Peer reviewed article

Inhaled nitric oxide for ARDS due to sickle cell disease

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Summary

A 36-year-old male with a known history of sickle cell disease (SCD) and acute chest syndrome (ACS) was treated in our hospital. Gas exchange deteriorated and the patient was transferred to our intensive care unit (ICU). Low dose inhaled nitric oxide (iNO) during pressure controlled mechanical ventilation (pcMV) induced a clinically relevant increase in arterial oxygenation. The patient was weaned from pcMV after five days and discharged home 14 days later. ACS evolving to acute respiratory distress syndrome (ARDS) is a rare but severe complication. In ACS iNO should be considered a beneficial therapeutic option.

Key words: inhaled nitric oxide; acute respiratory distress syndrome; sickle cell disease; oxygenation; gas exchange

Introduction

Sickle cell disease (SCD) is a hereditary disorder of the haemoglobin chain caused by replacement of glutamin by valin. Its reach is worldwide, affecting predominantly people of equatorial African descent, although persons of Mediterranean, Indian and Middle Eastern lineage may also be affected. The primary features of SCD include severe haemolytic anaemia, vaso-occlusive episodes and shortened life expectancy. When sickle haemoglobin is deoxygenated it aggregates into large polymers, resulting in a marked decrease in the deformability of erythrocytes. This results in vaso-occlusive crises, the hallmark of SCD. One of these manifestations is the acute chest syndrome (ACS). It is the second most common cause of hospitalisation and is the leading cause of both morbidity and mortality. It is characterised by fever, chest pain and radiographic evidence of new pulmonary infiltrates. ACS evolving to acute respiratory distress syndrome (ARDS) is a rare, albeit severe complication of SCD.

A controlled study in paediatric SCD patients recently demonstrated beneficial effects on pain relief with inhaled nitric oxide (iNO) [1]. However, the effects of iNO have not yet been determined in patients with SCD and ARDS.

Case report

A Turkish male aged 36 with a known history of SCD and recurrent vaso-occlusive crises is presented. The patient complained of a two days' history of pleuritic chest pain, shortness of breath and cough. The past medical history revealed an unexplained episode of jaundice approximately twenty years prior to the present hospitalisation. On physical examination the patient had a temperature of 39.5 °C, a heart rate of 110 beats/min, a respiratory rate of 35/min and blood pressure of 140/75 mm Hg. Heart sounds were normal, the lung was dull to percussion on the lower left side and crackles were heard. The abdomen was not tender and bowel sounds were normal. A pulmonary infiltrate was seen on the chest x-ray. The patient was initially treated with antibiotics (ciprofloxacin and clarythromycin), oxygen and intravenous fluids. Deterioration in gas exchange, however, prompted transfer to our intensive care unit (ICU).

Here the patient presented with severe respiratory distress and exhaustion. Orotracheal intubation was performed and low tidal volume, pressure controlled mechanical ventilation (pcMV) was initiated (Evita 4, Dräger AG, Lübeck, Germany). Arterial blood gas results and other laboratory findings are given in Table 1. Blood pressure was low, with systolic pressure <90 mm Hg despite adequate fluid resuscitation and transfusion of two units of packed red blood cells. Continuous i.v. norepinephrine was administered. Haemodynamic monitoring revealed a state of hyperdynamic vasodilatory shock. A Swan-Ganz

No financial support declared.

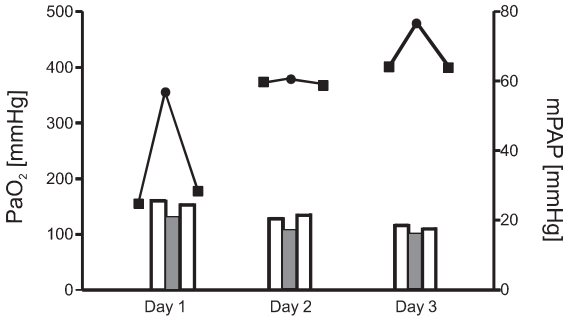
Table 1

Laboratory analysis and blood gas results.

	Day 1	Day 2	Day 3
WBC (/nl; normal 4.5–11)	26.2	20.6	16.8
Haemoglobin (g/dl; normal 14–17.5)	10.0	11.2	9.8
Platelets (/nl; normal 150–400)	266	176	145
Creatinine (mg/dl; normal 0.5–1.2)	1.1	1.2	1.3
Aspartate aminotransferase (U/l; normal 0–50)	27	41	65
PaO_2/FiO_2 (mm Hg; normal 500–640)	156	376	406
$PaCO_2$ (mm Hg; normal 35–45)	48	48	47
pH (7.35–7.45)	7.44	7.4	7.42
$HbaO_2$ (%; normal 94–98)	96	97	97

Figure 1

On-off effects of iNO on PaO_2 (lines) and on mean pulmonary artery pressure (mPAP, bars) (iNO-on: circles/solid bars; iNO-off: squares/open bars) on three consecutive days during ICU treatment.



pulmonary artery catheter demonstrated cardiac output of 10.5 L/min (normal range: 7 ± 0.5 L/min), systemic vascular resistance (SVR) of 450 dyn*sec*cm^{-5} (normal range: 900–2000 dyn*sec*cm^{-5}), pulmonary capillary wedge pressure (PCWP) of 16 mm Hg (normal range: 5–12 mm Hg), mean pulmonary artery pressure (mPAP) of 27 mm Hg (normal range: 17 ± 3 mm Hg) and central venous pressure (CVP) of 13 mm Hg (normal range: 1–8 mm Hg). The patient was ventilated in the prone position according to our clinical algorithm, and loop diuretics were started to achieve a negative fluid balance.

