Case Report

Treatment of pulmonary hypertension in the general adult intensive care unit: a role for oral sildenafil?

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Use of inhaled nitric oxide for treatment of pulmonary hypertension in adult critical illness is limited by its mode of delivery and high costs, prompting evaluation of alternative therapies. We report the use of oral sildenafil in a patient with severe secondary pulmonary hypertension and right ventricular dysfunction. Following reduction in mean pulmonary artery pressure and pulmonary vascular resistance with inhaled nitric oxide, crossover to sildenafil therapy maintained control of pulmonary hypertension, facilitating discontinuation of respiratory and cardiovascular organ support. The relative pulmonary vascular specificity of oral sildenafil, and its low cost, makes it an attractive therapeutic alternative to inhaled nitric oxide, and warrants further study.

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Inhaled nitric oxide (INO) is widely used for critically ill adult patients with acute respiratory distress syndrome (ARDS) and severe hypoxaemia, and for patients with right-sided cardiac failure and pulmonary hypertension.1 Despite the absence of clinical trial data showing that INO confers a survival advantage in such patients, several studies have demonstrated improved oxygenation in ARDS2–4 and reduction in pulmonary artery pressure without systemic effects in patients with pulmonary hypertension.5,6 These findings are attributed to highly selective pulmonary vasodilatation preferentially distributed to ventilated lung units, thereby improving ventilation–perfusion matching and arterial oxygenation.

The cost of INO has recently increased markedly. In addition, INO therapy has other limitations. It requires continuous inhalation via a closed breathing circuit, rendering it unsuitable for non-ventilated patients, and its efficacy may be limited in certain patients who demonstrate tachyphyaxis.7 Taking these factors into consideration, we propose that other pulmonary vasodilators require evaluation in the critically ill.

We report the safe oral administration of the pulmonary vasodilator sildenafil, a type 5 phosphodiesterase (PDE5) inhibitor, to treat a critically ill patient with severe right ventricular dysfunction related to secondary pulmonary hypertension. To our knowledge, this is the first such report of the use of oral sildenafil to manage severe pulmonary hypertension in the general adult intensive care unit (ICU).

Case report

A 73-year-old morbidly obese (BMI 35 kg m−2) female patient presented to local hospital with acute renal failure, presumed secondary to tubulo-interstitial nephritis following a course of cephalaxin. She had long-standing type 2 diabetes mellitus and hypothyroidism for which she was taking insulin, metformin and thyroxine. Initial efforts at management were unsuccessful as she developed a progressive metabolic acidosis, culminating in respiratory arrest necessitating emergency tracheal intubation and mechanical ventilation. She was transferred to our general adult ICU.

On arrival, she was hypotensive (mean arterial pressure [MAP] 43 mm Hg) and oliguric. Laboratory investigations revealed urea 41.5 mmol litre−1, creatinine 738 μmol litre−1 and potassium 5.7 mmol litre−1. Arterial blood gas analysis showed \( P_{\text{aO}_2} \) 8.7 kPa (\( F_{\text{IO}_2} \) 0.6), \( P_{\text{aCO}_2} \) 4.6 kPa, pH 7.23 and base excess −12.3 mEq litre−1. Chest radiography showed clear lung fields. Oesophageal Doppler flowmetry demonstrated a low cardiac output state (cardiac index
1.8 litre min$^{-1}$ m$^{-2}$) with stroke volume unresponsive to colloid challenge. An epinephrine infusion was commenced, increasing cardiac index to 3 litre min$^{-1}$ m$^{-2}$ and continuous veno-venous haemofiltration was initiated. It was noted that her central venous pressure was increased (30 mm Hg), with a waveform characteristic of tricuspid regurgitation. Transthoracic echocardiography confirmed right ventricular systolic dysfunction, while left ventricular dimensions and function appeared normal, albeit supported by epinephrine. There was no biochemical or electrocardiographic evidence of right ventricular infarction.

Additional history obtained from the patient’s husband revealed that she was a heavy smoker (150 pack–year history) with poor exercise tolerance, snored loudly and suffered from daytime somnolence. Therefore we speculated that her right ventricular dysfunction was secondary to long-standing pulmonary hypertension, associated with chronic obstructive pulmonary disease and sleep-disordered breathing, which was exacerbated by the acute illness.

A pulmonary artery catheter was inserted to monitor pulmonary pressures continually. Mean pulmonary artery pressure (mPAP) (46 mm Hg) and pulmonary vascular resistance (PVR) (387 dyn s cm$^{-5}$) were raised, confirming the diagnosis of pulmonary hypertension. A titrated trial of INO was instituted with the aim of decreasing mPAP and right ventricular afterload, thereby increasing cardiac output. Within 30 min, INO reduced mPAP to 29 mm Hg (Fig. 1) and PVR to 185 dyn s cm$^{-5}$, and increased cardiac index to 3.8 litre min$^{-1}$ m$^{-2}$. These effects were observed at an INO concentration of 5 ppm, with no concurrent changes in epinephrine dose. Continuous INO therapy allowed withdrawal of epinephrine over 24 h, with maintenance of cardiac index at 2.5 litre min$^{-1}$ m$^{-2}$.

