CASE REPORT

Use of enoximone in management of anaphylaxis complicated by labetalol use

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SUMMARY

A 42-year-old woman with end-stage renal failure was admitted to the intensive care unit following resuscitation from a pulseless electrical activity cardiac arrest after intravenous piperacillin/tazobactam. Persistent bradycardia and hypotension, unresponsive to epinephrine and norepinephrine, were suspected to have been exacerbated by chronic labetalol therapy for resistant arterial hypertension. As an alternative, the non-adrenergic inotrope, enoximone, was started. This, combined with thrombolysis for possible pulmonary embolism, heralded significant haemodynamic improvement, allowing weaning from inotropic support. A clear CT pulmonary angiogram 2 days post-arrest and significantly raised mast cell tryptase levels confirmed anaphylaxis rather than pulmonary embolism as the precipitating cause. We believe this to be the first case report of phosphodiesterase-III inhibitor use in the management of anaphylaxis complicated by α/β -blockade, and discuss the mechanism behind this effect and comparison with the more commonly reported use of glucagon.

BACKGROUND

Severe hypotension secondary to anaphylactic shock requires adequate inotropic support to maintain tissue perfusion and, therefore, life. Epinephrine, having specific effects on mast cell, as well as eosinophil degranulation and positive inotropic and vasopressor effects,¹ is generally the first-line agent of choice in anaphylactic shock. However, for a patient who has been exposed to therapeutic adrenergic-receptor blockade, responsiveness to epinephrine is reduced, and additional agents are required to augment its effects.² Arterial hypertension remains a significant and growing public health concern,³ with an estimated 10% of hypertension being classified as resistant.⁴ This is resulting in an increased requirement for long-term treatment with multiple second to fifth line antihypertensives, often acting via α -adrenergic and/or β -adrenergic blockade.⁵ It is estimated that anaphylaxis affects up to 1.6% of the population,⁶ and patients with chronic multisystem morbidity are at increased risk due to repeated exposure to potential allergens such as antibiotics or anaesthetic agents.⁷ It is therefore likely that we will see increasing numbers of cases of anaphylaxis among patients on concurrent antihypertensives, and it is useful for us to identify non-adrenergic inotropes that can be used to manage hypotension in this patient group.

CASE PRESENTATION

A 42-year-old woman with end-stage renal failure secondary to membranoproliferative glomerulonephritis, with a history of three failed renal transplants, was admitted to hospital with otitis media unresponsive to oral co-amoxiclav. She had undergone a prolonged admission earlier in the year requiring intensive care admission and treatment for posterior reversible encephalopathy syndrome. Other medical history of note included difficult to control hypertension requiring labetalol, doxazocin, amlodipine and candesartan, a tumour of the parotid gland, a previous pulmonary embolism (PE) (radiologically and clinically resolved 2 months previously) and a suggestion of a thrombus associated with the haemodialysis line on transthoracic echo (TTE) 2 months previously.

Twenty minutes after the start of an intravenous infusion of piperacillin/tazobactam, the patient suffered a pulseless electrical activity cardiac arrest, with return of spontaneous circulation after 12 min of cardiopulmonary resuscitation, intubation and positive pressure ventilation, and three boluses of 1 mg epinephrine administered intravenously. Post-arrest, systolic hypotension (64 mm Hg) and bradycardia of 45 bpm were managed with boluses of 0.1 mg epinephrine, atropine and intravenous fluids, alongside 100 mg hydrocortisone and 10 mg chlorpheniramine for treatment of possible anaphylaxis. All anti-hypertensives were withheld (the oral labetalol had been given 2 h previously although no other agents had been taken that day), and the patient was transferred to intensive care where she was established on infusions of norepinephrine and epinephrine, and sedated with midazolam and remifentanyl. She remained hypotensive and bradycardic despite escalating doses of norepinephrine and epinephrine.

INVESTIGATIONS

Minimally invasive cardiac output monitoring was established with lithium calibrated LiDCO, which demonstrated low cardiac output (cardiac index <1 L/min/m²) and no improvement following a 250 mL fluid bolus. ECG showed sinus bradycardia with left ventricular hypertrophy by voltage criteria. Bedside transthoracic echocardiogram showed a poorly contractile, under-filled left ventricle and normal-sized right ventricle, and confirmed a likely thrombus associated with the dialysis line tip in the right atrium, thus acting as a potential source of embolism. Initial arterial blood gas revealed a lactic acidosis (pH 7.27, base excess -4.8 , lactate 6.3 mmol/L, with type 2 respiratory failure PO₂

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13.7 KPa, PCO₂ 6.6 KPa on FiO₂ 1.0). Samples were taken for mast cell tryptase shortly after the return of spontaneous circulation, 6 and 24 h following arrest. The results were not available until 2 weeks after the event but, once available, showed levels of >200 ng/mL immediately postcardiac arrest, 44 ng/mL at 6 h and 4 ng/mL at 24 h post-arrest, confirming anaphylaxis as the precipitating cause of arrest. At the time of resuscitation, the patient was deemed too unstable to be moved to the radiology department for CT pulmonary angiogram (CTPA), however, once recovery had occurred, CTPA was undertaken, which showed no evidence of PE.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis was of anaphylaxis, with piperacillin/tazobactam being the likely precipitant, and massive PE. The likelihood of anaphylaxis as a precipitant was thought decreased by the absence of all key clinical features (bronchospasm, rash, angio-oedema) other than hypotension, and with the previous safe administration of piperacillin/tazobactam and other β lactams to the same patient, with the only documented allergy being a rash following flucloxacillin. The results of the bedside echo, with a potential source of thrombus identified, combined with further worsening of the haemodynamics, prompted empiric thrombolytic therapy with recombinant human plasminogen activator (alteplase).

