

# Inotropes in Children

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## Introduction

Despite much research into the various systemic effects of the agents available, there are few (if any) trials demonstrating a survival advantage offered by any one inotropic agent over another. Despite this, some guidelines have begun to emerge.

The complexity of adrenoceptor biology continues to be elucidated and some explanations for the variability of patient responsiveness have emerged. The role of endocrine supplementation post-bypass and in catecholamine refractory states of septic shock has been enhanced, as has the use of the phosphodiesterase inhibitors such as milrinone.

New agents may offer advances over current therapies. These include the myocyte calcium sensitizer, levosimendan, which has both inotropic and vasodilating effects, the natriuretic peptide agonist, nesiritide, and endothelin antagonists such as tezosentan. Paediatric experience is limited but increasing.

## The adrenoceptors and their agonists

Research into adrenergic receptor biology continues. Insel<sup>2</sup> has written an extensive review of their classification and function. Of note, the simple  $\alpha$  and  $\beta$  classification has expanded to include at least nine membrane receptor subtypes. New understanding of transmembrane signalling and its control has been highlighted. The importance of receptor desensitization and the mechanisms of uncoupling during exposure to the adrenergic agonists has also been reviewed.<sup>3</sup> Similar changes appear following exposure to cardiopulmonary bypass<sup>1</sup> and sepsis.<sup>4,5</sup> This information suggests that the optimal choice of agent and required dose will probably change over time in the same patient.

Age related differences in agent response and dosage requirements are further complicated by genetic heterogeneity at several levels,<sup>3</sup> with important considerations for dose responsiveness and probably disease outcome. Heterogeneity of response to  $\beta_2$  agonists has been documented in asthmatic patients.<sup>6</sup> Similarly, genetic predispositions for both  $\beta_1$  blockade and heart failure provide insight into the variability of patient responsiveness to adrenergic agents of all types.<sup>3,7</sup> This work has important implications for the use of adrenergic agonists in intensive care and the genetic origins of disease susceptibility, severity and therapeutic response.

Work by Myburgh<sup>1</sup> and others has begun to emphasize dose rather than agent, particularly when comparing dopamine, noradrenaline and adrenaline. Agent selection may be guided by better understanding of the timing of responsiveness in disease states.<sup>8</sup>

This bewildering array of information is yet to (and may not ever) tell us which agent is the inotrope to use at which dose and when, but some consensus is beginning to emerge.

### Consensus Guidelines

The publication of Clinical Practice Parameters for haemodynamic support in septic shock for children<sup>9</sup> and, more recently, adults<sup>10</sup> provides templates for the care of these patients. They are coupled with the inevitable (and low) levels of evidence for each recommendation, including the use of monitoring methods. Despite the paucity of high quality evidence within the guidelines, there is data suggesting that both standardization of medical care<sup>11</sup> and the utilization of these guides<sup>12</sup> (at least for paediatric and neonatal sepsis) does improve outcome.

#### *Preterm and VLBW (Very Low Birthweight) Infant*

Despite the recognized limitations of the Cochrane style meta-analytic approach, the review by Subedhar et al<sup>13</sup> of dopamine vs dobutamine for hypotensive preterm infants deserves comment. Dopamine was concluded to be more effective than dobutamine for the short term treatment of systemic hypotension. The absence of data confirming longer term benefit and safety precluded firm recommendations. A review by Dasgupta<sup>14</sup> et al highlighted many of the controversies in the management of hypotension in this group. They suggested that both agents may need to be used in higher doses than are usual (10-20 mcg/kg/min) and that a response was often seen when used the drugs were used together. Does this reflect age related pharmacokinetic differences or yet to be characterized differences in  $\beta$ -receptor subtype expression and intracellular response?

As with the recommendations for other age groups, noradrenaline or adrenaline for non-responders and steroids for catecholamine resistant hypotension were recommended.

#### *High dose adrenaline (epinephrine)*

Earlier guidelines supporting the use of high dose adrenaline were based on retrospective in-hospital data. A more recent prospective randomized controlled trial from the NEJM,<sup>15</sup> where in-hospital arrest patients were randomized to receive rescue dose adrenaline (10 vs 100 mcg/kg), demonstrated no benefit and the potential for harm in the high dose group. This would support similar studies in adults.

#### *Endocrine agents: hydrocortisone, tri-iodothyronine, vasopressin and angiotensin*

Abnormalities of the pituitary-adrenal axis have been well documented in septic adults<sup>16</sup> and children.<sup>17</sup> Inadequate endocrine and metabolic response appears to differentiate survivors from non-survivors in meningococcal sepsis.<sup>17</sup> Annane<sup>18</sup> documented improvement in cardiovascular parameters with supra-physiologic replacement in adults. Less data is available in children; thus current guidelines suggest that corticosteroid replacement be “reserved for children with catecholamine resistance and evidence of or suspected adrenal insufficiency”.<sup>9</sup>

Thyroid hormone suppression has also been demonstrated in both children and adults with critical illness<sup>17, 19</sup> and following surgery.<sup>20</sup> The postoperative myocardial dysfunction and vasoplegia resembles that seen in hypothyroidism.<sup>21</sup> T3 has beneficial

inotropic effects post-cardiopulmonary bypass, preventing low cardiac output state (LCOS).<sup>22</sup> These effects appear to be mediated by both adrenergic and  $\text{Ca}^{++}$  potentiation without oxygen wasting.<sup>23, 24</sup> A randomized placebo controlled trial of tri-iodothyronine in children after cardiac surgery was published by Bettendorf.<sup>25</sup> Improved myocardial function was demonstrated, especially in those with a low cardiac output state and this was associated with a trend towards reduced ICU stay.

