Beneficial effects of ACE inhibitors in severe mitral stenosis.

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Summary

There are several reports of beneficial effects of ACE inhibitors in both primary and secondary pulmonary hypertension. However the effect of ACE inhibitors in mitral stenosis is not documented. The authors report three patients with severe mitral stenosis in whom surgery was delayed. They had initial symptomatic improvement with diuretics and sodium restriction, but had recurrence of their symptoms while on treatment. Enalapril not only relieved their symptoms in particular exertional dyspnoea and haemoptysis but prevented recurrence and improved their effort tolerance without causing excessive fall of blood pressure or impairment of renal function.

Key words: Mitral stenosis, effort tolerance, ACE inhibitor.

Introduction

Rheumatic fever still remains as the major aetiological factor for mitral stenosis. Patients with pure mitral stenosis remain symptom-free for several years. Once they become symptomatic the disease process rapidly progresses leading to serious complications. Symptomatic patients with moderate to severe mitral stenosis (mitral valve orifice area less than 1 cm^2/m^2 of body surface area) warrants surgical treatment.[1] Medical treatment is required in those patients who cannot have surgery done for some reason or the other and in cases of delayed surgery. Restriction of sodium and diuretics give relief of symptoms of exertional dyspnoea and haemoptysis to most of the patients initially, without any improvement in their effort tolerance. However this symptomatic relief is often temporary and recurrence of symptom does occur while they are on treatment. Digitalis has no place in the treatment of patients with pure mitral stenosis who are in sinus rhythm.

Angiotensin converting enzyme (ACE) is a membrane-bound enzyme found in the luminal surface of the endothelial cells throughout the body, particularly in high concentrations in pulmonary capillary endothelial cells. However the role of Angiotensin II in the regulation of pulmonary vascular tone in normal subjects or in patients with primary or secondary pulmonary hypertension is not well established. There are several reports of beneficial effects of ACE

inhibition in various conditions of raised pulmonary arterial pressure and resistance. Teprotide was reported to reduce pulmonary artery pressure and resistance in man and thus improve pulmonary circulation.[2] Long term administration of captopril showed beneficial effects in patients with pulmonary hypertension secondary to schistosomiasis.[3] Escudero and his colleagues studied the haemodynamic changes with enalapril in pulmonary arterial hypertension in patients with congenital heart disease like atrial septal defect, ventricular septal defect and patent ductus arteriosus.[4] They observed that enalapril produced significant reduction in mean pulmonary artery pressure and total pulmonary resistance. At the end of their 16 weeks' period of study PaO_2 and exercise tolerance were significantly increased in these patients. Small dose enalapril was reported to give symptomatic relief and improvement of effort tolerance in a patient with primary pulmonary hypertension.[5] Captopril was also shown to produce positive response in primary pulmonary hypertension.[6] Prouse et. al. clearly demonstrated successful reduction of pulmonary arterial pressure with captopril in a case of long standing systemic sclerosis.[7] In patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease, captopril was also found to reduce significantly the mean pulmonary arterial pressure, mean pulmonary wedge pressure and total pulmonary resistance.[8]

We studied the effect of enalapril in three patients with severe mitral stenosis who had severe exertional dyspnoea and haemoptysis in whom conventional medical treatment with sodium restriction and diuretics failed to give satisfactory response and surgical treatment was delayed.

Case Reports

Case 1: A 47 year old Iban female labourer was referred to our unit for investigation of recurrent episodes of paroxysmal nocturnal dyspnoea. She could not recall any history suggestive of rheumatic fever or other major illness in the past. Her symptoms started one year prior to referral with several episodes of nocturnal dyspnoea for which she was admitted to the nearby hospital. She also gave the history of exertional dyspnoae and occasional streaks of blood in the sputum for about two years. She smoked about 20 cigarettes a day and drank locally brewed rice wine (tuak) in moderate amounts regularly.

She was treated by the referring physician with frusemide and supplementary potassium and vitamin B complex on the provisional diagnosis of alcoholic cardiomyopathy leading to heart failure.

On examination she was comfortable at rest. Pulse 78 per minute and in sinus rhythm. All pulses felt equal and normal. Blood pressure was recorded 110/70 mm of Hg. Auscultation of the heart revealed the presence of moderate to severe mitral stenosis with pulmonary hypertension. X-Ray chest showed mitral heart and ECG P-mitrale. A 2-D echocardiogram confirmed moderate to severe mitral stenosis with a mitral valve area of 0.96 cm^2.

She was advised to have surgery done fairly soon. But after discussion with the family she refused to have surgical treatment and requested for medical management. In view of the recurrence of symptoms despite being on frusemide and sodium restriction for 12 months she was advised to take enalapril 2.5 mg daily in addition. After one week enalapril was increased to 5 mgm daily. She was reviewed at regular intervals and after a period of four weeks frusemide and potassium supplements were withdrawn.

When she was reassessed after six months she did not have any more episodes of paroxysmal nocturnal dyspnoae. Moreover her exercise tolerance had improved and she was able to go back to work as a labourer.

Case 2: A 30 year old Sri Lankan housewife was admitted to the hospital with acute episode of shortness of breath. She was not sure about the possible rheumatic fever in the past nor of any other serious illness. She had two uneventful pregnancies ending in normal full term delivery. She was nonsmoker nor did she drink alcohol. She had never been on contraceptive pills. She gave a history of increasing difficulty in breathing on exertion for about 18 months prior to admission to the hospital, and recently she found routine household work very tiresome. She also gave a history of occasional haemoptysis.

