studied were those undergoing intervention for unstable myocardial ische-
mic syndromes. The primary composite end point of death, MI, or urgent revascularization at 30 days was reached in 11.6% of patients receiving placebo, 9.1% of patients receiving low-dose Integrilin (bolus 135 μg/kg and infusion 0.5 μg · kg⁻¹ · min⁻¹) for 24 hours, and 10.1% of patients receiving high-dose Integrilin (bolus 135 μg/kg and infusion 0.75 μg · kg⁻¹ · min⁻¹) for 24 hours. A significant difference compared with placebo was seen only in the low-dose group (P=0.035). The committee noted that the publication of the IMPACT II results reported this P value at 0.063, indicating the sensitivity of the conclusions to different assumptions regarding the analysis.

At the recent meeting, a second large trial (PURSUIT) was presented. PURSUIT was conducted in North America, Europe, and Latin America and was designed to evaluate the efficacy of eptifibatide in preventing death or reinfarction in patients hospitalized with unstable angina or non–Q-wave MI. The doses were higher than those used in IMPACT II, because the goal was to achieve 80% platelet inhibition, and in vitro data suggested that this was not achieved with either the low or the high doses in IMPACT II. In PURSUIT, patients were randomized to 1 of 3 groups: placebo, low-dose (180 μg/kg bolus and 1.3 μg · kg⁻¹ · min⁻¹ infusion), or high-dose (180 μg/kg bolus and 2.0 μg · kg⁻¹ · min⁻¹ infusion) for up to 72 hours, or up to 96 hours if balloon intracoronary intervention (stent and/or percutaneous transluminal coronary angioplasty) was performed. At a prespecified review after 3218 patients were recruited, the high-dose regimen appeared to be safe, so recruitment into the low-dose arm was stopped. The primary end point was death or reinfarction at 30 days. Of a total of 10 948 patients enrolled, 4739 were assigned to placebo and 4722 to high-dose reinfarction at 30 days. Of a total of 10 948 patients enrolled, the high-dose arm was stopped. The primary end point was death or reinfarction. Conversely, the outcome in the subset of patients in IMPACT II who underwent revascularization procedures, along with the outcome of IMPACT II, was thought to be sufficiently compelling that, in a split vote, the committee recommended approval of eptifibatide as concomitant therapy in the treatment of coronary intervention for patients with characteristics similar to those of patients who entered the IMPACT II trial. The dose recommended was the one found to be effective in IMPACT II, 135 μg/kg bolus and 0.5 μg · kg⁻¹ · min⁻¹, for up to 24 hours.

Reference
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