Be Not Afraid! How to Use Alpha-2 Agonists with Confidence in your Clinical Practice

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The alpha-2 receptor is an adrenergic receptor which is located in the CNS (brain and spinal cord) and the periphery, particularly on the vasculature. There are 3 subtypes of alpha-2 receptors, A, B and C and the subtype and location of the receptor determines the effect of stimulating them.

In general, alpha-2 agonist drugs provide excellent sedation, analgesia, and muscle relaxation. The profound chemical restraint is extremely useful in angry or fearful dogs and cats and leads to safer experiences for both the animals and the staff. Administration in the premedication results in a reduction of induction drug dose as well as maintenance inhalant MAC (dose). The side effects are relatively dose dependent in severity and duration with the cardiovascular side-effects being most noticeable. Cardiovascular depression is in the form of decreased heart rate and cardiac output, increased systemic vascular resistance, and development of atrioventricular nodal block. Respiratory depression is minimal when alpha-2 agonists are given alone, however they can potentiate the respiratory depressant effects of opioids when given in combination. Other side effects include vomiting, hyperglycaemia, polyuria, increase myometrial activity, mild hypothermia, and sensitivity to light and sound.

The central effects of alpha-2 agonists agents (CNS) in the brain include sedation and sympatholysis, important is it decreases systemic sympathetic tone, and analgesia mediated in the spinal cord. On the vasculature in the periphery, alpha-2 agonists cause vasoconstriction which stimulated peripheral baroreceptors and results in a negative feedback reflex to the sinoatrial node of the heart. This results in bradycardia. However, when the peripheral and central effects are taken together, the bradycardia is in excess of the reflex effect owing to the sympatholytic CNS effect. As cardiac output is dependent on heart rate and stroke volume, a significant decrease in heart rate is to blame for the decrease in cardiac output seen with alpha-2 agonists. Multiple studies in dogs and cats have supported this effect and have shown that the effect is even more pronounced when the alpha-2 agonist agent has been administered to animals under inhalant anaesthesia. In these circumstances, clinical hypotension (mean arterial pressure less than 60 mmHg) is often noted. Multiple studies have also examined the results of administration of anticholinergic drugs such as atropine or glycopyrrolate to attempt to prevent or treat the bradycardia and have demonstrated that the combination is not recommended due to development of severe hypertension, tachycardia, arrhythmias and increased myocardia work. Other methods such as decreasing the depth of anaesthesia, fluid boluses, ephedrine, dopamine, and/or reversal of the alpha-2 agent should be considered in the face of systemic hypotension. If blood pressure is fine, however, generally the bradycardia associated with medetomidine and dexmedetomidine does not need to be treated.

It is important to know that healthy dogs and cats have good cardiac reserves, meaning that, even at rest, their cardiac output exceeds their tissue metabolic needs. This is why we

can administer drugs like medetomidine and dexmedetomidine in routine healthy patients without extreme fear of mortality. On the other hand though, if patients have significantly decreased cardiac reserves due to cardiac disease, haemodynamic instability, or geriatric age, further decreases in cardiac output may prove detrimental and medetomidine and dexmedetomidine should be avoided in these patients.

Dexmedetomidine is the "R" isomer of the racemic mixture drug medetomidine. It is thought that the "L" isomer might actually interfere with sedation, hence the potential advantage to dexmedetomidine. Dexmedetomidine is, in theory, twice as potent as medetomidine meaning that ½ of the medetomidine dose is used for dexmedetomidine. Several studies have supported this with no differences in the degree of sedation between medetomidine and dexmedetomidine when dosed as above. However, some other studies looking at IM dosing found that medetomidine seemed to provide greater sedation than dexmedetomidine at equipotent doses, potentially suggesting that dexmedetomidine is less than 2x the potency of medetomidine. Clinically, I typically dose dexmedetomidine at ¾ of the medetomidine dose meaning that if I was planning to give 10 mcg/kg of medetomidine, I administer 7.5 mcg/kg of dexmedetomidine. Ideally IM injections should be given into either the cervical musculature or the semimembranosus muscle.

My suggested dosing chart:

<table>
<tr><td></td><td colspan="2">IM (~15 min onset)</td><td colspan="2">IV (~2-3 min onset)</td></tr>
<tr><td></td><td>Dogs</td><td>Cats</td><td>Dogs</td><td>Cats</td></tr>
<tr><td>Medetomidine alone</td><td>5-15 mcg/kg</td><td>10-20 mcg/kg</td><td colspan="2">2-5 mcg/kg</td></tr>
<tr><td>Dexmedetomidine alone</td><td>5-10 mcg/kg</td><td>7-15 mcg/kg</td><td colspan="2">1-3 mcg/kg</td></tr>
<tr><td rowspan="2">+ Butorphanol (0.3-0.5 mg/kg IM) or (0.1-0.2 mg/kg IV)
OR
+ Methadone (same doses as butorphanol)</td><td>(M) 5-12 mcg/kg</td><td>7-15 mcg/kg</td><td colspan="2" rowspan="2">IV doses same as above</td></tr>
<tr><td>(D) 3-7 mcg/kg</td><td>5-12 mcg/kg</td></tr>
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Finally, routine reversal of either dexmedetomidine or medetomidine with atipamezole is not necessary. Administration of atipamezole reverses the sedative and analgesic effects of the alpha-2 agonists but may not fully reverse the cardiovascular side-effects, particularly if the original dose was given IM. Atipamezole should be given IM except in emergency cases (cardiac arrest or impending arrest) as IV administration can lead to reversal of the vasoconstriction before the bradycardia, potentially inducing a shock-like state. Atipamezole lasts for about 3 hours so if it is given, further doses of medetomidine or dexmedetomidine in that time frame may be ineffective.