Adrenergic Agents

Catecholamines and other adrenergic agonists

Naturally occurring catecholamines

Epinephrine

Epinephrine acts non-selectively and directly as an agonist at all of the adrenergic receptors (i.e., α1, α2, β1, and β2)

In veterinary anesthesia, epinephrine is principally used to support cardiovascular function during cardiopulmonary resuscitation

In animals, it is administered systemically by intravenous injection or via the airway during resuscitation (intratracheal administration), although for humans, epinephrine is also available in a metered aerosol preparation to treat swelling associated with upper airway obstruction due to its vasoconstrictive effects

Cardiovascular system effects

The cardiovascular effects of epinephrine are dose dependent. Low doses of epinephrine administered by bolus (0.01 mg/kg IV) cause β1- and β2-adrenergic agonist effects to predominate.

The cardiac effects of β1-adrenergic receptor agonism result in increased cardiac output, myocardial oxygen consumption, coronary artery dilation, and a reduced threshold for arrhythmias. In low doses, peripheral β2-adrenergic agonist effects result in a decrease in diastolic blood pressure and peripheral vascular resistance.

At high doses (0.1 mg/ kg IV), α1-adrenergic effects predominate, causing a **marked rise in systemic vascular resistance**.

However, in cats anesthetized with isoflurane, the cardiovascular effects of epinephrine infusion at dose rates of 0.125–2 μg/kg/min were dose dependent .

All infusion rates caused increases in packed cell volume (PCV) due to α1-adrenergic- **induced splenic contraction**, arterial oxygen content, heart rate, cardiac index, and stroke volume index (SVI) .

Increases in SVI were greatest with infusion rates of 1 and 2 μg/kg/min. Mean arterial blood pressure increased at infusion rates of 0.5 μg/kg/min and higher.

Other effects

Epinephrine will produce a small increase in minute volume through its bronchodilator effects, which are β2-adrenergic receptor mediated. Pulmonary vascular resistance is increased at higher dose rates reflecting agonism at pulmonary vascular α1-adrenergic receptors

Pharmacokinetics
Epinephrine has a very short half-life due to rapid metabolism, necessitating frequent redosing or administration by infusion for a prolonged effect.

Norepinephrine

Norepinephrine acts as an agonist at α1-, α2- and β1-adrenergic receptors, with effects at α-adrenergic receptors predominating at clinically used dose rates.

Norepinephrine is predominantly used during anesthesia to manage hypotension, particularly when caused by a reduction in systemic vascular resistance (i.e., vasodilation) due to sepsis or administration of volatile anesthetic agents.

Norepinephrine will also cause coronary vasodilation to promote increased coronary blood flow**. Tachycardia is less likely when compared with administration of epinephrine.**

At low doses (1–2 μg/kg/min), effects on dopamine (DA)-1 and DA-2 receptors predominate. As dose rates increase further, β1- and β2-adrenergic receptor effects predominate.

Dopamine

is available as an injectable preparation, typically as a 40 mg/mL

Cardiovascular system effects
At dose rates less than 10 μg/kg/min, the β1-adrenergic effects of dopamine predominate, leading to **increases in myocardial contractility, heart rate, cardiac output, and coronary blood flow**. At dose rates greater than 10 μg/kg/min, α1-adrenergic agonist effects dominate, leading to increased systemic and pulmonary vascular resistance, venous return, and PCV due to **splenic contraction**. Tachycardia can occur at higher dose rates.

يحدث انخفاض في متوسط ضغط الدم الشرياني والناتج القلبي بشكل عام بعد توقف ضخ الدوبامين ، مع العودة إلى قيم ما قبل التسريب في غضون 30 دقيقة ، مما يؤدي إلى التوصية بإيقاف إعطاء الدوبامين بطريقة تدريجية.

Synthetic catecholamines
Dobutamine
Dobutamine is principally used to augment low cardiac output states associated with reduced myocardial function. It is very commonly used in equine inhalant anesthesia to manage hypotension.

يستخدم الدوبوتامين بشكل أساسي لزيادة حالات النتاج القلبي المنخفض المرتبطة بوظيفة عضلة القلب المنخفضة. يستخدم بشكل شائع في التخدير المستنشق للخيول للتحكم في انخفاض ضغط الدم.

Isoproterenol (isoprenaline)

Isoproterenol is a very potent synthetic catecholamine that is an agonist at β1- and β2-adrenergic receptors. It has no α-adrenergic receptor effects. Isoproterenol is used to increase heart rate and myocardial contractility during anesthesia.

Phenylephrine
Phenylephrine is used systemically during anesthesia to increase systemic vascular resistance and therefore increase blood pressure. **Phenylephrine can also be administered topically to mucosal surfaces to produce localized vasoconstriction and reduce edema or hemorrhage**. **In the horse, phenylephrine may be used in the medical management of nephrosplenic entrapment prior to rolling or laparoscopic surgical correction of the condition. The aim of phenylephrine administration is to reduce splenic size and therefore facilitate medical or surgical correction of the entrapment**

α2-Adrenergic receptor agonists
Dexmedetomidine, medetomidine, detomidine, xylazine, romifidine they are used extensively in veterinary medicine for their excellent sedative and analgesic properties

β2-Adrenergic receptor agonists
Clenbuterol, albuterol (salbutamol), terbutaline
Clenbuterol, albuterol, and terbutaline are predominantly used for the **management of bronchospasm in people with asthma.** In veterinary medicine, they are used to treat bronchospasm in both awake and anesthetized animals. In addition, clenbuterol has been used illegally to increase the muscle mass and reduce the fat composition of carcasses of food-producing animals.