The pharmacology of vasopressin has recently been reviewed by Kam.<sup>26</sup> It is an osmoregulatory hormone providing maintenance of normovolaemia (V2 receptors). It also has direct systemic and pulmonary vasodilator effects (via oxytocin receptors) at low to normal serum concentrations and direct systemic and pulmonary vasoconstrictor (via V1 receptors) at high to normal serum concentrations. Interestingly, during hypovolaemia there would appear to be V1 induced augmentation of vasoresponsivity to noradrenaline. Patients with vasodilatory shock states have documented low vasopressin concentrations.<sup>27</sup> Benefits have been shown in children with excessive vasodilation post-cardiopulmonary bypass<sup>28</sup> and in catecholamine resistant septic shock in adults.<sup>29</sup> There has also been the recent demonstration in adults of improved survival in out-of-hospital arrest compared with adrenaline.<sup>30</sup>

Similarly to vasopressin, the vasoconstrictive effects of angiotensin are non  $\beta$ -adrenoceptor mediated. Initial reports in adults of the successful use of angiotensin II in refractory septic shock unresponsive to noradrenaline<sup>31</sup> have been followed by case reports in children.<sup>32</sup> The published guidelines provide for its use in the "catecholamine resistant" group pre-ECMO.<sup>9</sup>

### *Milrinone*

Milrinone is a type III phosphodiesterase inhibitor that prevents cAMP degradation, leading to a potentiation of  $\beta$ -receptor effects in cardiac and vascular smooth muscle. It has been shown to overcome  $\beta_1$  and  $\beta_2$  receptor down-regulation<sup>33</sup> and has been recommended for nitrovasodilator resistant LCOS in sepsis.<sup>9, 34</sup> Recently, the PRIMACORP study<sup>35</sup> demonstrated the safety and efficacy of milrinone in preventing LCOS in infants and children after corrective surgery for congenital heart disease. These were biventricular repairs only and the absolute risk reduction for death or an episode of LCOS only 17% (a number needed to treat of 5.8) in the high dose group (75 mcg/kg load +0.75 mcg/kg/min).

### **Newer agents**

#### *Levosimendan*

Levosimendan is a new myocardial myofilament calcium sensitizer that binds to troponin C, stabilizing the calcium induced change in conformation and enhancing contractility.<sup>36</sup> There also appears to be ATP-dependent potassium channel induced peripheral and coronary vasodilation<sup>37</sup> and, perhaps, phosphodiesterase III inhibition at high doses.<sup>38</sup> It has inotropic and lusitropic actions in failing human myocardium with the inotropic effect dominating at low dose. The active metabolite (OR-1896) has a prolonged half life providing sustained benefit.<sup>39</sup> Significant survival benefit was demonstrated in two large adult trials.<sup>40, 41</sup> Paediatric data has been limited to case reports until the publication of Turanlathi's pharmacokinetic data in a mixed group of patients being evaluated for cardiac surgery.<sup>42</sup> Trials in refractory LCOS in children are eagerly awaited.

### *Nesiritide*

Nesiritide is the recently introduced human recombinant form of Brain Natriuretic Peptide (BNP). Its physiology and potential role in heart failure has been reviewed recently.<sup>43</sup> The natriuretic family (ANP BNP CNP) of peptides are released in response to myocardial stretch and BNP levels have been shown in adults to be both diagnostic and prognostic in congestive cardiac failure.<sup>3,43</sup> Similarly, both ANP and BNP were recently demonstrated to be increased in congenital heart defects with clinical signs of heart failure.<sup>44</sup>

Nesiritide has been shown to provide dose dependant vasodilation via cGMP. This improves cardiac index without inotropy or changes in heart rate (improved VO<sub>2</sub>). No change to intracellular cAMP or Ca<sup>++</sup> has been documented and therefore this agent is not as arrhythmogenic as dobutamine<sup>45</sup> and milrinone.<sup>46</sup> No evidence of tolerance to the vasodilating effects has emerged when compared with nitrovasodilators.<sup>47</sup> It increases urine volume and sodium excretion.<sup>43</sup> It may also be more effective and cheaper than milrinone in acute decompensated heart failure in adults.<sup>46</sup> Paediatric experience is limited.

### *Tezosentan*

Tezosentan is another recently introduced compound that has actions as an endothelin antagonist.<sup>48</sup> The endothelin receptors mediate vasoconstriction (via ETA and ETB2) and vasodilation (via ETB1). Tezosentan has 30 times the affinity for ETA, functioning as a potent vasodilator at low doses. Its pharmacokinetics render it suitable for infusion and it has been used successfully in humans with congestive cardiac failure.<sup>49,50</sup> It has been shown to improve cardiac performance in septic shock at low doses (with reductions in SVR and PVR in pigs) whilst ETB1 mediated vasoconstriction appears to predominate with dose escalation.<sup>51</sup>

## **Conclusions**

Paediatric inotropic therapy has been furnished with some new understanding of older agents, and new ways of using them. Some agents are gaining an evidence base, whilst even newer agents need such a base. Guidelines are emerging to facilitate their use.

For the moment, in children requiring inotropic therapy (as in adults)

“... individual experience and preference (will continue to) determine selection...”

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