DEXMEDETOMIDINE: A NEW ALPHA-2 AGONIST FOR SMALL ANIMAL PRACTICE
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Introduction:
The alpha2-adrenergic agonist dexmedetomidine is the active optical enantiomer isolated from the racemic compound medetomidine. Although alpha2-adrenergic agonists have been used in veterinary anesthesia since the late 1960s, the development of dexmedetomidine in the 1990s has led to a renewed interest in the perioperative use of alpha2-agonists in human beings (1). In dogs and cats, dexmedetomidine produces dose-dependent levels of sedation and the intensity of these effects is similar to that produced by twice the dose of medetomidine (2,3).

Sedative effects:
In dogs, a dose of 5 mcg/kg administered intravenously produces moderate to profound sedation lasting to up to 30 minutes; the combination of dexmedetomidine with acepromazine (0.05 mg/kg) does not modify the intensity nor prolongs dexmedetomidine's sedative effects (4). Profoundly sedated animals will remain spontaneously in lateral recumbency; the mouth can be opened and the tongue may be manually exposed without difficulty (4). In dogs, it appears that a ceiling sedative effect is achieved with a dose of 10 mcg/kg; increasing the intravenous dose of dexmedetomidine from 10 to 20 mcg/kg increases the duration but not the intensity of sedation (3).

Analgesic effects:
Studies evaluating the analgesic effects of dexmedetomidine are scarce. Comparatively to the duration of its sedative action, alpha2 agonist induced analgesia is relatively short lived (3). Dexmedetomidine’s analgesic effects (20 mcg/kg/IV) appear to last longer than the analgesic effects produced by an equipotent dose of medetomidine (40 mcg/kg/IV) (3). In cats receiving doses ranging from 5 to 40 mcg/kg of dexmedetomidine, only the highest dose showed antinociceptive effects to a thermal stimulus applied to the skin (5). The dose reported to produce analgesia in cats (40 mcg/kg) is relatively high and has the potential for causing unwanted side effects (excessive cardiopulmonary depression). Lower doses of dexmedetomidine (5-10 mcg/kg in dogs and 10-20 mcg/kg in cats) have been combined with opioid analgesics with the expectation of achieving a synergistic analgesic affect.

Cardiovascular and respiratory effects:
Similarly to other alpha-2 agonists a single dose of dexmedetomidine (10 mcg/kg/IV) will induce a transient vasopressor effect, characterized by substantial increases in systemic vascular resistance (SVR), moderate increases in arterial pressure, bradycardia, and a decrease in cardiac output (CO) (6). After 5 minutes of dexmedetomidine administration (10 mcg/kg/IV), CO was decreased by 50% from baseline values. Second degree atrioventricular blocks, periods of sinus arrest are not uncommon. In cases of marked decreases in heart rate (HR < 40 beats/min in dogs), ventricular escape beats may be observed. Routine anticholinergic administration (atropine, glycopyrrolate) to prevent dexmedetomidine induced bradyarrhythmias is contraindicated because it will cause significant hypertension and may be associated with premature ventricular depolarizations (4). Because dexmedetomidine may cause major increases in afterload (vasoconstriction) and in CO, its
use should be avoided in animals presenting with decreased cardiac reserve, such as geriatric patients and individuals with heart failure.

In healthy dogs, dexmedetomidine (5-20 mcg/kg) does not interfere with respiratory function or induces mild to moderate changes in arterial blood gases (4,7,8). This finding is interesting if one notices that high doses of dexmedetomidine and other alpha-2 agonists cause the tongue become dark red/bluish in appearance. The use of pulse oximetry monitoring (sensor placed in the tongue) in animals sedated with dexmedetomidine or medetomidine may result in values below the threshold for severe hypoxemia, (hemoglobin saturation < 90%), but these values are not reliable as hemoglobin saturation measured by arterial blood gas analysis will often display substantially higher values (8). Pooling of deoxygenated blood in the tongue due to peripheral vasoconstriction may explain the erroneously low hemoglobin saturation values displayed by pulse oximetry in animals sedated with alpha-2 agonists.