Clenbuterol has Marketing Authorization for administration to horses for the management of chronic obstructive pulmonary disease and is available as an injectable solution for administration intravenously, and also as syrup and granule preparations for oral administration. An injectable preparation is also licensed for administration to cattle to delay the onset of parturition by causing uterine relaxation.

كلينبوتيرول لديه تصريح تسويق للإعطاء للخيول لإدارة مرض الانسداد الرئوي المزمن ومتوفر كمحلول الحقن للإعطاء عن طريق الوريد ، وكذلك كمستحضرات شراب وحبيبات للإعطاء عن طريق الفم. كما أن المستحضر القابل للحقن مرخص أيضًا للإعطاء للماشية لتأخير بداية الولادة عن طريق التسبب في ارتخاء الرحم, tachycardia .

Mixed α- and β-adrenergic receptor agonists
Ephedrine
Ephedrine is used in the management of hypotension during anesthesia
Metaraminol
Similarly to ephedrine,

Adrenergic receptor antagonists
α1-Adrenergic receptor antagonists
Prazosin
It is used predominantly for the management of functional urethral obstruction in cats and dogs.

α2-Adrenergic receptor antagonists
Atipamezole, yohimbine, tolazoline

Non-selective α-adrenergic receptor antagonists
Phentolamine
During anesthesia, phentolamine is used in the management of hypertensive crises due to excessive administration of sympathomimetics and pheochromocytoma, especially during tumor manipulation.

In human dentistry, a preparation of phentolamine is available to reverse the effects of local anesthetic administration

Phenoxybenzamine
Phenoxybenzamine is a long-acting،
In veterinary patients, phenoxybenzamine is most commonly used for the preoperative management of pheochromocytomaورم القواتم الغدة الكضرية, administered orally. The aims of administration are to reverse chronic vasoconstriction due to increased circulating concentrations of epinephrine and norepinephrine that are produced by the tumor, and thereby facilitate expansion of intravascular volume.

β1-Adrenergic receptor antagonists
Atenolol
Atenolol is a relatively cardioselective is available as tablet and syrup formulations for oral dministration, and as an injectable preparation

atenolol is prescribed to delay the onset of adverse sequelae in cats with hypertrophic cardiomyopathy and for the management of ventricular arrhythmias in cats and dogs; therefore, knowledge of atenolol pharmacology is important.

Esmolol

it is the beta-blocker of choice for use during anesthesia to control tachycardia, hypertension, and acute supraventricular tachycardia associated with inappropriate sympathetic nervous system activity.

Metoprolol

It is available as an oral tablet preparation and has been evaluated in the management of dogs with acquired cardiac disease

Non-selective β-adrenergic receptor antagonists
Pindolol
In addition to the typical cardiovascular effects of the drug, pindolol may potentiate analgesia provided by tramadol in dogs

Propranolol
in animals it is most commonly administered orally for the control of heart rate and hypertension prior to thyroidectomy in cats with hyperthyroidism, or as part of the presurgical management of animals with pheochromocytoma.

Sotalol
It is most commonly used orally to treat ventricular tachyarrhythmias and has been shown to reduce the number of ventricular premature contractions in Boxer dogs with familial ventricular arrhythmias.

Opioids
An opiate is a drug derived from opium (a mixture of compounds prepared from a species of poppy, Papaver somniferum) and an opioid is a drug which is not derived from opium but interacts at the opioid receptor.

أفيونيات المفعول
المادة الأفيونية هي دواء مشتق من الأفيون (خليط من المركبات المحضرة من نوع من الخشخاش ، Papaver somniferum) والأفيون هو دواء لا يُشتق من الأفيون ولكنه يتفاعل مع مستقبلات الأفيون.

Opioids are the prototypical analgesics, antitussives, and antidiarrheal drug class.

Opioid receptors are located throughout the body, including the brain, spinal cord, chemoreceptor trigger zone, gastrointestinal tract, synovium, urinary tract, leukocytes, and uterus, among other tissues. Therefore it is not surprising to observe widespread effects of systemically administered opioids

توجد مستقبلات المواد الأفيونية في جميع أنحاء الجسم ، بما في ذلك الدماغ والنخاع الشوكي ومنطقة تحفيز المستقبلات الكيميائية والجهاز الهضمي والغشاء الزليلي والمسالك البولية والكريات البيض والرحم ، من بين الأنسجة الأخرى. لذلك ليس من المستغرب ملاحظة الآثار الواسعة الانتشار للمواد الأفيونية التي يتم تناولها جهازيا.

