

Dexmedetomidine in cardiac disease: whats the controversy?

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Alpha₂ adrenoreceptor agonists (α_2 agonists) are a group of drugs that are traditionally recommended only for administration to healthy animals, particularly animals without evidence of cardiovascular disease (Murrell and Hellebrekers 2005, Sinclair 2003). This is due to the reduction in cardiac output and increase cardiac afterload that follows α_2 agonist administration of (Lawrence et al. 1996a), which may be detrimental to animals with reduced cardiovascular system reserve function. However this dogma is being increasingly questioned in the veterinary profession due to the use of dexmedetomidine in adults with cardiovascular disease (Wijeyesundera et al. 2003). But, it is important to remember that cardiovascular diseases in man and animals are not directly comparable, therefore extrapolation of data between species may not be appropriate. Further, the use of dexmedetomidine during cardiac surgery in people is also not without controversy. Two editorials recently appeared in the Journal of Cardiothoracic and Vascular Anaesthesia discussing the evidence for and against the use of dexmedetomidine for infants and children during cardiac surgery.

Easley and Tobias (2008) make the argument *for* the use of dexmedetomidine in children with cardiac disease, and point out that even though there is currently no FDA approved usage in children, there are more than 1,000 reports of the use of dexmedetomidine in paediatric-aged children for various clinical conditions.

Their main arguments to support the use of dexmedetomidine during cardiac surgery in infants focus on the pharmacological actions of dexmedetomidine causing:

- reduced norepinephrine turnover and decreased central sympathetic outflow from the medullary vasomotor centre with sympatholysis, decreased heart rate and blood pressure.
- decreased renin and vasopressin levels resulting in increased diuresis.
- inhibition of output from the locus ceruleus resulting in sedation and anxiolysis.
- potentiation of opioid induced analgesia.

A number of studies have evaluated the use of a dexmedetomidine CRI in children with congenital heart disease undergoing a variety of procedures. Mester et al. (2008) reported the successful use of a combination of dexmedetomidine and ketamine in a prospective open label trial using these agents for sedation during cardiac catheterization in infants and children. They reported no significant cardiovascular events (for example hypertension,

hypotension or bradycardia), although mild hypercarbia was reported in approximately half of the patients.

During paediatric surgery, an adjuvant dexmedetomidine infusion has been shown to reduce peri-operative plasma concentrations of various stress hormones (Muhktar et al. 2006), and no adverse events were reported.

The potential benefits and efficacy of dexmedetomidine in providing postoperative sedation in infants and children with congenital heart disease undergoing mechanical ventilation have also been shown. Chrysostosmou et al. (2006) reported successful sedation and analgesia in 93% of 38 patients given a low dose dexmedetomidine CRI (0.5-1µg/kg/hour) after surgery for between 6 and 36 hours.

However it is important to consider that despite these favourable reports cited by Esaley and Tobias (2008), there is as yet no robust scientific evidence that supports an improved outcome following the use of dexmedetomidine in this paediatric patient population compared to other anaesthetic and sedative agents. Most of the work cited in this editorial can only demonstrate that administration of dexmedetomidine was not associated with harmful effects rather than demonstrating a positive benefit. Further the majority of the investigations cited are reports of the use of dexmedetomidine rather than prospective, randomised, blinded clinical trials, therefore the quality of the evidence provided must also be questioned.

Hammer (2008) makes the counter argument that dexmedetomidine should *not* be used for infants and children during cardiac surgery. Although he acknowledges that sympatholysis may be beneficial during cardiac surgery, he cites the same cardiovascular effects of dexmedetomidine as being potentially harmful as reasons not to include it in the anaesthetic protocol for these procedures:

- hypertension (due to peripheral vasoconstriction) associated with either a loading dose of dexmedetomidine or continuous infusion resulting in high plasma concentration.
- hypotension due to sympatholysis.
- decreased heart rate.

Firstly, Hammer (2008) makes the point that there are very few studies of the use of dexmedetomidine during paediatric cardiac surgery. He is critical of the study by Muktar et al. (2006), pointing out that the depth of anaesthesia between the two groups of patients (dexmedetomidine CRI or no dexmedetomidine CRI in combination with isoflurane maintenance and fentanyl) were not comparable. The group of patients receiving dexmedetomidine were more deeply anaesthetised, therefore the reduced plasma concentrations of stress hormones

may be attributed to differences in depths of anaesthesia rather than an effect of dexmedetomidine alone.

The negative chronotropic effect of dexmedetomidine may be beneficial in adult patients with coronary artery disease, but it is uncertain whether this effect is also beneficial in children. In children, drugs with positive chronotropic effects (e.g. dopamine, dobutamine and epinephrine) are commonly used after cardiopulmonary bypass to maintain heart rate in the range of 120-140 beats/minute. Therefore co-administration of a drug that is known to decrease heart rate with catecholamines seems illogical. Further haemorrhage, hypovolaemia and ventricular dysfunction are relatively common in neonates after cardiopulmonary bypass, under these circumstances the sympatholytic effects of dexmedetomidine may be detrimental (Blake et al. 2000).

