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Case Report Open Access

Drug-Induced Pulmonary Edema and Acute Respiratory Distress Syndrome in Children

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Abstract

Non-cardiogenic pulmonary edema, and to a lesser extent, Acute Respiratory Distress Syndrome (ARDS) are common clinical manifestations of drug-induced lung diseases. Clinical features and radiographic appearances are generally indistinguishable from other causes of pulmonary edema and ARDS. Typical manifestations include dyspnoea, chest discomfort, tachypnoea, and hypoxemia. Chest radiographs commonly reveal interstitial and alveolar filling infiltrates without cardiomegaly. The laboratory results are usually nonspecific. We illustrate potential aetiologies relating to ARDS and the recognition of mucolytic drug use as one of the pathophysiologic factors of ARDS.

Keywords: Acute respiratory distress syndrome (ARDS); Non-cardiogenic pulmonary edema; Interstitial and alveolar filling infiltrates; Mucolytic drug use

Introduction

ARDS is a severe manifestation of abnormal pulmonary gas exchange .With the recent improvements in critical care, the survival rate of patients with ARDS has improved. There are few case reports directly linking drugs with ARDS (e.g. antipsychotics) but no link has yet been established between mucolytics and ARDS. Our recent experience with 2 unique cases of patients who survived ARDS provides an excellent example of such an association. It is important that the intensivists are made aware of such a possibility, especially during infancy .We also found a similar association in the higher age group, when the mucolytic was prescribed in combination with an anti-histaminic drug.

Case 1

A $2^{1/2}$ year-old girl weighing 11 kg was admitted with dyspnoea, tachypnoea and hypoxemia. She had no known drug allergies. She had developed a left lower lobe pneumonia for which she received antibiotics and chest physiotherapy. She also had non-cardiogenic pulmonary oedema and required furosemide and high flow supplemental oxygen for 4 days. After this, she made a good recovery and was discharged. During the intervening period, her antihistaminic and mucolytic medication was stopped completely.

She was hypoxic (Spo_2=65% in room air) with signs and symptoms consistent with pneumonia and acute lung injury. Although her CXR showed pulmonary oedema, she did not have any evidence of heart failure. Her ECG and echocardiogram were both normal, which ruled out myocarditis. She was given ceftriaxone sulbactam and azithromycin for presumed atypical/community -acquired pneumonia. Her hypoxia was treated with high flow oxygen volumes between 4 and 6 ml/kg I.V. Furosemide was started simultaneously, to achieve a negative fluid balance. The patient's ARDS resolved completely over the next 7 days .The treatment involved treating the bilateral lower lobe pneumonia and non-cardiogenic pulmonary oedema.

We suggest that giving her ambroxol and cetirizine combination therapy three times a day during the respiratory illness may have influenced the outcome by triggering acute lung injury, which developed into ARDS.

Case 2

A 9 month old, boy weighing 9 kg presented with complaints of severe dyspnoea and wheezing. The complaints started as rhinorrhoea and cough, which apparently worsened after medications prescribed by a local practitioner viz. ambroxol syrup and paracetamol. There was no family history of asthma. His physical examination showed slightly emphysematous chest. The auscultation of the lungs revealed bilateral

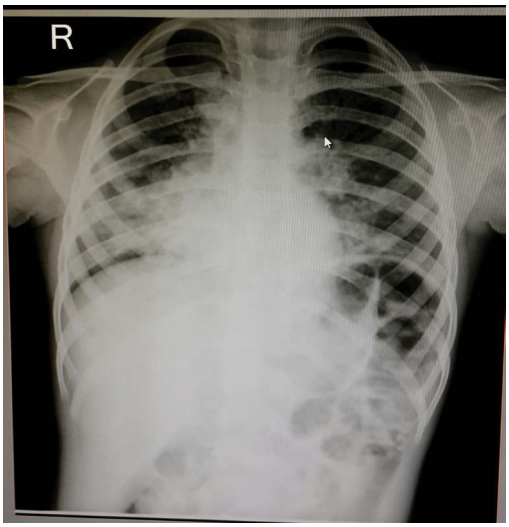

Figure 1: Radiograph of chest showing pulmonary edema.

