PRIME II: another disappointment in heart failure therapy

The results of PRIME II (Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy) have recently been published. PRIME II was a double-blind, randomized, placebo-controlled multicentre trial designed to study the effect of ibopamine on mortality in patients with advanced heart failure. Ibopamine is a dopaminergic receptor antagonist which causes peripheral and renal vaso-dilatation, and on the basis of studies showing an improvement of the symptoms of heart failure it was anticipated that ibopamine would also improve survival.

The patients included in PRIME II had heart failure of any cause, and symptoms in the NYHA Classes III and IV, despite optimal medical treatment which included angiotensin converting enzyme inhibitors, unless the patient was known to be intolerant of these drugs. The study protocol described in some detail the type of patient who should be included and all had evidence of heart disease based on one of the following: a left ventricular ejection fraction of less than 35%, a left ventricular end-diastolic diameter on echocardiography of greater than 6 cm, or a cardiothoracic ratio on chest X-ray of greater than 50%. The patients were randomly assigned to receive ibopamine 100 mg three times daily, or placebo, in addition to existing therapy.

Since there was published evidence of symptomatic benefit from ibopamine treatment, the primary objective of the trial was to exclude with 95% certainty the possibility that ibopamine treatment was associated with a 20% increase in fatality. Since the annual fatality rate in the placebo group was expected to be 20%, it was calculated that 2200 patients should be included and followed for a minimum of 6 months. No formal interim analyses were planned, but the results were reviewed at intervals by a Safety Committee using pre-defined ‘stopping rules’.

The trial was stopped prematurely on the advice of the study Safety Committee after 1906 patients had been included, because of an excess of deaths among patients in the ibopamine group. Two hundred and thirty-two of 953 patients receiving ibopamine died, compared with 193 of 953 patients allocated to placebo treatment: this difference was statistically significant (relative risk 1.26, 95% CI 1.04-1.53, P=0.017). There was no significant difference in the cause of death (sudden death, heart failure etc) in the two groups.

The study was not designed to investigate the effect of ibopamine in any patient subgroup, and the results of any subgroup analyses must therefore be treated with extreme caution. However, because of the unexpected increase in fatality in the ibopamine group a number of subgroups were constructed retrospectively in an attempt to develop hypotheses that might explain this adverse effect. Univariate analysis showed that ibopamine treatment was associated with excess fatality in patients with heart failure worse than NYHA Class III (on admission, investigators were permitted to describe a patient as having symptoms of Class III/IV if they felt that the symptoms were worse than Class III but did not strictly fulfil the criteria for Class IV), in males, in patients with heart failure of more than 2 years duration, and in those receiving antiarrhythmic therapy (in most cases, amiodarone) at the time of admission to the trial. On multivariate analysis, only the use of antiarrhythmic drugs remained a statistically significant independent predictor of increased fatality associated with ibopamine treatment.

This is the fourth drug which has been found to improve the symptoms of heart failure but which reduces survival—the others being milrinone, enoximone and flosequinan. Nevertheless, the results came as a surprise because ibopamine has been in widespread use for some years in several European countries; its vasodilating effects on the peripheral circulation and its impact on neurohormones are thought to benefit heart failure; in the dose used it was not thought to have an inotropic effect, and there has been no reason to suppose that it has any pro-arrhythmic effect. No interaction of ibopamine with amiodarone or any other antiarrhythmic agent has ever been noted, and there is thus no prior hypothesis that could explain an adverse effect on survival; this must increase our caution in interpreting the results of subgroup analyses. For what it is worth, however, it does seem that ibopamine is harmful mainly in patients with the more advanced degrees of heart failure, and a specific interaction with amiodarone cannot be excluded.

In general terms, the PRIME II results re-emphasize the importance of conducting studies of...
the effect of new anti-failure therapies on survival, rather than relying on surrogate end-points such as haemodynamic changes or improvements in symptoms. Patients with severe heart failure might well feel that an improvement in their symptoms would be a price worth paying for reduced survival, but this presents physicians and the pharmaceutical industry with an ethical and legal dilemma which will not be easy to resolve.

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References

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Smoking and outcome after PTCA

A substantial proportion of patients undergoing percutaneous coronary interventions have smoked cigarettes. Moreover, many continue to smoke after the procedure[1,2]. Indeed, in a recent study presented in the New England Journal of Medicine of 13 March 1997[3], of the 1169 patients who were smokers at the time of the index percutaneous intervention at Mayo Clinic, 734 (63%) continued to smoke. Cessation of cigarette smoking is a difficult challenge for the patient after percutaneous coronary interventions.

Patients often perceive percutaneous interventions favourably and are willing to repeat the procedure if needed[9]. In addition, patients after percutaneous procedures are confident about outcome, and are not overly concerned about the possibility of subsequent adverse events[4,5]. The availability of a non-surgical revascularization option and the quick resumption of an active lifestyle after percutaneous procedures[6] may explain why patients after percutaneous coronary interventions often do not practice strict risk-factor modification[1,2,7,8]. For example, as compared with patients after coronary bypass surgery, patients after percutaneous coronary revascularization are less likely to make changes in life-style[9]. Although cessation of cigarette smoking is advocated strongly after percutaneous revascularization, until recently there were few long-term data regarding mortality, morbidity, and need for repeat revascularization associated with cigarette smoking and cessation of smoking in patients undergoing percutaneous coronary revascularization.

In the study performed by researchers at Mayo Clinic[3], smoking status was determined at the time of index intervention in all patients who had undergone successful percutaneous coronary revascularization in the non-peri-infarction setting (no myocardial infarction within 24 h before the intervention) between 1979 and 1995. Patients were then periodically queried regarding their smoking status during a follow-up period extending up to 16 years (mean ± SD of 4.5 ± 3.4 years). Of the 5450 patients in whom the index procedure was clinically successful, 2009 were non-smokers, 2259 were former smokers (stopped smoking at least 6 months prior to