SCIENTIFIC LETTERS

Safety of an intravenous second generation contrast agent in patients with severe left ventricular dysfunction

Contrast echocardiography has been used to opacify the left ventricular cavity, delineate endocardial borders, and assess myocardial perfusion. Since capillary integrity is essential for myocardial viability, the presence of contrast in dysfunctional myocardial segments may be used as indirect evidence of preserved viability in patients with left ventricular dysfunction.[1] It has been shown that 50–60% of patients with severe left ventricular dysfunction and coronary artery disease have evidence of myocardial viability, and the demonstration of viable myocardium in these patients has profound therapeutic and prognostic implications.[2] The recent development of second generation contrast agents that can be administered intravenously has enhanced the applicability of contrast echocardiography. Contrast agents transit the pulmonary capillary circulation after intravenous administration. They could theoretically have adverse effects on pulmonary vascular resistance and oxygen saturation.[3] It has also been suggested that a high pulmonary vascular impedance could hinder the pulmonary transit of contrast agents, thereby compromising efficacy. Sonovue (Bracco, Spa, Milan, Italy) is an aqueous suspension of phospholipid encapsulated sulfur hexafluoride microbubbles, developed as an intravenous contrast agent for echocardiography.[4] Although the safety of transpulmonary contrast agents has been previously established in human studies, it has not been specifically examined in patients with severe left ventricular dysfunction where the technique is likely to be increasingly used to determine myocardial viability.

Thus, the purpose of this study was to determine the cardiopulmonary and haemodynamic effects of bolus doses of Sonovue in patients with severe left ventricular dysfunction and congestive cardiac failure, and the ability of this agent to opacify the myocardium in presence of pulmonary hypertension. This was performed as a single centre, randomised, placebo controlled study where patients were randomised to receive either two boluses of 2 ml and 4 ml of Sonovue and matching placebo, given alternately at intervals of at least 15 minutes (active group), or matching doses of placebo only (control group). Haemodynamic parameters were measured by pulmonary artery catheterisation. Myocardial opacification was assessed by two dimensional (cross sectional) echocardiography using intermittent harmonic imaging, to ensure effective pulmonary transit of Sonovue in the presence of pulmonary hypertension. Approval of the hospital ethics committee was obtained.

All haemodynamic parameters were recorded at 5, 4, 3, 2, and 1 minute(s) before the first administration of the study agent and again at 30 seconds, 2, 4, 6, 10 minutes after administration. Oxygen saturation was monitored throughout using fingertip pulseoximeter. Twelve lead ECGs were recorded 10 minutes before the first injection, and at 10 minutes and 1 hour after the final injection of the study agent. Local tolerability (local heat and pain) was evaluated immediately and at 5 minutes after each injection of the study agent. Patients were monitored throughout the study for any adverse symptoms and specifically for signs and symptoms of worsening heart failure. Echocardiography was performed using standard four and two chamber views at baseline and during each injection of study agent, starting before the administration of each dose and continuing until the end of the contrast effect. Second harmonic imaging was performed using broad bandwidth transducer (2–4 MHz). Images were acquired intermittently during the systole of each cardiac cycle by triggering on the T wave of the ECG, and stored on super VHS videotapes for off-line analysis. In each view left ventricle was divided into five segments and myocardial contrast activity was scored (0 = absent, 1 = weak, 2 = good).

Of the 19 patients recruited into the study, 18 were male. Thirteen and six patients were randomised to the active and control groups, respectively. Twelve and seven patients were in New York Heart Association (NYHA) functional class II and class III, respectively. The mean (SD) left ventricular ejection fraction of patients in the Sonovue and placebo groups was 30 (8)% and 24 (5)%, respectively (p = NS). Thirteen patients were known to have coronary artery disease and 10 had previous myocardial infarction. All patients received the full cumulative dose of 6 ml of the study agent in the predetermined sequence and were evaluable for safety.

Eleven patients in the active and five patients in the control group had pulmonary artery hypertension at baseline, defined as a systolic pulmonary artery pressure greater than 30 mm Hg or diastolic pulmonary artery pressure greater than 15 mm Hg. The changes in these parameters from baseline were short lasting and not significantly different following administration of either Sonovue or placebo. The peak changes from baseline in mean right atrial pressure, mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, systemic vascular resistance, and pulmonary vascular resistance are shown in fig 1. Baseline cardiac output was 5 (1) l/min. The changes in all these parameters from baseline were not significantly different between Sonovue and placebo groups. Oxygen saturation was maintained within normal limits in all patients throughout the period of monitoring. Of the 13 patients in the active group, one with a history of chronic renal impairment and hypertension experienced a transient worsening in renal function which improved to pre-study levels at one week. No patient had deterioration in symptoms or developed worsening signs of cardiac decompensation.