At the time of admission she was very dyspnoeic and had clinical evidence of acute pulmonary oedema secondary to severe mitral stenosis. X-Ray chest showed a mitral heart with evidence of pulmonary oedema. ECG showed sinus tachycardia with p-mitrale. The diagnosis was confirmed by a 2D Echo and the mitral valve area was 0.9 cm^2.

She made remarkable improvement with frusemide and sodium restriction. However she remained in Class II NYHA functional classification after a week of treatment. She was then prescribed enalapril 2.5 mg daily which was later increased to 5 mgm daily. Her effort tolerance improved remarkably in about two weeks' time. Therefore she was advised to stop frusemide and potassium supplements. She remained symptom-free until six months later when she had a mitral valvotomy.

Case 3: A 33 year old Malay lady was admitted to the medical ward in March 1984 with severe shortness of breath and haemoptysis. Clinical examination revealed acute pulmonary oedema secondary to moderate to severe mitral stenosis. ECG showed sinus rhythm with P-mitrale. X-Ray chest showed evidence of mitralisation of the heart with pulmonary oedema. 2-D Echo confirmed severe mitral stenosis with a mitral valve area of 0.97 cm^2.

Going back to her medical records we found that she was referred to the medical unit in April 1977 when she was found to have a murmur during a routine antenatal check up. She was working as a domestic help and had a normal pregnancy prior to the referral. The physician confirmed the presence of moderate mitral stenosis and decided to manage her medically. She had an uneventful second pregnancy ending in a normal delivery. She was then advised to have mitral valvotomy to which she disagreed. She was followed up regularly in the physician's clinic and remained symptom free.

She was treated with frusemide and potassium supplements and made a good recovery. She was reviewed regularly in the clinic but had several episodes of nocturnal dyspnoea and recurrent haemoptysis. Moreover, she always remained in NYHA functional class 2. She was also digitalised for persistent sinus tachycardia but it had to be stopped as patient did not tolerate it.

She was admitted again in February 1986 with severe shortness of breath and haemoptysis. At that time she was in NYHA functional class 4. She was treated with bed rest, sodium restriction and frusemide. She was also given captopril 25 mg twice daily to which she responded very well. She was discharged on frusemide 40 mgm daily, potassium supplements and captopril 25 mgm twice daily. In August 1986 she had another episode of haemoptysis and nocturnal dyspnoea. Captopril was stopped and enalapril 2.5 mgm was prescribed instead. It was increased to 5 mgm daily two weeks later. She remained absolutely symptom-free and her effort tolerance has improved from NHYA class 4 to class 1.

Eventhough she was advised surgery on several occasions she requested for postponement. She remained very well without any episode of nocturnal dyspnoea and haemoptysis for about 30 months when she had cardiac surgery.

Discussion

All the three patients we presented had significant mitral stenosis without involvement of any other valves or other illness. Unlike our other patients with mitral stenosis surgery was delayed in them due to various non-medical reasons. The presenting symptoms in all the three patients were exertional dyspnoea, paroxysms of nocturnal dyspnoea and haemoptysis.

In view of the delay in surgery they all had medical treatment with sodium restriction and diuretics giving initial symptomatic improvement. However their effort tolerance did not improve and they had recurrence of nocturnal dyspnoea and haemoptysis while on treatment.

Pulmonary hypertension in patients with mitral stenosis results from passive backward transmission of elevated left atrial pressure, pulmonary arteriolar vasoconstriction, and organic obliterative changes in the pulmonary vascular bed.[9] However there is also some evidence of reversible pulmonary vasoconstriction.[10] In patients with mild to moderate mitral stenosis pulmonary arterial pressure may be normal at rest and only elevated during exercise but in patients with severe mitral stenosis pulmonary arterial pressure is elevated even at rest and sometimes extreme elevation even exceeding the systemic pressure can occur during exercise.

Haemoptysis complicating mitral stenosis could be due to rupture of thin-walled dilated bronchial veins, blood stained sputum associated with episodes of nocturnal dyspnoea, pink frothy sputum of pulmonary oedema due to rupture of alveolar capillaries, or due to pulmonary infarction.[11]

Enalapril gave significant improvement of their symptoms and prevented their recurrence in particular episodes of haemoptysis and nocturnal dyspnoea. The most impressive beneficial effect of enalapril treatment in all the three patients is the remarkable improvement in their exercise tolerance. In two out of three patients we could completely withdraw diuretics after a short period without relapse of their symptoms.

The 2D echocardiographic indices were unchanged after six weeks of treatment in all the three patients. One fear, in theory, is that the vasodilator effect of enalapril may reduce blood pressure excessively and cardiac output might not increase sufficiently due to the stenotic valve lesion resulting in symptomatic hypotension and angina pectoris. This was not seen in any of our patients. Another concern is impairment of renal function. There were no changes in the urine output, plasma urea and creatinin levels.

None of these patients had any invasive investigation or haemodynamic assessment before commencing treatment or afterwards. Nevertheless we are very impressed by the remarkable symptomatic and clinical improvement they had with the ACE inhibitor.

Conclusion

Patients with significant mitral stenosis in whom surgery is delayed medical treatment is indicated. While sodium restriction and diuretics give symptomatic improvement, the symptoms may recur while on treatment and their effort tolerance does not usually improve. In all the three cases we

presented enalapril not only gave remarkable improvement of their symptoms and effort tolerance, but also prevented the recurrence of episodes of pulmonary oedema and haemoptysis.

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