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A. J. Slater
S. H. Nichani
D. Macrae
K. A. Wilkinson
V. Novelli
R. C. Tasker

Surfactant adjunctive therapy for *Pneumocystis carinii* pneumonitis in an infant with acute lymphoblastic leukaemia

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A. J. Slater · S. H. Nichani · D. Macrae
K. A. Wilkinson · R. C. Tasker (✉)
Paediatric Intensive Care Unit,
The Hospitals for Sick Children,
Great Ormond Street,
London WC1N 3JH, UK

V. Novelli
Department of Infectious Disease,
The Hospitals for Sick Children,
Great Ormond Street,
London WC1N 3JH, UK

Abstract We report successful treatment of adult respiratory distress syndrome (ARDS) with artificial surfactant (40 mg/kg, Colfosceril Palmitate, 'Exosurf', Wellcome) in an infant with severe *Pneumocystis carinii* pneumonitis.

Key words Surfactant · ARDS
Pneumocystis carinii pneumonitis

Introduction

Pneumocystis carinii is the commonest cause of interstitial pneumonitis in immunodeficient children. Although this pneumonitis usually responds to antimicrobial therapy, the disease may be complicated by severe respiratory failure. *Pneumocystis carinii* pneumonitis (PCP) can cause ARDS [1], exhibiting many of the clinical and pathological features associated with ARDS precipitated by other aetiological agents. In adults however, there is an important difference between ARDS precipitated by PCP and ARDS precipitated by other conditions: PCP responds to adjunctive corticosteroid therapy [2] whereas sepsis associated ARDS does not [3]. We report an infant with PCP associated ARDS who failed to respond to standard therapy, including corticosteroids, but improved dramatically with adjunctive surfactant therapy.

Case report

A 9-month-old boy developed PCP following intensification chemotherapy for acute lymphoblastic leukaemia (ALL). He presented with tachypnoea, cough, and hypoxaemia. The diagnosis was made by monoclonal antibody immunofluorescence of fluid obtained by bronchoalveolar lavage (BAL). Intravenous cotrimoxazole (trimethoprim 20 mg/kg/day) and methylprednisolone (2 mg/kg/day) were started, and at this time his complete blood count revealed; haemoglobin 10.9 g/dl, leukocyte count 0.9×10^9/l, neutrophil count 0.1×10^9/l, and platelet count 87×10^9/l. Despite treatment, the severity of the pneumonitis worsened both clinically and radiologically. On day 6 the infant was intubated and mechanically ventilated. His spontaneous respiration was assisted with positive end expiratory pressure and synchronised pressure limited ventilation. On day 8, in response to progressive deterioration, the antimicrobial therapy was empirically broadened and pentamidine (4 mg/kg/day) was also added. A second BAL failed to reveal evidence of infection by another organism or persistence of *Pneumocystis carinii* pneumocysts.

On day 10 the infant deteriorated further and required neuromuscular blockade to assist mechanical ventilation. A FIO_2 1.0, a positive end expiratory pressure of 10 cm H_2O, a mean airway pressure of 20 cm H_2O, and a peak inflation pressure of 34 cm H_2O were required. At this time the arterial pH and carbon dioxide tension were 7.34 and 7.3 kPa respectively. As rescue therapy, intratracheal artificial surfactant was then administered (40 mg/kg, Colfosceril Palmitate, 'Exosurf', Wellcome) (Fig. 1). The alveolar-arterial oxygen gradient fell from 512 mmHg before surfactant to 357 mmHg 1 h after therapy, and it became possible to wean mechanical ventilatory support – as reflected by the fall in ventilation index ([peak pressure]$\times$[$PaCO_2$ mmHg]$\times$[respiratory rate]$\times10^{-3}$) which fell from 51 to 45 over the same period

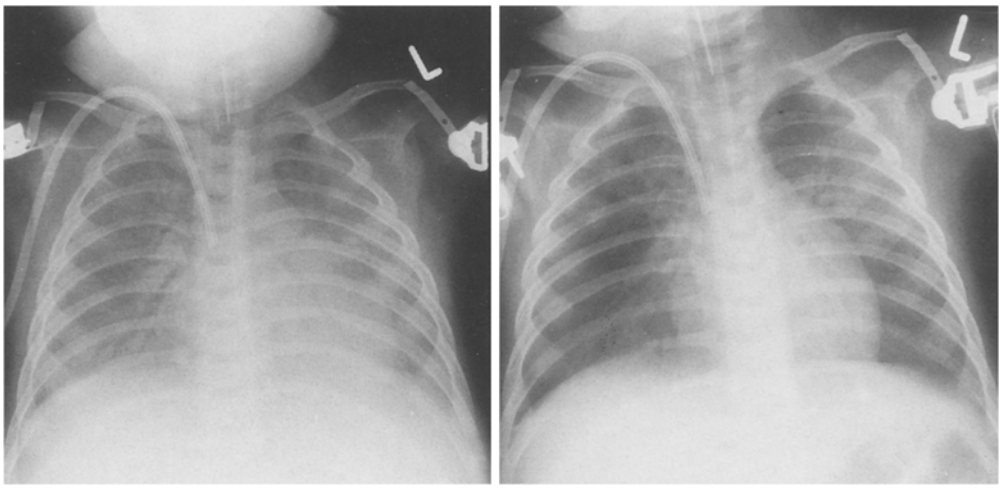

Fig. 1 Chest radiographs performed before (*left*) and 24 h after (*right*) surfactant therapy demonstrating clearing of the interstitial opacities and improved lung inflation

(Fig. 2). As part of our protocol a second dose of surfactant was given on day 11 and the patient was extubated on day 13 (72 h after the first dose of surfactant).

