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Acute respiratory distress syndrome in children with acute iron poisoning: the role of intravenous desferrioxamine

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Abstract The acute respiratory distress syndrome is a rare but potentially fatal complication of severe acute iron poisoning and its pathogenesis has been linked with direct and indirect iron toxicity as well as the use of the chelator drug desferrioxamine. We report a case of severe acute respiratory decompensation in a child treated according to the current protocol for chelation therapy and discuss its implications.

Conclusion We believe that the efficacy and safety of chelation therapy in severe acute iron poisoning may be improved by targeting the initial high levels of readily chelatable serum iron with adequate doses of desferrioxamine without prolonging its use unnecessarily.

Key words Acute respiratory distress syndrome · Acute iron poisoning · Desferrioxamine

Abbreviations *ARDS* acute respiratory distress syndrome · *DSF* desferrioxamine

Introduction

The accidental ingestion of iron is relatively common in childhood, has significant morbidity and a mortality of about 1%. Survivors have a good long-term prognosis. The severity depends on the amount of elemental iron absorbed; 60 mg/kg can cause severe toxicity while 150 mg/kg can be fatal [4]. Iron levels can roughly predict toxicity but can be deceptively low if checked more than 6 h after the ingestion, due to early tissue distribution of iron. Early coma and shock as well as liver impairment indicate a worse prognosis. Iron has a direct, corrosive effect on the gastro-intestinal mucosa, vascular effects causing hypovolaemia and effects on cellular and mitochondrial membranes [5]. The mainstay of treatment in severe cases is the use of desferrioxamine (DSF), a specific iron chelator which is itself associated with complications including hypotension, infection, ocular and ototoxicity and pulmonary toxicity [3].

Case report

A 3.5-year-old girl was admitted after an accidental ingestion of 50 to 60 iron sulphate (200 mg) tablets. She was unresponsive and the initial serum iron level was 138 μmol/l. She required resuscitation and ventilation and an intravenous infusion of DSF was started at a rate of 15 mg/kg per hour. This was reduced to 5 mg/kg per hour 20 h later when the iron level was 27 μmol/l. At that time, the liver function deteriorated with raised levels of aminotransferases (ALT of 57 IU/l) and bilirubin (56 μmol/l) and a coagulopathy with an INR of 2.7. An infusion of N-acetylcysteine was started at a rate of 12.5 mg/kg per hour and the hepatic function was stabilised. The cardiorespiratory parameters improved and the ventilatory support was reduced. About 40 h after the ingestion she had an acute respiratory deterioration with tachypnoea, hypoxaemia and an oxygenation index (PaO_2/FiO_2) of 138. A chest X-ray showed widespread bilateral infiltrates with a normal heart size. The diagnosis of acute respiratory distress syndrome (ARDS) was made and the patient was managed with high pressure ventilation. She slowly improved and was discharged from intensive care after a week. Until the onset of ARDS she had received 20 h of DSF at 15 mg/kg per hour and 14 h at 5 mg/kg per hour. There was no significant growth on microbiological cultures.

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Discussion

ARDS is the most severe manifestation of injury to the alveolar-capillary unit and the common causes in children include sepsis, shock, pneumonia and near drowning. Iron toxicity could have caused the syndrome in our patient either indirectly or directly. Indirectly, the hypotension, shock and metabolic acidosis, seen in severe acute iron poisoning, could contribute to pulmonary toxicity but this is unlikely in our case as it occurred after a period of ventilatory and cardiovascular stability. Directly, iron acts as a catalyst of lipid peroxidation which damages cellular and mitochondrial membranes, interferes with oxidative phosphorylation and has an effect on surfactant leading to early pulmonary toxicity. Children are more vulnerable to such toxicity as their anti-oxidant protective mechanisms are not as well developed. Exogenous anti-oxidants, like N-acetylcysteine, may be beneficial in the management of acute oxidative lung injury but the timing of their use and the required dose need to be explored. It is possible that direct iron toxicity contributed to the development of ARDS in our case. However, the late onset of the complication and the failure of N-acetylcysteine to prevent it, while stabilising hepatic function, would be more in line with an alternative cause.

The use of intravenous DSF has itself been implicated in the aetiology of ARDS [1, 6]. Most cases occurred after prolonged use (3 to 9 days) of high rates of infusion. In theory, intracellular iron chelation by DSF leads to reduced haem synthesis and influx of extracellular haem, causing the release of iron which catalyses oxidative damage [2]. The length of treatment may have contributed to the development of ARDS in our patient.

The early cellular distribution of iron and the associated toxicity determines the complications seen in the third phase of iron poisoning. The initial rate of 15 mg/kg per hour, suggested by current guidelines and used in this case, may have given too little DSF during that critical early stage. An alternative would be to match the initial infusion rate with the level of readily chelatable serum iron [3] provided any higher rates used are clinically tolerated. We also believe that continuation of the DSF infusion beyond a certain point carries its own risks and can augment the toxic effects of iron at the cellular level. In our case we knew the risks and, following current guidelines [4], we reduced the rate of infusion as soon as clinically tolerated but continued as long as the urine remained discoloured. Even that prudent use of DSF may have been harmful and its length may have precipitated the onset of ARDS.

Appropriate use of the chelator DSF is critical in minimising the cytotoxic effects of severe acute iron poisoning. We believe current guidelines may have to be reviewed in order to make chelation therapy safer and increase its efficacy.

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