Eventually, truly low hemoglobin saturation values (< 90%) may be recorded in some animals (8). A more intense respiratory depression may also be observed in animals receiving dexmedetomidine/ketamine combinations. In face of these observations, it is recommended that oxygen supplementation should be readily available whenever dexmedetomidine and other alpha-2 agonists are used for chemical restraint.

**Use of dexmedetomidine for chemical restraint**

Administration of a high dose of dexmedetomidine (20 mcg/kg [500 mcg/m²], IM) dogs results in sedative effects lasting for up to 120 minutes, with a peak effect recorded by 30 minutes after intramuscular administration; this dose of dexmedetomidine was highly effective for producing chemical restraint in dogs undergoing short ambulatory procedures (dental procedures, radiographs, etc) (9). In dogs, intramuscular dexmedetomidine (20 mcg/kg [500 mcg/m²]) combined with butorphanol (0.2 mg/kg) produces effective sedation and muscle relaxation for canine hip radiography (8).

Vomiting may occur after intramuscular administration of dexmedetomidine in cats, but its overall incidence is low (7%) (9). Feline patients appear to be less sensitive to medetomidine and dexmedetomidine sedation than dogs. In cats, a dose twice as much (40 mcg/kg, IM) produced sedation with similar characteristics to those reported in dogs, allowing minor ambulatory/diagnostic procedures to be performed (9). As an alternative to the use of high doses of dexmedetomidine in healthy cats, ketamine (5-10 mg/kg) can be combined with lower doses dexmedetomidine (10 mcg/kg). Ketamine/dexmedetomidine combinations will often produce moderate to deep sedation or light anesthesia and may be useful drug combination in feral cats.

Administration of the alpha-2 antagonist atipamezole (0.2 mg/kg [5000 mcg/m²], IM-IV) will reverse the sedative, analgesic and cardiorespiratory effects of dexmedetomidine. Rapid reversibility of dexmedetomidine effects is useful for outpatient procedures that are to return to their owners immediately after termination of the procedure.

**Use of dexmedetomidine as a premedication before general anesthesia**

As with other alpha2-adrenergic receptor agonists, higher doses of dexmedetomidine (20 mcg/kg) may induce profound hypnosis, substantially reducing injectable and inhalant anesthetic requirements for producing anesthesia (7,10). Dexmedetomidine also decreases inhalant anesthetic requirements for maintaining anesthesia (i.e., the minimum alveolar concentration, MAC) in a dose-related fashion. In dogs, isoflurane MAC was reduced by 89% after 30 minutes of dexmedetomidine administration (20 mcg/kg/IV) (10).

In dogs receiving dexmedetomidine (5-10 mcg/kg) combined with opioids, requirements of injectable agents for allowing orotracheal intubation may be markedly low. In this case, doses of propofol as low as 0.5 to 1 mg/kg may be enough for placing the orotracheal tube. Administration of inhalational
anesthetics should be carefully performed during the early phase of maintenance of anesthesia (30 minutes) as vaporizer settings may be less than 0.5% during this period. As the CNS depressing effect of dexmedetomidine wanes off over time, vaporizer settings need to be progressively increased to maintain surgical depth of anesthesia.

Intraoperative use of dexmedetomidine:

**Epidural administration:** Interest in epidural administration of alpha2-adrenergic receptor agonists, such as dexmedetomidine, has increased because alpha2-adrenergic receptors that play a functional role in the modulation of pain have been identified in the spinal cord of rats (11,12) Epidural administration of dexmedetomidine in dogs results in a prolonged analgesic effect, with the use of lower doses than those used by intravenous administration (13). In dogs, epidural administration of 3.0 and 6.0 mcg/kg of dexmedetomidine caused clinically relevant decreases in isoflurane MAC (defined as a reduction in MAC above 20%) for approximately 2 and 4.5 hours, respectively (14).

