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Sildenafil in acute pulmonary embolism: case report and review of literature

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We discuss the use of sildenafil in a patient who sustained a massive pulmonary embolism (PE). She remained haemodynamically unstable after thrombolysis, and needed large doses of inotropic support. She was treated with oral sildenafil at a dose of 75 mg three times a day which enabled weaning from inotropic support and clinical improvement.

Keywords: *phosphodiesterase inhibitors; sildenafil; pulmonary embolism; intensive care*

Introduction

Acute pulmonary embolism (PE) is a common disease with an overall incidence of about 60-70 cases/100,000 per year.[1] Massive PE is associated with a mortality of about 20-30%. The main cause of death is acute right heart failure and circulatory shock secondary to pulmonary vasoconstriction. Conventional treatment is mostly aimed at removing the mechanical obstruction by reducing clot size with thrombolysis, heparin, or surgery. More recently, the relevance of right heart failure had been appreciated and studies have focussed on treating the pulmonary vasoconstriction and right heart failure which accompany acute heart failure.[2,3] One of the treatments which has been studied in this context is sildenafil.

Case report

A 67-year-old woman presented to hospital with a history of sudden onset of shortness of breath, chest pain and loss of consciousness lasting a few seconds. On examination, she was tachypnoeic, with a respiratory rate of 22 breaths per minute, blood pressure (BP) 131/75 mm Hg, and heart rate of 130 beats per minute. On auscultation, she had a right pleural rub. Blood gases on air showed that she was in type one respiratory failure, with a pH of 7.52, pCO_2 4.28 kPa, pO_2 6.56 kPa, BE +2.9 mmol/L, HCO_3^- 27.4 mmol/L and lactate 1.8 mmol/L. ECG showed sinus tachycardia but no other abnormalities. She had a past medical history of hypothyroidism, cervical spine surgery for osteoarthritis resulting in a residual right lower limb neurological deficit, and peripheral vascular disease.

A clinical diagnosis of PE was made, confirmed with a computerised tomography pulmonary angiogram (CTPA) showing multiple bilateral vascular filling defects consistent with pulmonary emboli. She was admitted to a high-care medical ward and started on enoxaparin 1.5 mg/kg. Twelve hours later, she became more short of breath and was severely hypoxic. Oximetry showed an oxyhaemoglobin saturation of 82% on 28% oxygen. She was transferred to a coronary care unit (CCU) and given alteplase, 50 mg over 10 minutes, to attempt thrombolysis, as per hospital protocol. An IV heparin infusion was then started. She initially improved, but one hour later became severely haemodynamically unstable, BP was unrecordable, she was tachycardic, tachypnoeic and hypoxic. The ECG showed new T-wave inversion in the lateral chest leads and right ventricular strain. She was transferred to ICU for further management.

On ICU, cardiac output monitoring using Lithium-determined cardiac output measurement (LiDCO) showed a low cardiac output of 2 L/min, a low stroke volume of 25 mL/beat, and a high SVR of 2000 dynes·s/cm^5. Arterial blood gases showed pH 7.48, pO_2 11.8 kPa, and pCO_2 4.46 kPa on 28% oxygen. An echocardiogram showed severe pulmonary hypertension, with an estimated right ventricular (RV) systolic pressure of 67-72 mm Hg (normal 15-20 mm Hg) and right atrial pressure of 15-20 mm Hg (normal 15-30 mm Hg), moderately impaired systolic function, global hypokinesia with septal flattening suggestive of RV pressure/volume overload, mild RV hypertrophy and moderate tricuspid regurgitation. A repeat CTPA was not significantly different from the pre-thrombolysis CTPA. A dobutamine infusion was started. She required high doses (12 µg/kg/min) to maintain a systolic BP higher than 80 mm Hg, and an adrenaline infusion (1 µg/kg/min) was added.

She failed to improve in the next 24 hours. She still needed high doses of inotropic support to maintain a systolic BP >90 mm Hg, and cardiac function did not improve (cardiac output 1.7 L/min, stroke volume 24 mL/beat and SVR 2000 dynes·sec/cm^5). Further management was discussed with the local and specialist cardiac unit cardiologists. No surgical intervention was deemed possible as the thrombi were too distal. It was decided to start sildenafil at 50 mg eight-hourly; there were no complications after the first two doses and the dose was then increased to 75 mg eight-hourly. She became more haemodynamically stable and cardiac function improved. Adrenaline was weaned off and the dobutamine infusion reduced to 5 µg/kg/hr within 12 hours. She remained stable, and dobutamine was weaned off slowly over the next four days. Cardiac function improved, with a cardiac output of 3.3 L/min, SV 34 mL/beat, and SVR 1400 dynes·sec/cm^5.

The patient spent a total of seven days on the ICU. She was

then transferred to the CCU on a continuous IV heparin infusion, aiming to maintain an activated partial prothrombin ratio of 2.5-3; it was planned to start warfarin once the patient was stable. She was discharged from hospital eight days later. She still had shortness of breath on moderate exertion and her PaO_2 on air on day of discharge was 8.38 kPa. Sildenafil was continued at 80 mg tds. The patient is still followed up with respect to right-sided heart failure.