Myocardial perfusion was visualised in all patients who received Sonovue. Contrast activity was detectable in all 13 patients with the 2 ml dose and in 12 patients with the 4 ml dose. In one patient technical problems precluded image acquisition after the 4 ml dose, but myocardial perfusion was visualised after the 2 ml dose. As expected, no myocardial opacification was seen after the placebo injections in any patient. Intraobserver concordance for normal versus abnormal myocardial opacification was 92% ($\kappa = 0.78$).

This study represents the first evaluation of the safety of a second generation contrast agent, Sonovue, for echocardiography in this specific population of patients with severe left ventricular dysfunction and pulmonary artery hypertension. The administration of a cumulative dose of 6 ml of Sonovue as two bolus doses of 4 ml and 2 ml did not result in significant changes in clinical, ECG, laboratory or haemodynamic parameters compared to placebo. This was equally true for patients with and without pulmonary hypertension at baseline. The lack of any significant change in pulmonary arterial pressure, capillary wedge pressures, and oxygen saturation suggests that the administration of this agent is not associated with any worsening of left ventricular function. However, further data on the use of Sonovue in patients with impaired renal function needs to be collected before conclusions can be drawn about its safety in such patients. Bolus doses of 2 ml and 4 ml produced adequate myocardial opacification even in patients with pulmonary artery hypertension. This is contrary to previous suggestions that a high pulmonary vascular impedance in patients with elevated pulmonary arterial pressures may affect the pulmonary transit of contrast agents.

However, cardiac output, which is another important determinant of myocardial opacification, was normal in our group of patients.

In conclusion, Sonovue is a second generation echocardiographic contrast agent that does not appear to produce adverse cardiopulmonary haemodynamic effects in patients with left ventricular dysfunction and

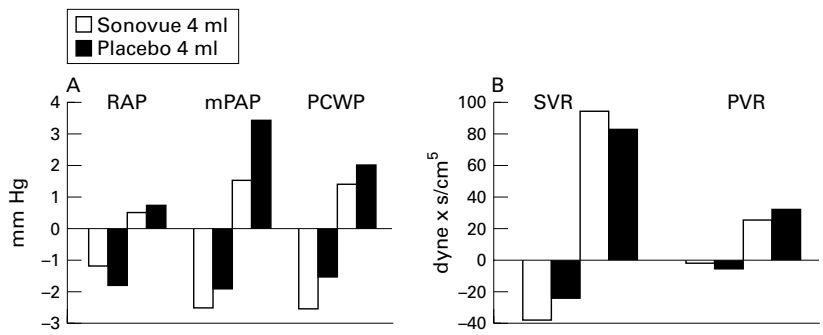

Figure 1 The mean deviation from baseline of the haemodynamic parameters (A) and systemic and pulmonary vascular resistance (B) measured after administration of Sonovue and placebo. RAP, right atrial pressure; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

pulmonary arterial hypertension. Furthermore, its efficacy is not compromised by the presence of pulmonary arterial hypertension.

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Intravenous amiodarone bolus immediately controls heart rate in patients with atrial fibrillation accompanied by severe congestive heart failure

Atrial fibrillation with a rapid ventricular rate often adds to the impaired haemodynamic status of patients with depressed left ventricular function.[1] Intravenous amiodarone has been shown to be effective in slowing the heart rate during atrial fibrillation.[2] For continuous infusion of the drug a central venous access is recommended.[3] We tested the hypothesis that amiodarone, given as a single bolus through a peripheral vein access, is effective and does not cause phlebitis.

Forty patients with documented heart disease and atrial fibrillation (ventricular heart rate ⩾ 135 beat/min) were included in the study. Mean (SD) age of the patients was 72 (12) years, 22 were men, and the mean ejection fraction was 38 (12)%. Cardiogenic shock was present in eight patients, 12 had pulmonary oedema, and 20 had exacerbated congestive heart failure. Mean systolic blood pressure was 111 (28) mm Hg. The onset of the tachyarrhythmia could be documented in 18 patients within 24 hours (15 (13) hours) before amiodarone treatment; in the remaining 22 patients the duration was unknown. Depending on clinical presentation and duration of the arrhythmia, patients were pretreated with digoxin, verapamil, or β blockers. All the patients were admitted to the coronary care unit and monitored during amiodarone treatment and for the following 24 hours.