**Constant rate infusions (CRIs):** Dexmedetomidine administered at CRIs ≥ 0.5 mcg/kg/min have the potential for use during anesthesia in dogs because it reduces the MAC of isoflurane. (15). The reduction in the requirement of inhalational anesthetic for maintaining anesthesia is dose dependent: a 0.5 mcg/kg bolus followed by a 0.5 mcg/kg/hour CRI decreased isoflurane MAC by 18%; whereas a 3 mcg/kg bolus followed by a 3 mcg/kg/hour CRI decreased isoflurane MAC by as much as 59%. (15). Dexmedetomidine CRIs of 0.1, 0.5, and 3.0 mcg/kg/hour caused dose-dependent reductions in HR but mean HR was below the value that is considered as bradycardia in dogs (< 60 beats/min) only at the highest CRI (15). In that study dogs received dexmedetomidine CRIs lasting approximately 5-6 hours, but recovery data (time to extubation, time until standing) was not reported (15).

Because dexmedetomidine CRIs may cause sustained decreases in blood flow due to vasoconstriction and to decreases in CO, there are concerns with decreased tissue oxygenation leading to increased anaerobic metabolism. Dexmedetomidine CRIs should not be used in animals that are hypovolemic or showing signs of poor tissue perfusion (e.g. plasma lactate > 2.5 mmol/L). However, dexmedetomidine CRIs have the potential for use in healthy dogs undergoing surgical procedures. In dogs undergoing surgery under isoflurane anesthesia, CRIs of dexmedetomidine ranging from 1 to 3 mcg/kg/hour did not result in evidence of increased anaerobic metabolism, as mean plasma lactate concentrations remained low (< 2 mmol/L) throughout anesthesia and during the early recovery period (30 minutes after reversal of dexmedetomidine with atipamezole [12.5 mcg/kg/IM]) (16). Authors concluded that the infusion rate of 1 mcg/kg/min resulted in most favorable effects in isoflurane-anesthetized dogs (16). Vocalization/sudden arousal from anesthesia, even before atipamezole reversal, was observed in some cases (16). The recovery characteristics during the course of prolonged dexmedetomidine infusion regimens and the need for antagonism of its effects need to be further elucidated before dexmedetomidine CRIs can be recommended for routine anesthetic procedures.

### Table 1: Doses of dexmedetomidine for premedication/chemical restraint in healthy dogs (ASA I or II)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>5-20 mcg/kg</td>
<td>IM</td>
<td>Use for short diagnostic/investigative procedures. High-end dose will induce more intense/prolonged sedation.</td>
</tr>
<tr>
<td>Dexmedetomidine Butorphanol</td>
<td>10-20 mcg/kg 0.2 mg/kg</td>
<td>IM</td>
<td>Use for short diagnostic/investigative procedures.</td>
</tr>
<tr>
<td>Dexmedetomidine Morphine</td>
<td>5-10 mcg/kg 0.5 mg/kg</td>
<td>IM</td>
<td>Useful premedication before inhalation anesthesia in fractious dogs that will undergo painful procedures</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>5-10 mcg/kg</td>
<td>IM</td>
<td>Same as for dexmedetomidine/morphine</td>
</tr>
</tbody>
</table>
**Table 2: Doses of dexmedetomidine for premedication/chemical restraint in healthy cats (ASA I or II)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>10-30 mcg/kg</td>
<td>IM</td>
<td>Use for short diagnostic/investigative procedures. High-end dose will induce more intense/prolonged sedation.</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>20 mcg/kg</td>
<td>IM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>5-10 mcg/kg</td>
<td>IM</td>
<td>Use as premedication before inhalation anesthesia in healthy cats that will undergo painful procedures</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.1 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>10 mcg/kg</td>
<td>IM</td>
<td>Use for chemical restraint in feral cats.</td>
</tr>
<tr>
<td></td>
<td>5-10 mg/kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Final considerations**

Dexmedetomidine produces reliable sedation/chemical restraint in hyperexcitable animals. These characteristics, combined with the reversibility of its effects with the use of atipamezole, make this drug a useful sedative for minor ambulatory procedures in animals that will return to their owners on the same day. The use of dexmedetomidine combined with opioid analgesics as a premedication before general anesthesia should be considered in hyperexcitable and/or aggressive dogs and cats that are otherwise in good health status (ASA I or II). Other uses of dexmedetomidine (e.g. epidural or CRIs) are under investigation.

**References:**