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CASE REPORT

Acute respiratory distress syndrome following a biphasic anaphylactic reaction to morphine: a case report and review of the literature

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Background: Biphasic anaphylactic reaction is a variant of the usual and more commonly seen monophasic anaphylactic reaction. However, recently it has been observed that biphasic anaphylactic reaction may not be as uncommon as previously believed. Furthermore, serious and life-threatening complications such as acute respiratory distress syndrome (ARDS) may ensue that require prompt intervention.
Case report: A 16-year-old boy is presented who was scheduled for bilateral orchidopexy under spinal anaesthesia. Anaesthesia was supplemented with i.v. midazolam 5 mg, ketamine 50 mg and morphine 5 mg. About 10 minutes after the administration of morphine, he developed an urticarial rash with mucocutaneous zones, which was promptly treated with i.v. hydrocortisone 100 mg stat.
The patient was transferred to the ward after an uneventful surgery and anaesthesia. However, about six hours postoperatively he developed respiratory distress with SpO2 of 20% associated with shock with a blood pressure of 80/40 mmHg, and heart rate of 40 bpm. He was immediately resuscitated with endotracheal intubation, chest compression and i.v. adrenaline and admitted to the ICU. He was managed in the ICU with ventilatory support and inotrope and discharged to the ward after 12 days.
Conclusion: A 16-year-old boy who developed a biphasic anaphylactic reaction secondary to morphine administered in the theatre was managed in the ICU and discharged to the ward after 12 days and home thereafter.

Keywords: ARDS, biphasic anaphylactic reaction, morphine

Introduction

Anaphylaxis is a severe hypersensitivity reaction that is rapid in onset with a wide spectrum of clinical presentation. Three patterns of anaphylaxis are recognised, namely monophasic, protracted and biphasic anaphylaxis.[1] Monophasic anaphylaxis is the most common type, which usually peaks within 30 minutes to one hour after symptoms appear and resolves either spontaneously or with treatment within the next 30 minutes to one hour. A protracted anaphylactic reaction, on the other hand, commonly lasts hours to days without complete resolution.[2] Characteristic clinical manifestations of anaphylactic reaction involve several organs. Circulatory shock is said to occur in about 30% of cases while up to half of patients develop respiratory symptoms that can progress to acute respiratory failure.[3]

Biphasic anaphylactic reaction is a rare variant monophasic anaphylactic reaction[4] with the most recently observed incidence as high as 18%.[5,6] It is said to occur within 72 hours of resolution of anaphylactic symptoms without re-exposure to the trigger, following an asymptomatic interval of at least one hour. Previously, acute respiratory distress syndrome (ARDS) has been reported following anaphylactic reactions to different triggering agents.[7,8] It is defined as an acute onset of difficulty with breathing associated with bilateral lung opacities not fully explained by effusions, lobar/lung collapse or nodules occurring with one week of a known clinical insult or new/worsening respiratory symptoms associated with an oxygen tension/inspired oxygen fraction less than 200 mmHg and a PEEP/CPAP >5 mmHg.[9] It is characterised by widespread inflammation in both lungs and it usually starts with activation of circulating neutrophils that stick to pulmonary endothelium. Several clinical situations can progress to ARDS but the common ones trigger an initial systemic inflammatory response with sepsis accounting for about 40%.[10]

ARDS could result from the inflammatory response of the lung parenchyma to anaphylaxis from medications. The 'leaky capillaries' that result from the activation of neutrophils lead to the formation of exudates. The resulting lung damage leads to further inflammatory response, which progressively precipitates respiratory insufficiency.

Here we present a case of ARDS following a biphasic anaphylactic reaction to morphine.

Case report

A 16-year-old male patient was admitted for elective bilateral scrotal orchidopexy secondary to retractile testes with history of testicular sub torsion. A pre-anaesthesia visit revealed no significant past medical history such as heart failure, hypertension or diabetic mellitus, the only exception being allergic rhinitis. There was no history of allergies to medications or any other known triggers. Spinal anaesthesia was supplemented with intravenous midazolam (5 mg), ketamine (50 mg) and morphine (5 mg) due to the fact that patient complained of pain immediately after commencement of surgery. Immediately after receiving morphine injection he developed an urticarial rash, which was initially treated with intravenous hydrocortisone with resolution of symptoms. Surgery continued without any further unfavourable event. At the end of surgery, he was discharged

to the ward after approximately 45 minutes' stay in the post anaesthetic care unit (PACU).

About six hours after exposure to i.v. morphine, the patient developed severe respiratory distress in the ward with in-room arterial oxygen saturation as low as 20%. He became cyanosed and hypotensive with a blood pressure of 80/40 mmHg. He was immediately intubated and transferred to the intensive care unit (ICU) for further management. Of note is that there was no history of any other medications from his discharge from PACU to the development of signs and symptoms on the ward.

