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Use of Alpha 2 Agonist in Septic Shock: A Case Report

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Abstract **Case Report**

In this case study the aim is to highlight the role of Alpha-2 agonists to reduce vasopressor requirements in septic shock. In fact the case presented to us is an 11-month-old child admitted for burns on the whole body. The usual treatment does not seem to be very effective, so the hospital's medical team decided to inject him with a α 2-adrenoceptor agonists: Remarkable results have emerged at the end of this treatment. It has been proven that Clonidine reduces sympathetic nerve activity to the heart and vasculature by a direct central action, which is its main mechanism of action as an antihypertensive drug. With reductions in sympathetic nerve activity to other organs, this is likely associated with a decrease in plasma catecholamines concentrations. This substance has a special mechanism which has proven a succes in septic shock.

Keywords: Alpha-2 agonists, vasopressor, treatment, sympathetic nerve activity.

INTRODUCTION

During septic shock, vasopressors are a cornerstone of therapy. In septic shock, very high doses of vasopressors sometimes have to be used due to vascular desensitization, the mechanisms of which are poorly understood. *Counterintuitively*, *α* 2-adrenoceptor agonists were shown to reduce noradrenaline requirements.

CASE REPORT

We present the case of an 11 month old male infant, well vaccinated and without particular history who was admitted for total burn of the head and right hand following a domestic fire. There are no other lesions elsewhere. The child was conscious, with good hemodynamics and without respiratory distress. The eyes are not affected and the hair is burnt. The mouth is intact. The lesions are estimated to be deep dermal.

The intubation was performed straight away because of the risk of airway obstruction. The care of the burn was performed under general anesthesia in the operating room. 12 hours after admission, clinical signs of hypo perfusion appeared. Echocardiography reveals left ventricular dysfunction. The baby responds well to the dobutamine / norepinephrine combination. The dobutamine perfusion was stopped after 24 hours.

In addition, the onset of fever led us to precribe antibiotic therapy (amoxicillin clavulanic acid + gentamycin).The heart being hyperkinetic; propranolol was administered at a dose of 0.8 mg / Kg / 6h. The next day, maintenance of blood pressure (MAP = 55mmHg) came at the cost of tachycardia (despite propranolol) and skin vasoconstriction. The diuresis remaining correct (1.5ml / Kg / h).

The filling is considered to be adequate (inferior vena cava, Doppler of renal veins). We decide to add an alpha2 agonist, clonidine (dexmedetomidine is not available) at a dose of 10µg / Kg / d. Heart rate drops to 95-100 / min and blood pressure drops to 45 on average. However, the diuresis is maintained or even increased, the capillary filling time improves. The color is pink and homogeneous. On echocardiography, the heart contracts well, the filling is considered correct. There is no increased respiratory requirement. We decide to respect this level of blood pressure.

The treatment sessions for burns under general anesthesia (sevoflurane / fentanyl) go without incident. Fentanyl requirements are lower than expected for the child's weight (10mcg IV per session). The baby was extubated after 10 days of ventilation. The noradrenaline was stopped after 8 days. Clonidine was stopped on the 11th day. The patient left the intensive care unit the day after his extubation.

DISCUSSION

The definition of septic shock includes a systolic blood pressure (SBP) <90 mmHg, after adequate fluid replacement (commonly >30 mL·kg-1 in <6 h) and the need for vasopressor drugs for more than 1 h [1] or for 4 h (minimal requirements of NA >0.05 μg·kg-1·min-1). Earlier series have reported a death toll of ≈70% [2] and recent series still report a high mortality (27% [3], 20% [4], and 16% [5]). Refractory septic shock is defined as a requirement for NA >0.25 μg·kg-1·min-1 (>1 mg·h-1/70 kg) [6] or >0.5 μg·kg-1·min-1 [7].

The initial treatment for septic shock is volume loading, but the adequacy of volume loading is poorly defined [8]. Presumably, the best index is the collapsibility of the vena cava (superior vena cava [9] or inferior vena cava) or absence of response to passive leg rising.

Thus, adequacy of volume load is assessed when little or no change occurs in the diameter of the inferior or superior vena cava or when additional volume loading evokes no additional increase in cardiac output (CO). There is ongoing controversy regarding the balance between the necessity to achieve adequate volemia, during the first 24–72 h, and the necessity to avoid increased lung water by normalizing the net weight gain, as early as possible.

The second line of therapy is the use of vasopressors, usually NA, to achieve a MAP ≥65 mmHg. The dose of NA required varies from ≈1 μg-1·kg-1·min-1 to ≈2.6 μg-1·kg-1·min-1, respectively, in nonrefractory versus refractory septic shock (4 to 11 mg·h-1) [11]. However, the same established group [12] uses NA as high as 50–100 mg·h-1 to treat refractory septic shock. Secondly, setting the MAP ≥65 mmHg may be arbitrary: BP is too low when dealing with patients with preexisting hypertension [13] or with low functional capillary density [13].

As the drugs cited above were not overwhelmingly successful in treating sepsis, our group has examined a novel and *counterintuitive* approach: the use of α 2-adrenoceptor agonists. In two cases [14], treatment with the α 2-adrenoceptor agonist, clonidine (1 μg·kg-1·h-1), in addition to state-of-the-art treatment, reduced NA requirements in (a) a patient presenting with HIV and terminal pulmonary sepsis (−45%) [14] and (b) a neonate presenting with necrotizing enterocolitis (−90%, submitted). In addition, we have documented this reduction in requirement for NA in rat [15] and sheep [16] experimental models of sepsis, using high and low doses, respectively, of the α 2-adrenoceptor agonists, clonidine and dexmedetomidine. Furthermore, the pressor responsiveness to a noncatecholaminergic vasopressor, angiotensin II, was also reduced by clonidine treatment [16].

One possible mechanism [17] for this effect of α 2-adrenoceptor agonists in sepsis is that, during septic shock, as during exercise [18], there is increased sympathetic nerve activity and endogenous plasma catecholamines [19, 20] with a downregulation in responsiveness to stimulation of α 1- and β-adrenoceptors, which may result from reduced binding or reduced sensitivity/intracellular coupling. Conversely, the other side of this working hypothesis [17] is that, during rest after exercise, or after lowering plasma catecholamine concentrations with either pharmacologically evoked α 2-adrenoceptor agonists or those occurring spontaneously during recovery from sepsis, the downregulation of α 1-adrenoceptors are converted to upregulation, with an increased pressor response to vasopressors.

Clonidine reduces sympathetic nerve activity to the heart and vasculature by a direct central action, which is its main mechanism of action as an antihypertensive drug [21, 22]. How can this central action of clonidine to reduce BP in hypertensive patients be reconciled with an increased pressor response and lowered NA requirement in patients with sepsis? A recent experimental study indicates that treatment with clonidine reduced renal sympathetic nerve activity from high to normal levels [16]. Together with reductions in sympathetic nerve activity to other organs, this is likely associated with a decrease in plasma catecholamines concentrations and is compatible with our case.

CONCLUSION

It remains to be determined whether the maldistribution of capillary perfusion in sepsis [23] is improved by treatment with α 2-adrenoceptor agonists and if so whether this is due to its central sympathetic deactivation or to a direct vascular action.

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