TREATMENT

The persistence of low cardiac output (cardiac index <1 L/min/m²), hypotension and bradycardia in the presence of labetalol prompted the initiation of enoximone as a non-adrenergic inotrope that could bypass the negative inotropy of the labetalol. Over the subsequent 2 h, there was a gradual improvement in cardiac index to 2.3 L/min/m², with blood pressure rising to 80/50 mm Hg (M58), resolution of lactic acidosis and improvement in pulmonary gas exchange. Six hours after the arrest blood pressure had risen to 104/57 mm Hg (M69), the cardiac index continued to improve to 3.5 L/min/m², and all vasopressors and inotropes were subsequently weaned off over the next 12 h. The patient was successfully extubated 18 h after the arrest, with minimal neurological disability.

OUTCOME AND FOLLOW-UP

The patient remained in hospital for 1.5 months following the arrest, and was discharged home to continue regular outpatient haemodialysis. The line with associated thrombus was removed and replaced with a new haemodialysis line. Allergy testing to confirm the precipitating allergen(s) is awaited.

DISCUSSION

This case presents the use of enoximone, an imidazole phosphodiesterase III inhibitor that prevents the inactivation of cyclic AMP (cAMP) and cyclic guanosine monophosphate (cGMP) in anaphylactic hypotension unresponsive to epinephrine secondary to long-term α and β blockade, with a successful outcome. This report is of use in investigating the employment of non-adrenergic inotropes, since recommended first-line and second-line inotropic agents in anaphylaxis act by adrenergic receptor activation,^{1 8} and the recommendation for the unlicensed use of glucagon in refractory anaphylaxis is supported by case report evidence only.⁸ Furthermore, the quantities of glucagon used in this situation can readily deplete hospital and, indeed, regional stocks. Glucagon is also relatively poorly tolerated, frequently causing nausea and vomiting. In contrast, enoximone is licensed as an inotrope in patients with heart failure unresponsive to

catecholamines. The elevation of smooth muscle cAMP, which occurs with both glucagon and enoximone, can lead to marked vasodilation⁹ and worsening hypotension; we would suggest that, in the situation described above, it be used with concomitant vasopressor therapy and cardiac output monitoring. There are some limited *in vitro* as well as animal studies supporting both glucagon and phosphodiesterase inhibitors in the treatment of anaphylaxis, through prevention of mast cell degranulation, bronchodilation and improvement in metabolic acidosis.^{10 11}

Alternative non-adrenergic vasopressors, such as argipressin, may also have a role in this situation.¹² Similarly, hyperinsulinaemia, working via a number of diverse mechanisms, has been reported to work in β -blocker overdose,¹³ and while no reports exist in anaphylaxis complicated by adrenergic blockade, this therapy could have a role in situations such as those reported here.

In the case we have reported, it may be possible that the improvement seen was not solely attributable to the effect of enoximone. As the labetalol is metabolised, the previously blocked adrenoreceptors would have become available for catecholamine agonism. The half-life of oral labetalol is 6–8 h, so the full resolution in our patient's clinical state, seen around 12–18 h after the last labetalol dose, could have been associated with a gradually increasing availability of binding sites for the adrenergic agonists as much as to the enoximone.

Mast-cell tryptases may also be elevated in conditions other than anaphylaxis,¹⁴ including in end-stage renal failure, as seen in this patient. However, the pattern of a sudden massive rise and subsequent resolution to near undetectable levels 24 h later is not consistent with chronic release or failure to clear constitutive release, and is specific to anaphylaxis.¹

Why the patient developed apparent anaphylaxis to piperacillin/tazobactam, having been previously—without apparent allergy—exposed to penicillins, remains open to speculation. It is possible that it was the tazobactam element that produced the anaphylactic reaction, or that the patient was sensitised during recent prior exposure and then subsequently manifested an anaphylactic reaction.

In addition to this, thrombolysis for possible PE apparently seemed to coincide with this improvement. Although CTPA shortly after this was clear, and the alternative diagnosis of anaphylaxis was ultimately confirmed, there is a remote possibility that thrombolytic therapy had by this time lysed the thrombus to an extent beyond that which could be identified radiologically, or that, with the known sensitivity of CTPA of 83%,¹⁵ there was a false-negative result. Therefore a PE might have been a contributing factor in the arrest.

Learning points

- ▶ Anaphylaxis-related hypotension unresponsive to epinephrine due to concurrent α and β blockade is rare, but of potentially increasing importance considering the increasing prevalence of resistant hypertension.
- ▶ Adrenergic inotropes have little or no effect in this setting, and the recommended use of glucagon as an alternative is supported by limited evidence and is, furthermore, poorly tolerated by patients due to emesis.
- ▶ The use of enoximone as a non-adrenergic inotrope in this case, although complicated by an evolving diagnosis, appeared to herald an improvement in clinical state, and merits the consideration of use of phosphodiesterase III inhibitors in similar scenarios.

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Contributors SH drafted the report, reviewed the literature and approved the final version. VN supervised the case, drafted the report and approved the final version. ACM managed the case, drafted the report and approved the final version.

Competing interests None declared.

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