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rhonchi and fine crepitations. Laboratory examination, including complete blood count, renal function and liver function tests were normal. The chest radiograph showed a picture of pulmonary edema (Figure 1).

The infant was considered exposed to a mucolytic drug as he had received ambroxol for at least 5 days (>200 mg) until the day before admission. The symptoms had worsened into dyspnoea and bronchorrhea according to the mother since the introduction of the medications. The clinical examination and radiographs revealed a picture of ARDS with pulmonary edema. The mucolytic drug treatment was withdrawn. High flow supplemental oxygen therapy was given along with antibiotics, inhaled β2 agonists and furosemide. Evolution was favorable with aggressive management, despite the pulmonary oedema.

Discussion

Several case studies and series have previously reported a link between ARDS, neuroleptic malignant syndrome and anti-depressant drugs (including antipsychotic drugs). Although there is not sufficient evidence to accurately describe the pathophysiological mechanism from these observations, they may be classified as:

A dose-related effect [1]

A part of the neuroleptic malignant syndrome [2]

Neurogenic pulmonary oedema [3], and/or

An allergic reaction involving general activation of neutrophils in many tissues including the lung [4,5].

Several alerts have concerned the safety and benefit risk ratio of such mucolytic medicines. In 2010, the French drug agency and later an Italian drug agency, withdrew the licenses (for children younger than 2 years) for carbocysteine and acetylcysteine, because their use was associated with paradoxically increased bronchorrhea and acute respiratory distress during respiratory tract infections [6]. The cysteine derivatives (carbocysteine, acetylcysteine) are mucolytic drugs that act by breaking disulphide bridges between macromolecules and lead to reduced mucus viscosity in the respiratory tract [7]. A hypothesis to explain the mechanisms by which the use of mucolytic drugs worsens the acute respiratory tract illness in infants is also found in literature [8,9].

The anatomical and physiological specificities of the airways of infants (numerous mucus glands, small bronchial diameter, and muscular immaturity) further pre disposes the paediatric age group [10]. During infection, the modifications of the airway (i.e., bronchorrhea, reduced bronchial diameter & inflammation) enhance this predisposition. Chest radiographs commonly reveal interstitial and alveolar filling infiltrates, as was in our case. Unlike pulmonary edema that is due to congestive heart failure, cardiomegaly and pulmonary vascular redistribution are generally absent in cases that are drug-related. This was also true in our case.

It is possible to say with confidence that our patient's mucolytic and the antihistaminic medication (either mucolytic alone in the infant or in combination with antihistaminic in the older child) predisposed them to develop ARDS. Although ARDS is common in critically ill patients, it does not often follow an intracTable and relentless course if the triggering event is effectively stopped, as it happened in our case. The possible mechanism could be as follows:

1. The increase in bronchial mucus flow induced by mucolytic drugs exceeded the ability for spontaneous drainage in the infant and then induced prolonged cough and worsened the respiratory distress during the acute airway infection.
2. Young infants are more affected because the paediatric anatomical peculiarities described previously are more pronounced in the young infants.
3. Finally, the dosages of mucolytic given by paediatricians are quite variable and arbitrary as in Case No. 2.
4. Even in the Case No 1, the increase in bronchial mucus flow induced by mucolytic drugs was further compounded by inhibition of mucociliary action, by giving cetirizine thrice daily along with ambroxol.

Ambroxol is still largely used for children despite no clear evidence of efficacy. Thus, parents, physicians, and pharmacists should know that whatever the benefits one may achieve are miniscule compared to the risk posed by this drug. The intensivists should also be aware of the association between antihistaminic and mucolytic medication and ARDS, so that this general principle can be reviewed in light of the clinical situation, especially if the ARDS develops.

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