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ALPHA-2 ADRENOCEPTOR AGONISTS IN DOGS AND CATS ALFA 2 AGONISTI NEL CANE E NEL GATTO

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Alpha-2 adrenoceptor agonists, or alpha-2 agonists, are widely used in dogs and cats (and other species), for their sedative, analgesic and anesthetic sparing effects. Agents in this class, however, also have many other physiological effects.

Alpha-2 receptors were originally thought to be distributed presynaptically only, acting as a negative feedback mechanism regulating the release of noradrenaline by noradrenergic neurons. It is now known that postsynaptic alpha-2 receptors exist in various tissues, where they exert many of the effects of alpha-2 agonists.

Alpha-2 agonists commonly used in dogs and cats include (dex)medetomidine, xylazine, and romifidine. They differ in their selectivity for the alpha-2 receptors (medetomidine >>> romifidine > xylazine), in their pharmacokinetics, and of course in their chemical structure. Medetomidine and romifidine are imidazolines, whereas xylazine is not. Some of the effects of medetomidine and romifidine are likely mediated by imidazoline rather than alpha-2 receptors.

Central nervous system

In the brain, alpha-2 agonists inhibit noradrenalin release. The locus ceruleus is particularly rich in alpha-2 receptors, and is involved in the regulation of sleep and wakefulness. It is believed that the sedative/hypnotic effect of alpha-2 agonists is mediated at that level. Alpha-2 agonists also decrease anxiety, although, at high dose, xylazine might cause anxiety, due to an effect on alpha-1 receptors.

Alpha-2 agonists decrease the requirements for anesthetic drugs, by up to 80 % in dogs and 100 % in rats. In cats, the only study available reported a 27% reduction in the minimum alveolar concentration of halothane after 15 µg/kg of dexmedetomidine administered orally. The anesthetic sparing effect is thought to be mediated by the decrease in noradrenaline release, mainly from the locus coeruleus. However, because MAC is reduced by a maximum of 40 % when noradrenergic transmission is totally abolished, additional mechanisms are likely involved.

Alpha-2 agonists cause analgesia. This effect is mediated by receptors in the dorsal horn of the spinal cord and brainstem. Alpha-2 agonists may potentiate the analgesia induced by opioids and ketamine. When given by subarachnoid route, alpha-2 agonists and midazolam, neostigmine, lidocaine, or NMDA antagonists produce synergistic antinociception. Xylazine may have additional analgesic effect, due to its interaction with alpha-1 receptors. However, clinically, the analgesia mediated by medetomidine is more profound and lasts longer than that produced by xylazine.

Alpha-2 agonists induce hypothermia, by inhibition of central noradrenergic mechanisms responsible for the control of body temperature, and by decreasing muscle activity.

Cardiovascular system

Alpha-2 agonists, when administered intravenously, induce a biphasic cardiovascular response. Initially, blood pressure increases, due to an increase in systemic vascular resistance. Blood pressure then decreases, due to a decrease in heart rate and cardiac output. Systemic vascular resistance remains elevated, or progressively returns to normal, depending on the drug and the dose used. Blood pressure therefore is maintained within a normal range, or decreases below normal. Bradyarrhythmias may be present. The cardiovascular effects of alpha-2 agonists appear to be dose-dependent, although a ceiling effect may exist.

The increase in systemic vascular resistance is due to vasoconstriction in response to stimulation of alpha-2 receptors on the vascular smooth muscle. The decrease in cardiac output is related to the bradycardic effect. Bradycardia is initially due to a baroreceptor reflex, then to central sympatholysis. Because the decrease in cardiac output appears to be mainly related to bradycardia, the combination with anticholinergics has been advocated. However, the concomitant use of anticholinergics with alpha-2 agonists causes hypertension, and adverse effects on cardiac function. It is therefore not recommended.

Alpha-2 agonists induce blood flow redistribution. Blood flow to more vital organs (e.g. heart, brain, kidney) might be partially or totally preserved at the expense of poor blood flow in less vital organs (skin, muscle, intestine, etc).

Alpha-2 agonists have historically been reported to cause arrhythmias. However, dexmedetomidine has been shown to increase the threshold for adrenaline-induced arrhythmias, via an effect on imidazoline receptors.

Respiratory system

In dogs and cats, the effects of alpha-2 agonists on the respiratory system are considered minimal. Respiratory rate may decrease, but minute ventilation is maintained. Alpha-2 agonists may potentiate the respiratory depression due to other agents such as opioids, inhalant anesthetics, etc.

Endocrine

Alpha-2 agonists inhibit sympathetic outflow and modulate the stress response to anesthesia and surgery. Alpha-2 agonists cause direct inhibition of insulin release, and, depending on the dose administered, may cause hyperglycemia. Alpha-2 agonists increase the release of growth hormone, which may contribute to the hyperglycemic effect. They inhibit the secretion of ACTH and cortisol. They inhibit the release of ADH, and possibly of aldosterone.

Urinary system

Alpha-2 agonists promote diuresis and natriuresis. They inhibit ADH release from the pituitary, as well as its action on renal tubules. They inhibit the release of rennin and increase the secretion of atrial natriuretic peptide. They may increase glomerular filtration rate.

Gastrointestinal system

Alpha-2 agonists induce a decrease in salivation, gastro-esophageal sphincter pressure, esophageal, gastric and small intestinal motility and gastric secretion. They may promote ulcer formation. They induce vomiting in 8-20 % of dogs and up to 90-100 % of cats. Xylazine has been used for that effect in cats.

Blood

Alpha-2 agonists and adrenaline stimulate platelet aggregation. The net effect depends on the balance between direct activation by the alpha-2 agonist and decreased aggregation due to decreased plasma adrenaline concentration.

Uterus

Alpha-2 agonists increase the intensity of uterine contractions. Uterine blood flow and oxygen delivery are decreased, as are arterial pH and PO₂ in the mother and fetus. Alpha-2 agonists cross the placenta, but drugs with high lipid solubility may be partly trapped in the placenta, decreasing the amount of drug reaching the fetal circulation. Nevertheless, fetal heart rate significantly decreases in bitches treated with alpha-2 agonists.

Eye

Alpha-2 agonists cause mydriasis in cats and miosis in dogs. Imidazoline alpha-2 agonists decrease intraocular pressure, but high doses of medetomidine have been reported to increase intraocular pressure in some dogs.

Miscellaneous

Alpha-2 agonists inhibit lipolysis. They have been reported to increase mortality in endotoxin shock. They are potent inhibitors of shivering.

Alpha-2 antagonists

The effects of alpha-2 agonists can be reversed with alpha-2 antagonists. Yohimbine and atipamezole have been widely used in dogs and cats. Yohimbine, when administered intravenously, can cause tachycardia, severe hypotension and death. Atipamezole is a highly selective alpha-2 antagonist. It is more effective than yohimbine. Although it is claimed to be particularly well adapted to the reversal of the effects of medetomidine, it has been used successfully to antagonize other alpha-2 agonists as well. Transient hypotension follows the administration of atipamezole in medetomidine-treated dogs. The intravenous administration of atipamezole can be followed by a rough recovery. Although atipamezole is reported to have a longer duration of action than medetomidine, a return of the effects of medetomidine is sometimes seen after antagonization with atipamezole.

Summary

In summary, alpha-2 agonists affect many bodily systems. When used for their sedative, analgesic, and/or anesthetic sparing effects, these other effects should be taken into account. Of particular interest in anesthetized animals are the cardiovascular effects, that likely result in compromised oxygen delivery to some organs. It is therefore not recommended to use these drugs on patients that are not healthy or may be at risk of adverse cardiovascular events.

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