Side effects of amrinone therapy

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SUMMARY We gave intravenous amrinone to 40 patients in heart failure, and oral amrinone to 18 patients. Acute intravenous administration caused a significant reduction in mean blood pressure and this was severe enough to require correction by plasma infusion in five patients. Oral amrinone was accompanied by thrombocytopenia in 10 patients but no complications were associated with the low platelet count. Other potentially serious adverse effects were: abdominal pain (two patients), nausea and vomiting (three patients), jaundice (one patient), myositis (one patient), pulmonary infiltrates (two patients), and polyserositis (one patient). Less serious adverse effects observed were: splenomegaly, eosinophilia, fever, headache, reduced tear secretion, dry skin, and nail discoloration.

The potentially severe adverse reactions with amrinone need to be weighed carefully against its benefits in the treatment of heart failure.

Amrinone (Sterling-Winthrop) is a new bipyridine derivative, which increases cardiac output and reduces filling pressures in patients with cardiac failure.1 These improvements have been attributed by some workers1,2 to the drug having a predominant positive inotropic action, while others3 have suggested that, in congestive cardiac failure, the drug acts as a vasodilator with little or no inotropic effect. Its mode of action, however, may prove less important than its potential adverse effects4 in determining its final usefulness in the treatment of patients with heart failure.

Patients and methods

Forty-one patients with impaired left ventricular function (NYHA grade 2-4) were studied. Each was in chronic left ventricular failure despite conventional medication. During cardiac catheterisation 40 patients (mean age 47 years, range 19 to 71 years) received infusions of intravenous amrinone in less than two minutes on one or more occasions; 1·5 to 2·0 mg/kg on any single occasion and a maximum dose of 3·5 mg/kg in any 24 hours was given.

Seventeen patients (mean age 52 years, range 30 to 71 years) who had all increased their resting cardiac output after intravenous amrinone, were given oral amrinone and one additional patient, age 58 years, received oral treatment without prior intravenous treatment. As far as possible, each patient continued their previous antifailure therapy without alteration during treatment with amrinone. Two patients were given up to 600 mg of amrinone daily, but no other patient received more than 300 mg daily. Tear secretion was measured by Schirmer’s test in nine patients during oral amrinone therapy, and either before starting or after ending the drug treatment.

Steady state plasma amrinone concentrations were measured by high performance liquid chromatography5 at Sterling-Winthrop Laboratories. Blood was taken before dosing (trough level) and two hours after dosing (peak level). The mean plasma amrinone concentration was taken to be the antilog of the mean of log peak and log trough concentrations.

Results were analysed using the paired t test and linear regression as appropriate. A p value of less than 0·05 was taken to be significant. Results are expressed as mean ± SEM.

Written informed consent was obtained before the trial which had the approval of the St Thomas’s Hospital ethical committee.

Results

LESS SERIOUS SIDE EFFECTS

Hypotension

Blood pressure was reduced in 36 patients after intravenous amrinone administration and unaltered in four. Mean blood pressure fell significantly (p<0·01) from 81·9±2·2 mmHg to 67·7±2·4 mmHg seven minutes after the highest dose of amrinone. In five patients, three of whom had received a total of only 1·5 mg/kg, hypotension was severe enough to require

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correction by intravenous infusion of plasma. During oral amrinone treatment, one patient developed mild postural hypotension 30 to 60 minutes after each oral dose of the drug.

Thrombocytopenia
A reduction in platelet count was commonly seen in patients on oral amrinone. One patient with coronary artery disease died suddenly within 24 hours of starting oral amrinone treatment before the drug could have had any measurable effect on his platelet count. In each of the remaining 17 cases who received oral amrinone, the platelet count fell. In 10 patients, counts below 100 x 10^9/l were recorded and in four patients the platelet count fell below 50 x 10^9/l. In every case the platelet count returned to normal on withdrawing the drug and no bleeding problems were experienced.

Skin and nails
Two patients complained of dryness and flaking of the skin and one noticed bright yellow discoloration of her nails while receiving oral amrinone. These effects disappeared on withdrawing the drug.