Since oxygenation remained impaired during conventional therapy, inhaled NO (iNO) was administered in a dose of 10 parts per million (ppm). Continuous inhalation induced a substantial and sustained improvement in PaO_2 and a reduction in mPAP (Figure 1). Concomitantly, the patient's condition stabilised and it was possible to reduce the FiO_2. NO was discontinued 96 hours after intubation. The initially impaired liver function normalised, a rise in serum creatinine proving transient. The patient was successfully weaned from mechanical ventilation and vasoactive medication 5 days after admission to the ICU and was subsequently transferred to a normal ward. Fourteen days after admission to hospital the patient was discharged home. When last seen, he was well without pulmonary symptoms. Liver and renal functions were normal.

Discussion

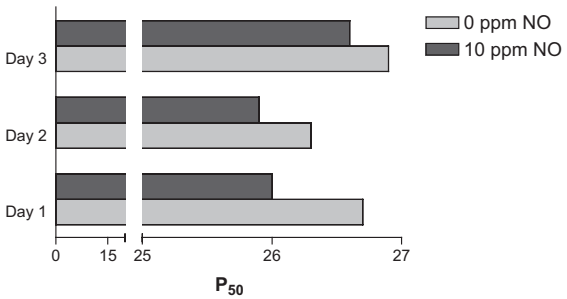
Although the prognosis of SCD has improved in recent years, ACS is still a leading cause of morbidity and mortality in SCD patients [2]. Multiple aetiological factors such as infection and hypoxaemia may increase intravascular sickling of erythrocytes, resulting in vascular obstruction [3–5] further aggravating impaired gas exchange and pulmonary hypertension.

Reactive oxygen species as possible antagonists of endogenous NO may enhance the adherence of sickle red blood cells to the vascular endothelium. Dias-da-Motta and co-workers reported increased release of superoxide from mononuclear cells of SCD patients compared to control mononuclear cells [6]. Increased amounts of superoxide inhibit the vasodilatory properties of endogenous NO, representing an additional risk factor for vaso-occlusion in SCD patients. Inhalation of exogenous NO may therefore offer a therapeutic option in restoring pulmonary vasoreactivity.

In ARDS inhaled NO has been shown to act as a selective pulmonary vasodilator redirecting pulmonary blood flow from shunt areas to better ventilated lung regions [7]. The effect of iNO is limited to ventilated lung areas, since the gas is rapidly bound and inactivated by contact with haemoglobin. In addition to beneficial effects of exogenous NO on gas exchange and pulmonary blood flow in the ARDS lung, NO was reported by Head et al. to increase oxygen affinity of sickle cell erythrocytes *in vivo* and *in vitro* [8]. The authors demonstrated a significant effect, with an averaged increase in P_{50} of 4.6 mm Hg during inhalation of NO. Thus far these results have not been substantiated by others [9–10], although experimental investigations have shown that iNO improves survival rates in a hypoxic sickle cell mouse model [11]. The patient described here developed ACS evolving to ARDS despite advanced intensive care treatment including transfusion, antibiotics, intravenous fluids and pcMV in the prone position. Inhalation of 10 ppm NO acutely resulted in substantial and sustained improvement of oxygenation. Inhalation of NO induced only a slight reduction in P_{50} values, demonstrating a clinically insignificant left-shift in the oxygen dissociation curve within the normal range of values (24–28 mm Hg, Fig. 2). It is unlikely that this left shift impaired oxygen delivery to the tissue. The more pronounced effect of iNO on the P_{50} of sickle cells *in vitro* and *in vivo* [8] reported by Head et al. may have been related to use of the substantially higher dose of 80 ppm NO in their study.

Figure 2

P_{50} on three consecutive days with and without iNO. Inhalation of NO induced a slight but persistent reduction in P_{50} values (normal: 24–28), indicating only a small left-shift in the oxygen dissociation curve.



In SCD patients with ACS and ARDS, inhalation of low concentrations of NO may not only improve arterial oxygenation and pulmonary vascular resistance, but may also increase the oxygen affinity of sickle cells and compensate for increased superoxide release. The present report indicates that low concentrations of iNO may be beneficial, but clinical studies are needed to further determine the optimum use of iNO in SCD patients with ACS and ARDS.

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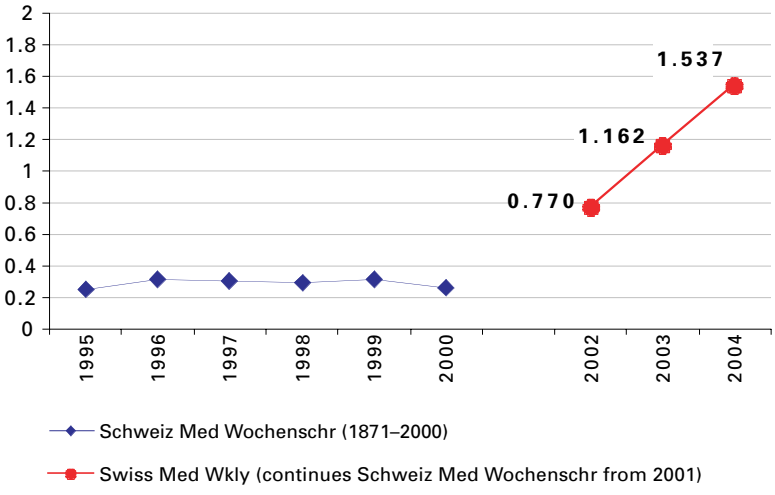

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