Unit V: Introduction and classification of the drugs acting on: a. Central nervous system

Xylazine

It is approved by the FDA for use in the cat, dog, horses, and wildlife, for example, deer and elk. However, it is also frequently used in other species, particularly the cattle. It is administered IM, IV, or SC

Adverse effects:

(1) Because of the GI stasis associated with xylazine administration, bloat may be a result.

(2) Xylazine-induced bradycardia with sinus arrhythmia/arrest can be severe. Close monitoring is needed; in very severe cases, the use of an α2-antagonist may be necessary to save the animal.

(3) Xylazine affects the thermoregulation center in the hypothalamus, thus it produces hypothermia when the ambient temperature is low, and hyperthermia when the ambient temperature is high. Thus, the use of xylazine to immobilize wildlife should be performed with caution and the use of α2-antagonist to control the pharmacological effects of xylazine (or other α2- agonists) in wildlife is a must.

Contraindications:

(1) Cardiac aberrations

(2) Hypotension or shock

(3) Renal insufficiency

(4) Hepatic impairment

(5) Epilepsy (because xylazine may precipitate seizures in susceptible animals).

(6) Use of xylazine in combination with ketamine should be used only in young healthy animals because this combination synergistically suppresses cardiopulmonary function of the animal.

(7) Immediate collapse, convulsions, and sudden death can occur in horses given xylazine into the carotid artery.

(8) A cautious approach should be taken whenever xylazine is used in treatment of colic, because xylazine's powerful analgesic effect can mask the underlying problem and because xylazine can paralyze the GI tract.

(9) Xylazine should not be given to animals (particularly mares and ruminants) within the last month of pregnancy, since it may induce abortion.

(10) Xylazine should not be given to dehydrated animals or those with urinary obstruction because of its potent diuretic effect.

Detomidine (Dormosedan R)

It is approved by the FDA for use in horses. It is administered IM or IV.

Pharmacokinetics:

(1) The elimination t 1/2 is 1.2 hours for the IV dose and 1.8 hours for the IM dose.

(2) Metabolism to detomidine carboxylic acid and hydroxydetomidine glucuronide and thereafter excretion into the urine seems to be the major elimination route.

Adverse effects:

(1) Following the recommended dose, piloerection, sweating, partial penis prolapse, and salivation, and occasionally, slight muscle tremors may be seen.

(2) Excessive doses of detomidine can induce CNS excitation. The above two side effects of detomidine are also seen with the administration of other α2-agonists.

(3) IV sulfonamides should not be used in detomidine-treated horses as potentially fatal dysrhythmias may occur.

(4) Detomidine at 400 μg/kg (10× of recommended dose of 40 μg/kg) daily for three consecutive days can produce myocardial necrosis in horses.

(5) Other adverse effects seen with xylazine administration may also occur in animals treated with detomidine.

Medetomidine (Dormitor R)

It is the most potent and selective α2-agonist available for use in veterinary medicine. It can induce light anesthesia in some individual animals; short examinations/procedures can be performed in these animals.

Adverse effects: These are the same as stated in the xylazine section and are the extension of the pharmacological effects of the α2-agonist. However, since medetomidine is a very potent α2-agonist, the adverse effects can be very severe. Thus, the use of an α2-antagonist, for example, atipamezole may be needed to reverse these adverse effects of medetomidine.

Romifidine (Sedivet R)

It is for IV use in horses.

Adverse effects: The adverse effects of romifidine are similar to those of xylazine and detomidine.