Reduced tear secretion
The patient with the nail discoloration also complained of dry eyes and her tear secretion was found to be 2 mm/5 min in each eye (normal>10 mm/5 min). After stopping the drug her tear secretion was measured on three occasions and was always within the normal range in each eye. Similar measurements were subsequently made in a further eight patients. Tear secretion remained unchanged during amrinone treatment in one patient who had the lowest mean plasma amrinone concentration. In the remaining seven patients tear secretion was reduced while on the drug. Tear secretion in all nine patients was significantly (p<0.02) lower on amrinone (9.3±2.9 mm/5 min) compared with control (16.8±3.5 mm/5 min). The Fig shows the percentage reduction in tear secretion plotted against mean plasma amrinone concentration.

MORE SERIOUS SIDE EFFECTS
Sixteen patients received oral amrinone for over a week. Five experienced severe clinical events (probable adverse effects) while receiving the drug.

Case 1
A 67 year old woman with a six month history of progressive cardiac failure underwent right heart catheterisation on 5 August 1980 when intravenous amrinone (total 3.5 mg/kg) increased her resting cardiac index from 1.4 to 3.2 l/min per m^2. Two days later oral amrinone was added to her regular medica-

tion, daily dosages of which were frusemide 250 mg, metolazone 5 mg, spironolactone 100 mg, digoxin 0.25 mg, verapamil 240 mg, prazosin 30 mg, aminophylline suppository 360 mg, and insulin 30 units. Over three days the dose of amrinone was increased to 300 mg/24 hours. Platelet count fell from 277 x 10^9/l to 77 x 10^9/l in 20 days. On 4 September she complained of epigastric pain and was noted to have splenomegaly, a rub over the left lower ribs, and a neutrophilia (20.5 x 10^9/l). Her haemoglobin fell from 13-3 to 10-1 g/dl, ESR (Westergren) rose from 34 to 90 mm/hr, and platelet count increased to 162 x 10^9/l. The following day she collapsed with epigastric pain, nausea, hypotension, tachycardia, raised central venous pressure, and pericardial rub. Emergency pericardiocentesis produced 150 ml straw coloured fluid with clinical improvement. Microscopy and culture of the pericardial fluid was unhelpful and both rheumatoid factor and antinuclear antibody titres were normal. Next day she developed ascites without apparent worsening of heart failure and the day after that she complained of right pleural pain and had a pleural rub and small effusion. Next day she became distressed, vomited, and died. She had been apyrexial throughout. Permission for necropsy was refused.

Case 2
A 53 year old man remained in congestive cardiac failure after his third myocardial infarct in January 1981. On 1 June 1981 at cardiac catheterisation, intravenous amrinone (total 3.5 mg/kg) increased his resting cardiac index from 1.8 to 6.6 l/min per m^2. Oral amrinone (300 mg daily) was therefore added to
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[...]

his previous medication (frusemide 500 mg, spironolactone 200 mg, isosorbide dinitrate 40 mg, and prazosin 8 mg daily) on 17 June. His platelet count fell progressively from $177 \times 10^9/\text{l}$ to $30 \times 10^9/\text{l}$ in 21 days without evidence of bleeding. Amrinone was reduced to 200 mg daily and pirbuterol 30 mg daily was added. On 22 July platelet count had risen to $79 \times 10^9/\text{l}$ when he developed acute abdominal pain. A perforated duodenal ulcer was repaired surgically but postoperatively he had a fatal myocardial infarct. The cause of death was confirmed at necropsy.