Undiluted amiodarone was administered through a peripheral vein access within one minute, followed by a flush of 10 ml saline solution. All patients received 450 mg regardless of their weight. Heart rate was monitored continuously, and blood pressure and clinical status were documented every 10 minutes. During this time no other drugs with potential effects on heart rate were administered.

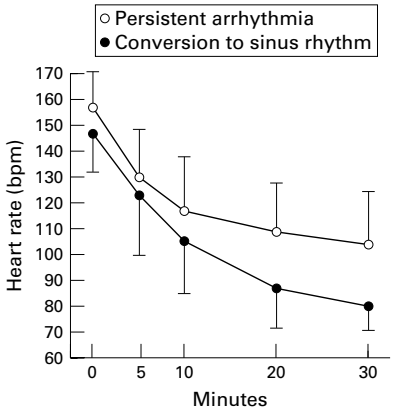

Figure 1 Ventricular heart rates in response to a bolus dose of intravenous amiodarone. The time of amiodarone administration was 0 minutes. Error bars = SD.

All values are expressed as mean (SD). Intraindividual changes of haemodynamics are compared with the paired Student's *t* test. Probability values of $p \leqslant 0.05$ were considered significant.

Normal sinus rhythm occurred in 13 patients within 30 minutes, and another eight patients converted during the following 24 hours. Heart rate reduction was smaller in the group with persistent arrhythmia as compared to the group who was in sinus rhythm after 30 minutes (fig 1). In both groups the reduction in heart rate was significant ($p < 0.0005$ for each group). After 30 minutes, treatment with conventional drugs was initiated if considered necessary.

In the group of patients who reverted to sinus rhythm there was a moderate increase in systolic blood pressure from 106 (17) mm Hg to 120 (20) mm Hg within 30 minutes after drug administration ($p < 0.05$). In the group with persistent arrhythmia there was no significant effect. No prolongation of the QTc interval, ventricular tachyarrhythmia, or inadvertent bradycardia could be observed. In two patients a decrease in systolic blood pressure from 115 to 80 mm Hg and from 130 to 100 mm Hg occurred and was reversible without specific treatment.

At the site of venous access no inflammatory reaction was documented until the needle was removed.

Thirty minutes after administration of amiodarone, the ensuing antiarrhythmic treatment was based on the individual clinical course. All patients were followed until discharge from hospital. During this period nine patients died because of pump failure 3.5 (4) days after amiodarone infusion; six of these patients initially presented with cardiogenic shock. One additional patient died from pulmonary embolism.

Intravenous amiodarone reduces the ventricular rate during atrial fibrillation by affecting the atrioventricular node. This was proven clinically in a series involving 38 patients with different atrial tachyarrhythmias in which intravenous amiodarone was used at a mean dose of 242 mg in the first hour followed by a continuous infusion.[4] The differences between doses used were remarkably high (60–1000 mg within the first hour). In this study the mean heart rate was reduced from 146 to 109 beat/min within one hour. We achieved a similar reduction in heart rate within 10 minutes with our more aggressive protocol (fig 1). In addition, 13 patients (32%) in our study population converted to normal sinus rhythm within 30 minutes compared to no patients in the series of Clemo and colleagues.[4]

Clinical use of intravenous amiodarone has been limited by reports of severe decreases in blood pressure. A 26% incidence of this complication has been reported and considered to be one of the most limiting side effects of the drug.[5] However, the patients treated had had ventricular tachyarrhythmias, and it is not fully clear whether the blood pressure response was a side effect of the drug or represented the natural course of severely ill patients. The latter appears to be more likely with respect to Clemo's report on 38 patients with atrial tachyarrhythmias, where no significant drop of blood pressure occurred with a similar infusion rate of amiodarone.[4]

In our study 10 patients died during their hospital stay. In view of the number of severely ill patients, the number of deaths as a result of pump failure may not be unexpected.

The obvious benefits of the dose regimen used were: (1) the rapid reduction of heart rate within minutes after amiodarone application; (2) the absence of contraindications in severely ill patients, even in the settings of low blood pressure and cardiogenic shock; and (3) the ease of application without the necessity of a central venous access. However, further studies involving a great number of patients are needed to demonstrate clearly the clinical benefit of lowering heart rate using intravenous amiodarone.

Our study was not a placebo controlled trial. The degree of heart rate reduction and the relatively high conversion rate to normal sinus rhythm within 30 minutes after drug administration could be attributed in part to the drugs previously administered and the short duration time of atrial fibrillation in some patients.

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