Hammer et al. (2008) found that dexmedetomidine significantly depressed sinus and atrioventricular node function in children. Bradyarrhythmias are a significant concern after intracardiac repair in paediatric patients, commonly necessitating placement of temporary or permanent atrioventricular pacemaker devices. Therefore use of dexmedetomidine in patients already at high risk of clinically significant bradyarrhythmias may not be appropriate.

Pulmonary arterial hypertension is also common in paediatric patients undergoing cardiac surgery for repair of lesions with left to right shunts. Dexmedetomidine has the potential to cause increases in pulmonary arterial pressure (Ebert et al. 2000), and although the effects of dexmedetomidine in children and neonates with increased pulmonary vascular resistance is unknown, administration of a drug known to have the potential to further exacerbate pulmonary hypertension may be disadvantageous.

So what is the relevance of this discussion to veterinary patients?

It appears that the situation regarding the use of dexmedetomidine in veterinary patients with cardiovascular disease is at a similar stage to use of dexmedetomidine in children and infants undergoing cardiac surgery: *we don't know!*

Hammer (2008) and Easley and Tobias (2008) both use the same physiological properties of dexmedetomidine to argue for and against the use of this drug in this patient population. Easley and Tobias make an argument that is heavily dependent on the results of non-randomised and non-blinded trials and also extrapolate data from adult patients to the child population. It is important to remember that cardiovascular diseases in children requiring surgery and mainly

congenital and therefore are very different from adult cardiovascular pathologies.

Veterinary anaesthetists also tend to fall into the same trap regarding the use of dexmedetomidine in dogs and cats with cardiovascular disease. Studies in dogs have shown that administration of low doses of dexmedetomidine (< 10 µg/kg) slows heart rate and may preferentially result in improved perfusion of the endocardium (Lawrence et al. 1996b). The reduction in heart rate is also associated with reduced myocardial oxygen consumption. However these studies have all been conducted in healthy dogs without evidence of cardiovascular disease. Data regarding the effects of dexmedetomidine on the cardiovascular system cannot be safely extrapolated between adult people, dogs and cats, all of which show a range of species specific cardiovascular pathologies.

Before recommendations regarding the use of dexmedetomidine in veterinary patients with cardiovascular disease are made, robust scientific evidence describing the CVS effects of the drug in these patient populations is required. Unfortunately these data may be hard to come by, but until we have them in the scientific arena we can only make judgements about the safety and efficacy of dexmedetomidine in patients with cardiovascular disease based on an outcome of *did the patient survive or not?* This, for a scientific profession, is not satisfactory.

References

Blake DW, Ludbrook J, Van Leeuwen AF (2000). Dexmedetomidine and haemodynamic responses to acute central hypovolaemia in conscious rabbits. *Clin Exp Pharm Physiol*, 27, 801-809.

Chrysostomou C, Di Filippo S, Manrique AM et al. (2006). Use of a dexmedetomidine infusion in children after cardiac and thoracic surgery. *Pediatr Crit Care Med*, 7, 126-131.

Easley RB and Tobias JB (2008). Pro: Dexmedetomidine should be used for infants and children undergoing cardiac surgery. *Journal of Cardiovascular and Thoracic Anaesthesia*, 22, 147-151.

Ebert TJ, Hall JE, Barney JA et al. (2000). The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology*, 93, 382-394.

Lawrence CJ, Prinzen FW, de Lange S (1996a). The effect of dexmedetomidine on nutrient organ blood flow. *Anaesth Analg*, 83, 1160-1165.

Lawrence CJ, Prinzen FW, de Lange S (1996b). The effect of dexmedetomidine on the balance of myocardial energy requirement and oxygen supply and demand. *Anaesth Analg*, 82, 544-550.

Hammer GB, Drover DR, Cao H et al. (2008). The effects of dexmedetomidine on cardiac electrophysiology in children. *Anaesth Analg*, 106, 79-83.

Hammer GB (2008). Con: Dexmedetomidine should not be used for infants and children during cardiac surgery. *Journal of Cardiothoracic and Vascular Anaesthesia*, 22, 152-154.

Mester R, Easley RB, Brady KM et al. (2008). Monitored anaesthesia care with a combination of ketamine and dexmedetomidine during cardiac catheterization. *Am J Ther*, 15, 24-30.

Murrell JC & Hellebrekers LJ (2005). Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog. *Vet Anaesth Analg*, 32, 117-127

Sinclair MD (2003). A review of the physiological effects of alpha2-agonists related to the clinical use of medetomidine in small animal practice. *Can Vet J*, 44, 885-897.

Wijeysundera DN, Naik JS, Beattie WS (2003). Alpha-2-adrenergic agonists to prevent peri-operative cardiovascular complications: a meta analysis. *American Journal of Medicine*, 114, 742-752