Case 3

A 56 year old man had had aortic and mitral valve replacements (Starr-Edwards) for rheumatic valve disease in 1967. Postoperatively he remained in heart failure. During right heart catheterisation on 6 August 1981 resting cardiac index rose from 0.9 to 1.1 l/min per m$^2$ with intravenous amrinone (total 1.5 mg/kg). Thirteen days later oral amrinone (300 mg daily) was added to his previous medication, (amiodarone 600 mg, prazosin 20 mg, digoxin 0.25 mg, amiloride 10 mg, hydrochlorothiazide 100 mg, warfarin, lorazepam 1 mg daily). The following day he developed nausea and vomiting which persisted despite antiemetics (prochlorperazine 10 mg, ondansetron 8 mg, metoclopramide). Platelet count fell from $215 \times 10^9/\text{l}$ to $123 \times 10^9/\text{l}$ on 5 September 1981. On 2 September he complained of tenderness of the muscles of his back and limbs and myositis was diagnosed. His ESR (Westergren) had risen from 1 to 25 mm/hr, his serum creatine kinase was consistently raised, the isoenzymes coming entirely from skeletal muscle, and his serum contained skeletal muscle autoantibodies. Other autoantibodies including antinuclear antibody were negative. Serum taken before starting amrinone and stored did not contain skeletal muscle or other autoantibodies. Chest x-ray film on 2 September showed “fine interstitial shadowing in the lung fields...a drug reaction is a real possibility”. His weight had decreased by 5 kg. Amrinone was discontinued on 4 September and his vomiting disappeared within 24 hours, serum creatine kinase had returned to normal in five days, and muscle pain disappeared in 10 days. Pulmonary infiltrates cleared, and his platelet count returned to normal. He regained his lost weight and antiemetics were discontinued one month after stopping the amrinone. At the present time he is taking the drugs that he was on before he started amrinone.

Case 4

A man aged 54, who had undergone mitral valve replacement (Björk-Shiley) for rheumatic mitral valve disease in 1979, developed heart failure in January 1981. On 11 July 1981 he sustained a cardiac arrest from which he was successfully resuscitated. Mexiletine (600 mg daily) and amrinone (600 mg daily) were then added to his regular medication (bumetanide 15 mg, spironolactone 300 mg, warfarin, prazosin 28 mg, and aminophylline 450 mg daily). The amrinone was discontinued two days after his arrest. During right heart catheterisation four days later his resting cardiac index increased from 1.8 to 4.8 l/min per m$^2$ after intravenous amrinone (total 3.5 mg/kg). Oral amrinone (300 mg daily) was restarted on 18 July. Two days later he developed pruritis, pyrexia, and confusion. His mental state improved when the mexiletine and aminophylline were discontinued. On 24 July he developed generalised vasculitis (confirmed by skin biopsy) and the next day chlorpheniramine was added for his pruritis. The following day splenomegaly was detected. On 28 July ethacrynic acid (200 mg daily) was substituted for bumetanide. By 30 July his dyspnoea was worse and a chest x-ray film on 4 August showed “widespread nodular opacities throughout both lung fields...The appearances are suggestive of an intrapulmonary drug reaction”. The patient’s weight had fallen on amrinone and the x-ray appearances were not affected by increasing his diuretics. It thus seemed unlikely that the nodular opacities were the result of pulmonary oedema. Blood gas tensions were $P_O_2$, 49, $P_CO_2$, 28 mmHg. At this time he also developed clinical jaundice (conjugated bilirubin 37 $\mu$mol/l, total bilirubin 42 $\mu$mol/l), his ESR (Westergren) had risen from 14 to 85 mm/hr, and his platelet count had fallen from $233 \times 10^9/\text{l}$ to $105 \times 10^9/\text{l}$. Autoantibodies including antinuclear antibody were negative. On 7 August amrinone was stopped and three days later the jaundice had cleared, his rash was improving, his platelet count was rising, but his blood gas tensions were unaltered. A short course of prednisolone (initially 45 mg daily) was started on 17 August and three days later his blood gas tensions began to improve. On 21 August ethacrynic acid was changed to frusemide (500 mg daily) and two weeks later he was back to his usual self and off steroids. He remains alive and is taking frusemide, spironolactone, prazosin, and warfarin.

Case 5

A 50 year old woman, who had undergone mitral and aortic valve replacements (Starr-Edwards) in 1974 for rheumatic valve disease, developed heart failure in 1981. During right heart catheterisation on 17 August 1981 resting cardiac index increased from 2.2 to 4.3 l/min per m$^2$ after intravenous amrinone (total 3.5 mg/kg). Oral amrinone (300 mg daily) was added to her previous medication (digoxin 0.25 mg, frusemide 240 mg, amiloride 20 mg, warfarin, prazosin 6 mg, and folic acid 5 mg daily) on 2 September. After the first dose she complained of frontal headache and...
within 24 hours became pyrexial. Her platelet count fell from 156 x 10^9/l to 49 x 10^9/l on 9 September, and her ESR (Westergren) rose from 8 to 50 mm/hr. Autoantibodies including antinuclear antibody were negative. She also developed anorexia and nausea. On 9 September amrinone was discontinued. Her fever disappeared within 24 hours and her headaches and nausea within 48 hours. She had a mild transient eosinophilia in the week after discontinuation of amrinone. Platelet count and ESR returned to preamrinone levels by 29 September. One year later she remains alive though in cardiac failure.