μ Opioid receptor κ Opioid receptor δ Opioid receptor

μ agonists (e.g., morphine, hydromorphone, fentanyl, remifentanil, alfentanil, oxymorphone, and methadone) produce the most profound analgesic effects.

Opioid agonists
Morphine
Morphine is still widely used in veterinary medicine due to its safety, efficacy, tolerability, and cost-effectiveness. Morphine elicits its effects primarily as a full μ opioid agonist, but higher doses can also result in κ receptor agonist effects.

Oxymorphone is a synthetic opioid that elicits its effect as a full μ opioid agonist. it is more potent than morphine.

Hydromorphone is a full μ opioid agonist which produces effects very similar to morphine when administered in equianalgesic doses. It is more potent than morphine

Fentanyl is a full μ opioid agonist which is much more potent than morphine with a short duration of effect when administered IV (bolus), IM, or SC. it results in less nausea and vomiting than morphine and produces a predominant antiemetic effect.

Methadone is a μ opioid agonist with similar effects and potency to morphine.

Meperidine (Pethidine) is a μ opioid agonist.

Codeine is a naturally occurring alkaloid structurally similar to morphine. a μ opioid agonist.

Partial opioid agonists and agonist/ antagonists

Buprenorphine is a μ opioid receptor partial agonist, approximately 25 times more potent than morphine.

Tramadol is a centrally acting analgesic that elicits its effects through several different mechanisms

Opioid antagonists
Naloxone
Naloxone is a commonly administered opioid antagonist. It acts primarily as a μ opioid antagonist, but antagonist effects can also occur at κ and δ opioid receptors.

Naltrexone
Naltrexone is an opioid antagonist at the μ, κ, and δ receptors. Naltrexone is often administered to reverse the sedative effects of carfentanil in wildlife and zoo animals, but would be effective in reversing other opioids as well.

Non-Steroidal Anti-Inflammatory Drugs

Prostaglandin synthase-1 (COX-1) is usually simplistically described as a constitutive enzyme expressed in tissues. Prostaglandins, prostacyclin, and thromboxane synthesized by this enzyme are responsible for normal physiologic functions.

Prostaglandin synthase 2 (COX-2), on the other hand, is inducible (upregulated) and synthesized by macrophages and inflammatory cells after stimulation by cytokines and other mediators of inflammation.

The COX-3 enzyme is a splice variant from the COX-1 gene, which to date has only been identified in the canine brain, human brain, and heart. It is hypothesized that the mechanism of action of acetaminophen (paracetamol) is by inhibition of COX-3.

COX-1 is the dominant enzyme in platelets and COX-2 is the dominant enzyme in inflammatory cells.

COX-1هو الإنزيم السائد في الصفائح الدموية و COX 2 هو الإنزيم المهيمن في الخلايا الالتهابية.

it is assumed that prostaglandin inhibition in both peripheral and nervous system (spinal and brain) tissues is the most important mechanism of action for most NSAIDs

من المفترض أن تثبيط البروستاغلاندين في كل من أنسجة الجهاز العصبي المحيطي (النخاع الشوكي والدماغ) هو أهم آلية عمل لمعظم مضادات الالتهاب غير الستيرويدية

carprofen is one of the most commonly used NSAIDs in dogs

gastrointestinal problems are the most frequent reason to discontinue NSAID therapy or consider alternative treatment

Gastrointestinal toxicity is likely caused by at least two mechanisms: direct irritation of the drug on the gastrointestinal mucosa and the result of prostaglandin inhibition.

acidic NSAIDs become more lipophilic in the acid milieu of the stomach and diffuse into the gastric mucosa cells, where they cause injury. Direct effects also occur in the intestine where NSAIDs within the lumen can directly injure the intestinal villi.

Prostaglandins have a cytoprotective effect on the gastrointestinal mucosa. Inhibition of prostaglandins by NSAIDs results in decreased cytoprotection, diminished blood flow, decreased synthesis of protective mucus, and inhibition of mucosal cell turnover and repair.

مشاكل الجهاز الهضمي هي السبب الأكثر شيوعًا للتوقف عن العلاج بمضادات الالتهاب غير الستيروئيدية أو التفكير في العلاج البديل

Selection of NSAIDs for dogs (carprofen)

drugs have been used in the short term to decrease fever and decrease pain from surgery or trauma, relief of osteoarthritis-related pain.

some veterinarians have also used human-label drugs such as aspirin, piroxicam, and naproxen

The approved veterinary drugs used most often in dogs are carprofen، etodolac, meloxicam, firocoxib, and deracoxib.

Selection of NSAIDs for cats
Veterinarians have been reluctant to prescribe NSAIDs to cats because of a fear of adverse effects. The adverse effects of salicylates (aspirin) in cats are well documented.

Selection of NSAIDs for horses
For horses, phenylbutazone has been used more often than any other NSAID, and many experts still believe that it is the most costeffective treatment, especially for oral treatment of musculoskeletal inflammation and pain. Flunixin meglumine is the most commonly utilized injectable NSAID for acute soft tissue injury, endotoxemia, and abdominal pain