Discussion

The importance of pulmonary vasoconstriction to the patient's condition in acute PE has been recognised for several years. The size of the clot does not always correlate with the degree of haemodynamic instability nor with the clinical features. Many cases of PE are first diagnosed at autopsy, and are completely asymptomatic. This has led to studies on the role of various pulmonary vasodilators in acute PE. Several drugs have been investigated, including sildenafil, inhaled nitric oxide (NO), prostacyclin, ketanserin, hydralazine, amrinone, bosentin, isoproterenol, nitroglycerine, nitroprusside, and captopril.[3]

Sildenafil is licensed in the US, Europe, and many other countries as Revatio®, for use in chronic pulmonary arterial hypertension. It is also commonly used in the management of pulmonary hypertension in neonates. It acts as a selective, competitive inhibitor of cyclic GMP (cGMP)-specific phosphodiesterase type 5 (PDE-5), the enzyme responsible for degradation of cGMP. This in turn mediates NO-mediated vasodilatation. The effect is short-lived, as cGMP is rapidly degraded by PDE-5. PDE-5 is predominantly present in the smooth muscle of lung tissue and corpus cavernosum. In the lung, it increases the concentration of cGMP in vascular smooth muscle cells, leading to relaxation of the arterial wall. This leads to a decreased pulmonary arterial resistance and increased mean pulmonary arterial pressure. This in turn reduces the workload of the right ventricle of the heart and improves symptoms of right-sided heart failure without causing systemic hypotension.[4] The beneficial effect of sildenafil in acute PE is probably related to protection from impaired vascular NO bioavailability which seems to be present in pulmonary hypertension secondary to acute PE. However, this effect is not improved with L-arginine, which is the substrate for NO synthesis, or another NO-donor compound.[5,6] This suggests that it is sildenafil alone which is producing maximum benefit in the NO-cGMP pathway.[7]

We found only one clinical case report and few reports of experimental studies of the use of sildenafil in the management of massive acute PE.[8-10] Garnière *et al* describe the use of sildenafil in a patient who had persistent respiratory failure after thrombolytic therapy. The patient improved dramatically after being started on sildenafil 50 mg tds.[8] In animal studies of induced PE, Dias *et al* showed that IV sildenafil decreases mean pulmonary arterial pressure and pulmonary ventricular resistance index without any significant effect on MAP and systemic vascular resistance index. The effect was sustained with sildenafil infusion.[9] Our patient had severe right heart failure leading to haemodynamic instability which had got worse despite being treated with thrombolysis. She only started to improve after the sildenafil was started, and she was then weaned off all inotropic support within four days.

The optimal dose of sildenafil in acute PE is not known. The approved dose for chronic pulmonary arterial hypertension is 20 mg eight-hourly. At this dose, sildenafil increases exercise capacity, improves WHO functional class of heart failure, and improves haemodynamic parameters, with minimal effect on systemic BP.[4] We started our patient on 50 mg eight-hourly and increased the dose to 75 mg eight-hourly. The patient did not have any side-effects. Her cardiac function improved, and she was weaned off inotropes after sildenafil was started. The post-thrombolysis CTPA was similar to the initial CTPA, indicating that the amount of mechanical obstruction caused by the clots had remained the same. Thus, it seems likely to us that it was the sildenafil which lead to a clinical improvement in the patient's condition.

In conclusion, sildenafil is easy to administer, cheap, and has minimal side-effects. Most reports point towards a beneficial effect in acute PE. However, more clinical studies are needed to investigate the optimum dose and safety profile in acute PE. Thus, we suggest that sildenafil can be recommended for use in acute PE in cases where the patient is still haemodynamically unstable after conventional treatment.

Conflict of interest – None declared.

References

1. **British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group.** British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax* 2003;58:470-84.
2. **Stratmann G, Gregory GA.** Neurogenic and humoral vasoconstriction in acute pulmonary embolism. *Anesth Analg* 2003;97:341-54.
3. **Smulders YM.** Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: the pivotal role of pulmonary vasoconstriction. *Cardiovasc Res* 2000;40:23-33.
4. **Croom KF, Curran MP.** Sildenafil – A review of its use in pulmonary arterial hypertension. *Drugs* 2008;68:383-97.
5. **Souza-Silva AR, Dias-Junior CA, Uzuelli JA *et al*.** Hemodynamic effects of combined sildenafil and L-arginine during acute pulmonary embolism-induced pulmonary hypertension. *Eur J Pharm* 2005;524:126-31.
6. **Dias-Junior CA, Tanus-Santos JE.** Haemodynamic effects of sildenafil interaction with a nitric oxide donor compound in a dog model of acute pulmonary embolism. *Life Sci* 2006;79:469-74.
7. **Dias-Junior CA.** The use of sildenafil in the therapy of massive pulmonary embolism. *Intensive Care Med* 2006;32:1284.
8. **Ganière V, Feihl F, Tagan D.** Dramatic beneficial effects of sildenafil in recurrent massive PE. *Intensive Care Med* 2006;32:452-54.
9. **Dias-Junior CA, Tadeu FV, Moreno H *et al*.** Sildenafil selectively inhibits PE-induced pulmonary hypertension. *Pulm Pharm Therap* 2005;18: 181-86.
10. **Dias-Junior CA, Souza-Costa DC, Zerbini T *et al*.** The effect of sildenafil on pulmonary embolism-induced oxidative stress and pulmonary hypertension. *Anesth Anal* 2005;101:115-20.

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