On arrival in the ICU, he was put on a mechanical ventilator in pressure-regulated synchronised intermittent mandatory ventilation (PRCV/SIMV) mode. He was also commenced on adrenaline at 0.2 µg/kg/min. The chest radiograph showed bilateral infiltrates of the lung fields (Figure 1) and an arterial blood gas analysis obtained on arrival in the ICU revealed severe hypoxaemia with a partial pressure of arterial oxygen and fractional inspired concentration of oxygen ratio (PaO2/FiO2) of 90 mmHg (Figure 2). Thus an impression of severe acute respiratory distress syndrome following biphasic anaphylactic reaction to i.v. morphine was made.

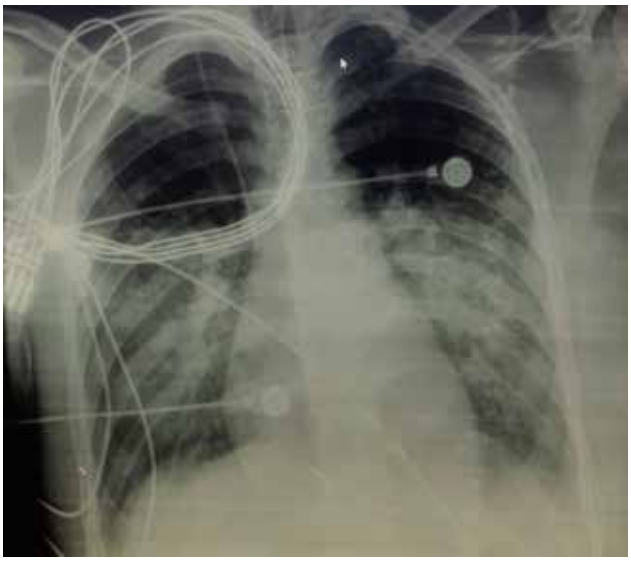

Figure 1: CXR of the patient showing bilateral opacities.

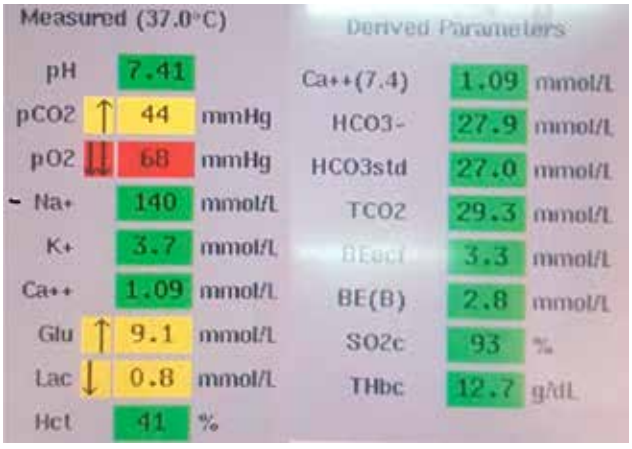

Figure 2. ABG results of the patient on arrival in the ICU.

About 48 hours after commencement of mechanical ventilation, a repeat CXR showed marked improvement and serial arterial blood gas indicated a significant improvement in the hypoxic ratio and oxygenation. He was subsequently weaned off the ventilator and extubated after spending four days on the mechanical ventilator. The patient was later discharged to the ward and later home and given an appointment to be seen in the outpatient department of the hospital.

Discussion

Some anaesthetic drugs have been implicated in the development of anaphylactic reactions. These include steroid-based neuromuscular blockers (e.g. vecuronium and pancuronium), induction agents such as sodium thiopentone, benzodiazepines and opioids, especially morphine.[11] In this case report, morphine is suspected to have been responsible for the initial anaphylactic response in the theatre due to the immediate development of urticarial rash and thus the biphasic manifestation observed later as the patient developed an urticarial rash only immediately after injection of this.

Biphasic anaphylaxis is a recurrence of anaphylactic symptoms within 72 hours of initial resolution without re-exposure to the trigger, following an asymptomatic interval of at least one hour.[12] Our patient developed signs and symptoms of anaphylactic reactions such as difficulty with breathing and hypotension six hours after the initial exposure to the suspected trigger, morphine. Different factors have been postulated for the development of basic anaphylactic reactions. These include an influx of inflammatory cells (e.g. eosinophils, basophils and lymphocytes) occurring in response to cytokines released during the initial response,[13] a second wave of mast cell degranulation occurring between 30 min and 72 hours after initial exposure,[14] late production of platelet activating factor secondary to released TNF-α from mast cells during the initial response,[15] 'wear off' of initial treatment thus making the second phase a form of protracted anaphylaxis, and uneven absorption of antigens, which is more important in the case of oral antigens.[16]