During the course of this episode of severe respiratory failure the neutropenia resolved with a count of 11.2×10^9/l on day 10. Fluid administration on days 10 and 11 had been at maintenance levels (90 ml/kg/day) and consisted mainly of drugs and parenteral nutrition. The fluid balance was positive 130 ml, and negative 44 ml, on days 10 and 11 respectively. Eight months after the episode of pneumonitis the patient was free from discernable cardiorespiratory difficulty.

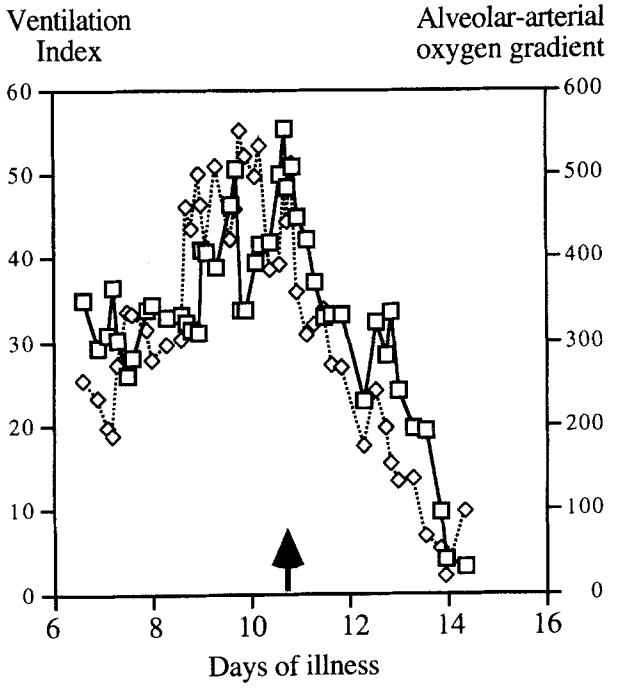

Fig. 2 The alveolar-arterial oxygen gradient (*dotted line* and '◇') and the ventilation index ([peak pressure]× [$PaCO_2$ mmHg]×[respiratory rate]$\times10^{-3}$) (*solid line* and '□') during the period of mechanical ventilation. The *arrow* indicates the time of the first of two surfactant treatments separated by 24 h

Discussion

From published series of paediatric respiratory failure, the expected mortality for this infant at the time of surfactant administration was 80–100%. Extracorporeal membrane oxygenation is sometimes considered for disease of this severity. Although the surfactant therapy was only one of many interventions in this child we believe it played a crucial role in his recovery. In fact, following 10 days of unrelenting disease with deteriorating lung function, the first improvement in gas exchange was temporally related to the initial surfactant treatment.

Pneumocystis carinii undoubtedly initiated the severe respiratory illness which occured in this infant with ALL, but barotrauma, oxygen toxicity, and activated neutrophils within the lung parenchyma continued to perpetuate the lung injury. In patients with PCP and acquired immunodeficiency syndrome, an elevated percentage of neutrophils in the BAL differential cell count is predictive of a poor outcome or respiratory failure [5]. It could be proposed that either the organism or the products of inflammation have a direct deleterious effect on lung tissue, or on the production and function of surfactant. In vitro, impairment of surfactant function by activated neutrophils appears to be mediated predominantly by oxygen radicals [6].

ARDS is characterised by non-cardiogenic pulmonary oedema, ventilation-perfusion mismatch, and reduced pulmonary compliance. Histologically there is a generalised loss of air spaces, and alveoli are lined by hyaline membranes and filled with protein and oedema fluid. Since many of these clinical and pathological features would be expected in surfactant deficiency, abnormalities in the quantity or function of surfactant have been implicated in the pathogenesis of ARDS. Experimentally, exogenous surfactant therapy has been used effectively in some models of ARDS. Improvement of gas exchange

and lung compliance have been observed in models of lung injury induced by saline lavage, intratracheal acid injection, influenza virus, and antilung serum injection, but not in models induced by oleic acid infusion, prolonged oxygen exposure, or surfactant protein B antibody injection [8]. Thus, the response to surfactant appears to dependent on the model. This may be accounted for by the progression and severity of disease, or by the presence of surfactant inhibitors within the air spaces. A number of clinical case reports have described the beneficial effects of exogenous surfactant in children and adults with ARDS precipitated by trauma or sepsis [8]. A reduction in mortality, from 47 to 25% has been reported in a preliminary report of a multicentre prospective randomized placebo controlled study of aerosolized surfactant in ARDS induced by sepsis [9].

In relation to ARDS induced by PCP, there may also be specific features which contribute to surfactant dysfunction and depletion. In vitro, *Pneumocystis carinii* pneumocysts bind surfactant protein A, a finding which has also been noted in rats with PCP [10]. Surfactant protein A regulates alveolar phospholipid homeostasis. Interaction with the organism may contribute to the pathogenesis of the disease [11]. Interestingly, quantitative abnormalities of surfactant have been reported in specimens obtained by BAL from patients with PCP [12]. In rats with PCP, intratracheal surfactant therapy results in a marked improvement in arterial oxygen tension within 30 min of administration. The histology shows well aerated near normal alveoli, a marked contrast to the foamy oedema filled alveoli of placebo treated animals [13].

In our young patient with PCP we speculate that the cotrimoxazole successfully treated the underlying infection, although prolonged oxygen exposure together with a significant pulmonary influx of activated neutrophils – associated with bone marrow regeneration – resulted in progressive lung injury and depletion of surfactant, which ultimately responded to surfactant replacement. We are not aware of any other clinical treatment of PCP with surfactant and suggest that its role as an adjunctive therapy warrants further evaluation and clinical trial.

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