Given the likelihood that continuous pulmonary vasodilatation would be required to facilitate weaning from mechanical ventilation, we commenced oral sildenafil 25 mg every 8 h with the aim of withdrawing INO treatment.

Within 15 min of sildenafil administration, we observed a transient decrease in MAP from 67 to 54 mm Hg, but no deterioration in arterial oxygen saturation. INO therapy was immediately discontinued, following which haemodynamic stability was rapidly restored. A rebound increase in mPAP was observed immediately after INO cessation (up to 59 mm Hg); this was short-lived as mPAP decreased once sildenafil’s therapeutic actions were established, approximately 7 h after administration of the first dose (Fig. 1). In view of the systemic hypotension described above, the dose of sildenafil was reduced to 12.5 mg every 8 h for 24 h, increasing to 25 mg thereafter.

Sildenafil treatment induced a sustained reduction in pulmonary pressures (Fig. 1), with a maximal fall in mPAP to 28 mm Hg (PVR 112 dyn s cm$^{-5}$), effects equivalent to those found after INO therapy. Importantly, there were no further adverse systemic effects throughout the subsequent course of sildenafil treatment; systemic arterial pressure, cardiac index and mixed venous oxygen saturations remained stable, and there was no requirement for reintroduction of inotropic therapy. The patient’s condition continued to improve, renal function recovered and artificial ventilation was discontinued 18 days after ICU admission. Sildenafil was discontinued prior to the patient’s discharge from the ICU. There were no adverse effects following sildenafil withdrawal.

**Discussion**

This case report illustrates the successful management of right ventricular dysfunction related to secondary pulmonary hypertension following crossover of INO to the pulmonary vasodilator sildenafil. Given that the patient’s pulmonary hypertension was, in part, nitric oxide reversible, we predicted that sildenafil, a PDE5 inhibitor, would produce similar beneficial haemodynamic effects to INO. Indeed, the data show a comparable decrease in mPAP (Fig. 1) and PVR following sildenafil therapy. Furthermore, sildenafil’s oral route of administration allowed ongoing treatment after discontinuing artificial ventilation. Moreover, this case highlights the sensitivity of the right ventricle to alterations in its afterload, which may be more marked than those seen in the left ventricle. In our patient, initial pulmonary vasodilator therapy with INO allowed withdrawal of epinephrine and establishment of cardiovascular stability. Despite the growing literature concerning sildenafil’s pulmonary vasodilatory properties, this is the first description of oral sildenafil therapy in a critically ill patient with severe pulmonary hypertension in the general adult ICU. This case emphasizes that sildenafil can be a safe, simply delivered and effective alternative pulmonary vasodilator to INO, and therefore has important clinical implications for the general adult intensivist.

Pulmonary hypertension is typified by remodelling of the pulmonary vasculature resulting in vasoconstriction and
progressively increasing right ventricular afterload, ultimately leading to right-sided cardiac failure and death.\textsuperscript{8} Intensiivists frequently encounter patients with pulmonary hypertension, either in the context of acute lung injury/ARDS or related to pre-existing primary or secondary pulmonary vascular disease.\textsuperscript{9} The presence of pulmonary hypertension in critically ill patients is a poor prognostic indicator\textsuperscript{2} and is associated with an increased mortality in patients with ARDS.\textsuperscript{10} Therefore therapeutic strategies aimed at reducing pulmonary hypertension in critical illness have a rational basis. Given that the right ventricle works with a low-pressure circuit and has poor contractile reserve, the cornerstone of treatment is to reduce right ventricular afterload by selective pulmonary vasodilatation.

The current approach of using INO as a pulmonary vasodilator is based on its activation of guanylate cyclase, which catalyses conversion of guanosine-5-triphosphate to cyclic guanosine monophosphate (cGMP).\textsuperscript{11} In turn, cGMP activates several signalling pathways whose net effect is vascular smooth muscle relaxation. However, its cost implications, together with its necessary administration via continuous inhalation, have prompted a search for alternatives. In addition, rebound pulmonary hypertension may occur following withdrawal of INO therapy,\textsuperscript{12} as observed in our patient (Fig. 1). This phenomenon may prevent discontinuation of INO, necessitating the introduction of an alternative pulmonary vasodilator. The other class of pulmonary vasodilators, the prostacyclin analogues, also have several limitations, notably increased ventilation-perfusion mismatching and worsening oxygenation in some patients.\textsuperscript{13} Intravenous epoprostenol may cause hypotension (related to its non-selective vasodilator response) and tachyphylaxis, while inhaled iloprost requires up to 12 doses per day.\textsuperscript{14}