❖ Opioids

Effects	Receptor Types μ	κ	δ
Analgesia			
Supraspinal	+	+	+
Spinal	+	+	+
Sedation	+	+	0
↓Respiration	+	0	0
↓GI transit	+	0	0
Diuresis	0	+	0
NT Release			
↓Acetylcholine	+	0	0
↓Dopamine	+	0	+
Hormone Release			
Prolactin	+	0	0
Growth hormone	+	0	+
↓Vasopressin	0	+	0
Euphoria	+	0	0
Dysphoria	0	+	0
Miosis (dogs)	+	+	0
Vasodilatation	+	0	0
Bradycardia	+	0	0

Activities of drugs are given at the receptors for which the drug has an effect.
+, receptor mediates the effect; 0, no effect. NT, neurotransmitter

Receptors: Opioid receptors are naturally occurring sites in the body that respond to endogenous opioid neuropeptides (i.e., enkephalins, dynorphins, endorphins). All opioid receptors are Gi/o-coupled receptors that mediate the inhibition ofneurotransmission and endocrine secretion.

a. The receptors are present in numerous cells/tissues, including the brain, spinal cord, urinary tract, GI tract, and vas deferens.

b. Classification: There are at least three receptor subtypes. The following are information on the location of the receptor and effects mediated by the receptor

(1) Mu (μ) receptors are located throughout the brain and in laminae I and II of the dorsal horn of the spinal cord. Activation of μ-receptors causes supraspinal and spinal analgesia, euphoria, sedation, miosis, respiratory depression, chemical dependence, and inhibition of ACh and dopamine release, and decreased GI motility due to inhibition of ACh release.

(2) Kappa (κ) receptors are found in the cerebral cortex, spinal cord, and other brain regions, for example, hypothalamus. Activation of κ-receptors results in spinal and supraspinal analgesia, mild sedation, dysphoria, inhibition of vasopressin release to induce diuresis, and miosis.

(3) Delta (δ) receptors are located in the limbic system, cerebral cortex, and spinal cord. Activation of δ-receptors results in spinal and supraspinal analgesia, inhibition of dopamine release, and cardiovascular depression.

Actions and Selectivities of Some Opioid Drugs at the Three Receptor Classes

	Receptor Types		
Drugs	μ	κ	δ
Tramadol	+	0	0
Methadone	+++	0	0
Morphine	+++	+	0
Etorphine	+++	+++	+++
Fentanyl	+++	0	0
Sufentanil	+++	+	+
Butorphanol	P	+++	0
Buprenorphine	P	−−	0
Nalbuphine	−−	++	0
Naloxone	−−−	−−	−
Diprenorphine	−−−	−−−	−−

Activities of drugs are given at the receptors for which the agent has affinity. +, agonist; −, antagonist; P, partial agonist; 0, no affinity. The number of symbols is an indication of potency.

Pharmacological Effects:

1. **Analgesic effects:** Endogenous opioids (e.g., endorphins, enkephalins, dynorphins) are released by the neuroendocrine cells to activate opioid receptors. Exogenous opioids are used to activate or antagonize these receptors.
   - **a)** Opioid analgesia occurs at the level of the brain (supraspinal), spinal cord, and possibly the periphery.
   - **b)** μ-Receptor agonists produce profound analgesia.
   - **c)** The duration of opioid analgesia is usually shorter than the elimination t 1/2 for reasons that are not understood.
2. **Respiratory effects:**
   - **a)** μ-Receptor agonists are respiratory depressants; therefore, they cause an increase in the arterial CO2 tension and a decrease in the arterial O2 tension and pH. The hypercapnia results from a reduced sensitivity of neurons in the brain stem to CO2.
   - **b)** In dogs, μ-receptor agonists frequently cause panting, which may be a thermoregulatory response. The opioid resets the dog's hypothalamic temperature control point; by panting, the dog is trying to cool itself to a new set point.
3. **Cardiovascular effects:** Opioids generally spare the cardiovascular system.
   - **a)** The heart rate may decrease in dogs following administration of a μ-receptor agonist, this is mediated via vagal stimulation.
   - **b)** Hypotension may develop from peripheral vasodilatation, which is also mediated by μ-receptors.
4. **GI effects:** Antidiarrheal effects and constipation are caused by stimulation of central (i.e., μ) and peripheral (i.e., κ and μ) receptors.

Therapeutic uses: Opioids are used for

1) Analgesia
2) Preanesthetic medication
3) Induction and maintenance of anesthesia in dogs and cats. μ-Agonists produce a dose- dependent decrease in the minimum alveolar concentration (MAC) of inhalant anesthetic necessary to produce anesthesia, but usually they will not produce anesthesia alone.