Discussion

Hypotension after intravenous administration of amrinone has been previously reported by some workers though others using similar doses have not encountered this problem. Differences in the rate of administration of the drug and in the pretreatment filling pressures probably account for these disparities. In view of the known vasodilator properties of the drug this side effect is not unexpected. The postural hypotension and headaches each seen in one of our patients receiving oral amrinone may also be the result of vasodilatation.

Thrombocytopenia (aetiology unknown) has been described previously and was the commonest adverse reaction encountered in our patients on oral amrinone. Our incidence is higher than the 20% previously described; moreover, most of our patients were receiving a lower dose of amrinone than that previously thought to cause thrombocytopenia. This high incidence may be related to impaired drug metabolism and excretion in our patients, all of whom had some evidence of hepatic and renal dysfunction considered to be secondary to their cardiac failure. None of our patients in fact developed overt bleeding, but our experience underlines the need for careful monitoring of the platelet count with either withdrawal or reduction in amrinone dosage on development of thrombocytopenia. Withdrawal of the drug always led to rapid return of the platelet count to normal. (Full details of the haematological investigations related to oral amrinone treatment will be published elsewhere.)

Abdominal symptoms with oral amrinone have been described previously and two of our patients developed abdominal pain. In one the pain was caused by a perforated duodenal ulcer but in the other the cause was unknown. Three of our patients developed nausea and vomiting and one became jaundiced. Abnormalities of liver function have been described before in patients on amrinone. Pyrexia and a rise in the ESR have also been documented. Frank myositis has not previously been described with oral amrinone though myalgia has. Splenomegaly seen in three of our patients (two described in the case histories) has not been previously described; each of these patients had haematological abnormalities. Three of our patients on oral amrinone had pulmonary problems (not previously documented) and of the two with pulmonary infiltrates, one also had a vasculitis. The combination of vasculitis and pulmonary infiltration is a well recognised clinical syndrome. The vasculitis in our patient developed in relation to amrinone therapy though radiographic confirmation of the pulmonary infiltration was not obtained until after ethacrynic acid had also been added to the therapeutic regimen. The vasculitis disappeared once amrinone was discontinued and while the patient was still taking the ethacrynic acid, but the pulmonary infiltration took a further three weeks to clear by which time ethacrynic acid had also been discontinued and steroids started. There are no published reports of ethacrynic acid causing pulmonary infiltration. The occurrence of pulmonary infiltration in a second patient in association with myositis and clearly related to the start and finish of amrinone treatment make it likely that this drug was the cause of the pulmonary infiltration. In the third case with pulmonary complications, pleural rub and effusion, pericardial rub and effusion, splenomegaly, and a raised ESR occurred soon after starting amrinone.

The combination of problems experienced by some patients is suggestive of a drug induced immunological abnormality. Some of amrinone's side effects, however, may be explained by pharmacological rather than immunological mechanisms. The drug is a phosphodiesterase inhibitor and this class of drug may alter glandular secretion and visceral motility. Phosphodiesterase inhibitors increase gastric acid secretion in man which may account for the high incidence of abdominal pain and vomiting on amrinone. The reduced tear secretion, which appears to be dose related in our patients, may also be a phosphodiesterase inhibiting action on exocrine secretion.

In the patients who experienced the more serious adverse effects, we did not consider it ethical to rechallenge them with amrinone. The temporal relation of the clinical events to amrinone therapy, however, the similarities of the effects produced by the drug in different patients, and the previous published reports suggest to us that most if not all of the clinical events we describe were adverse reactions resulting from amrinone. We, therefore, agree with Dunkman and co-workers who suggest that "experience of frequent adverse responses suggests that early enthusiasm for amrinone in congestive heart failure must be tempered pending completion of properly controlled long-term trials".

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References


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