The inflammatory responses following anaphylactic reaction could affect many organs in the body. The inflammatory mediators such as histamine, tryptase, prostaglandins and leukotrienes produce varying effects depending on the organs affected. Cardiovascular or circulatory shock occurs in about 30% of cases of anaphylaxis, while up to 50% of these patients develop varying degrees of respiratory symptoms.[3] These symptoms range from dyspnoea, to stridor associated with wheezing, hoarseness and pulmonary oedema. ARDS could result from either direct injury to the lung parenchyma or secondary to systemic insults reaching the lung via the pulmonary circulation. The most common indirect cause of ARDS is sepsis, which accounts for up to 40% of cases.[10]

The consequences of the above include reduced alveolar ventilation, intrapulmonary shunting and reduced lung compliance with increased work of breathing. The patient thus presents with severe hypoxaemia and bilateral pulmonary infiltrates, as was observed in our patient. Progressive hypoxaemia may lead to the need for ventilatory support to correct the hypoxaemia and the acid-base disturbances that ensue.

Adverse reaction to drug administration has been known to precipitate ARDS. About two years ago, Park and co-workers[7] reported a case of ARDS following the administration of gadolinium-based contrast media in a 26-year-old female patient who

had undergone pelvic magnetic resonance imaging (MRI) after injection of 7.5 ml of gadobutrol. A chest radiograph revealed bilateral central 'bat-wing' consolidative appearance and was subsequently managed with mechanical ventilation and she was discharged home three days later. Although this is a very rare case of ARDS secondary to allergic reaction to a contrast medium, it shows that pulmonary complications as a result of anaphylaxis to drug administration could be life-threatening and thus require vigilance and prompt management. On a similar note, our patient developed ARDS following a delayed anaphylactic reaction to i.v. morphine and required mechanical ventilation.

Efeturi et al.[8] also reported a case of ARDS complicating an anaphylactic reaction in a 14-year-old male patient who developed a wheal-like pruritic erythematous rash associated with difficulty with breathing. His Chest X-ray revealed features of ARDS such as hyperinflation bat-wing shadows and Kerly B-lines and was managed as necessary. He was placed on oxygen therapy, adrenaline i.v. nebulised salbutamol and steroids. The authors could not ascertain the triggering agent in this case, which did not report the degree of hypoxaemia. Despite this, radiological findings and the clinical presentations were used to make a diagnosis of ARDS and the patient was managed successfully.

Although the most common causes of anaphylactic reactions in the perioperative period are muscle relaxants and antibiotics, opioid-induced anaphylaxis has also been reported.[11] About two decades ago, Stefanutto and Wright[17] reported a case of anaphylactoid reaction to i.v. morphine in a 56-year-old male patient who presented for revision and extension of fusion following repeated radiculopathy. After about 10 minutes of a bolus i.v. injection of 10 mg morphine, the patient was observed to become tachycardic and hypotensive, which was refractory to fluid administration and pressor agents such as ephedrine. He was also noticed to have become flushed and warm and was subsequently started on continuous infusion of adrenaline. Blood pressure normalised after about 45 minutes of continuous adrenaline infusion. A serum level of tryptase showed elevated levels compatible with anaphylactoid reaction. The authors concluded that this was a case of anaphylactoid reaction secondary to morphine administration.

Opioids such as morphine and pethidine are known to stimulate mast cell mediated release directly without a specific immunologic mechanism. This may lead to generalised pruritus and urticaria after administration of an opioid such as morphine, as noted in our patient. In addition, the patient may develop some form of respiratory symptoms such as occasional mild wheezing or may progress to ARDS. The fact that opioids normally cause histamine release makes skin-test results unspecific. Unfortunately, we could not obtain a skin sensitivity test or serum level of inflammatory mediators like tryptase due to the unavailability of these tests in our institution.

It is worth noting that perioperative administration of opioids either during general anaesthesia or as an adjunct during regional anaesthesia can precipitate allergic reactions with far-reaching consequences in terms of morbidity and/or mortality. Anaphylactic reactions to opioid administration may be immediate or delayed. It has been suggested that patients with severe anaphylactic reactions, patients with more than 30 minutes' delay in treatment after initial exposure, more than 60 minutes' delay between onset of symptoms and adrenaline treatment, slower response to adrenaline treatment and previous history of biphasic anaphylactic reactions should be admitted to a high-dependency unit.[18]

Conclusion

Although the recent publication of the National Audit Project on preoperative anaphylaxis omitted opioids as one of the triggering agents,[19] biphasic anaphylactic reaction to opioids, especially morphine, may occur with often severe and catastrophic consequences. One of the common consequences is acute respiratory distress syndrome which would require ICU admission and ventilatory support. It is indeed imperative to conduct a more inclusive study on this possibility as awareness of it, increased vigilance and prompt intervention are sine qua non to preventing unfavourable outcome.

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