Sildenafil displays several properties that make it an attractive pulmonary vasodilator. It is a selective inhibitor of cGMP-specific PDE5, the enzyme responsible for degradation of cGMP.\textsuperscript{15} Thus it enhances the effects of cGMP, leading to vascular smooth muscle relaxation. PDE5 is abundantly expressed in the pulmonary vasculature and corpus cavernosum,\textsuperscript{16} and sildenafil is about 4000-fold more selective for type 5 than for type 3 phosphodiesterase, which is involved in cardiac contractility.\textsuperscript{17} Hence, sildenafil exerts its actions on the pulmonary circulation without any direct inotropic effects. Its availability as an enteral preparation allows its use in ventilated and non-ventilated patients, and its potential for continued administration following discharge from intensive care. It has a half-life of about 4 h, it is rapidly absorbed via the stomach, and plasma levels peak within 30–120 min after ingestion.\textsuperscript{17,18} Importantly, data from large clinical studies of sildenafil in the treatment of patients with erectile dysfunction reveal an excellent cardiovascular safety profile.\textsuperscript{18,19} In healthy volunteers, sildenafil may produce a modest decrease in blood pressure, but no consistent orthostatic effects and no clinically relevant electrocardiographic changes.\textsuperscript{17–19} However, in patients receiving nitrates, sildenafil can produce severe hypotension.\textsuperscript{19} We observed a short-lived reduction in MAP during crossover to sildenafil, which resolved following INO withdrawal. This adverse systemic effect cannot be easily explained, but suggests that either the combination of sildenafil and INO acted synergistically to produce systemic vasodilatation and hypotension, or that the initial dose of sildenafil was too high. Indeed, systemic vasodilatation has also been described following concurrent administration of INO and intravenous sildenafil to infants following cardiac surgery,\textsuperscript{20} but the underlying mechanism was unclear. There are no prior reports of adverse systemic effects in adult patients receiving combined INO and oral sildenafil therapy for pulmonary hypertension.\textsuperscript{13,21} Notably, a 2-week course of 25 mg sildenafil every 8 h costs £205 (www.emims.net, October 2004), while the equivalent duration of INO\textsuperscript{max} therapy (the licensed INO product) costs £3553.

Mounting evidence suggests that sildenafil is an effective therapy for pulmonary hypertension. Sildenafil selectively reduced pulmonary artery pressures in animal models of pulmonary hypertension, without adverse systemic effects, when administered orally,\textsuperscript{22,23} intravenously\textsuperscript{24} or by nebulization.\textsuperscript{25} In humans, although there is emerging paediatric critical care data addressing sildenafil’s role as a pulmonary vasodilator,\textsuperscript{20,26} evidence supporting its use in general adult critical care is absent. Most studies performed to date have examined the effects of sildenafil in idiopathic pulmonary arterial hypertension. In the only randomized placebo-controlled double-blind crossover study of sildenafil in 22 patients with idiopathic pulmonary arterial hypertension, sildenafil increased cardiac index and improved symptoms and exercise tolerance.\textsuperscript{27} Other small uncontrolled studies using sildenafil in idiopathic pulmonary arterial hypertension showed reduced PVR and improved measures of cardiovascular performance.\textsuperscript{28,29} In secondary pulmonary hypertension, investigations of sildenafil’s actions have been restricted to small observational studies and case reports, albeit all demonstrating beneficial outcomes with regard to pulmonary haemodynamics.\textsuperscript{30,31} In a randomized open-label trial in 16 patients with pulmonary hypertension secondary to lung fibrosis, oral sildenafil caused preferential pulmonary vasodilation and improved oxygenation compared with INO and intravenous prostacyclin.\textsuperscript{32} The same group of investigators also reported similar benefits in 30 patients with severe idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, without adverse systemic effects.\textsuperscript{13} More recently, oral sildenafil safely reduced pulmonary hypertension in adults after cardiac surgery.\textsuperscript{33}

Taken together, the existing data support the concept that sildenafil is a relatively selective pulmonary vasodilator. This case shows good efficacy for sildenafil in terms of reducing pulmonary artery pressure, and suggests that oral sildenafil may be a useful therapy in the management of pulmonary hypertension in adult critical illness. Caution should be taken when using sildenafil and INO in
combination to avoid systemic hypotension. Further studies are warranted for accurate determination of the systemic haemodynamic effects and pulmonary selectivity of sildenafil in the critically ill.

References