Respiratory Pharmacology:-

INTRODUCTION.

The primary function of the respiratory system is:- gas exchange between the inspired air and the pulmonary artery blood. Because of the large surface area of the alveoli and exposure to the environment, this organ system is prone to antigen–allergy responses and infection.

The defenses of the respiratory system include1- hypersecretion of mucus, 2-sneezing , 3-coughing reflexes, 4-bronchoconstriction, 5- macrophage activation and,6- inflammation.

Pharmacology of the respiratory system centers around these defense mechanisms and can be simplified into seven categories:

(1) elimination of excess secretions and membrane congestion.

(2) bronchiole dilation when excessive constriction has occurred .

(3) cough suppression when it is nonproductive and detrimental to the animal.

(4) control of infection and inflammation.

(5) decrease pulmonary hypertension.

(6) stimulate the peripheral chemoreceptors and the central respiratory center.

(7) exogenous surface.

(1):- **Methods designed to loosen secretions by hydration of the mucus**:-

A. Nebulizer (aerosol) therapy with sterile or bacteriostatic water or saline produces a liquid particle suspension within a carrier gas (room air or oxygen) which, when inhaled, will add water to the airway mucus layer. Improve tidal ventilation by mild-forced exercise after nebulization .

B. N-Acetylcysteine (N-acetyl-l-cysteine) is a derivative of l-cysteine and acts as a mucolytic drug.

N-Acetylcysteine (NAC) breaks the disulfide bonds within the mucus molecules and decreases the viscosity. NAC will not only alter the viscosity of normal mucus but also the thick mucus that results from the addition of bacterial and neutrophil cellular debris.

C-Bromhexine HCl is a frequently prescribed mucolytic.By Enhances the hydrolysis of acid mucopolysaccharides that significantly contributes to mucus viscosity. Does not alter protein in the mucus, which originates from bacteria or neutrophil cellular debris.

May increase the concentration of certain antibiotics in the alveoli by altering the permeability of the alveolar/capillary membranes.

Expectorants theoretically make the bronchiole secretions less viscous :-

A-Potassium iodide is an oral saline expectorant.

B- Guaifenesin that acts as an expectorant.

- Enhances the hydrolysis of acid mucopolysaccharides that significantly contributes to mucus viscosity.

- May increase the concentration of certain antibiotics in the alveoli by altering the permeability of the alveolar/capillary membranes.

Decongestants:- shrink the nasal mucosa and allow air to pass more freely. Sinusitis or reverse sneezing are other indications for decongestants.

1.H1-antihistamines are commonly used for allergic-induced symptoms and chronic rhinitis in people but efficacy in animals is not documented.

Diphenhydramine b. Dimenhydrinate c. Chlorpheniramine d. Hydroxyzine.

2. Sympathomimetic drugs (α-receptor agonists) may be given orally or topically as nasal sprays to avoid their systemic effects. like sympathomimetics.

Ephedrine b. Pseudoephedrine c. Phenylephrine.

This drug has been used to relieve anesthesia (recumbency)induced nasal congestion and edema in horses. About 30 minutes before anesthetic recovery and removal of the endotracheal tube.

CONTROL OF INFECTION AND INFLAMMATION.

-Antibiotic:- choice should ideally be based on culture and sensitivity or cytology with a Gram's stain. Antibacterial drugs that have a good spectrum of activity.

1. Upper airway disease—Gram-positive spectrum is best.

2. Lower airway disease—Gram-negative spectrum is best.

a. Cephalosporins b. Potentiated sulfonamides c. Amoxicillin d. Amoxicillin /clavulanate e. Fluoroquinolones.

3. Aerosolized antibiotics may be helpful in selected cases of infectious tracheobronchitis.

-Glucocorticoids :- Corticosteroids are important for the treatment of antigen-induced inflammatory bronchial disease such as chronic obstructive pulmonary disease (heaves) in horses and feline bronchial disease (asthma), as well as chronic bronchitis in dogs. Glucocorticoids reduce mucus hypersecretion, bronchial mucosal thickening, and airway smooth muscle constriction.

(1) Prednisolone (2) Prednisone(3)dexamethasone.

-Leukotriene receptor antagonists:- are a new type of therapy. Leukotrienes are potent bronchoconstrictors and trigger inflammatory responses such as edema formation.

Drugs that antagonize leukotriene receptors are zafirlukast, Montelukast ,and zileuton,

-**Nonsteroidal anti-inflammatory drugs:-** are seldom used to treat inflammatory respiratory diseases because they tend to inhibit cyclooxygenase more than lipooxygenase enzymes.

Aspirin has been used in the treatment of thromboembolism in cases of heartworm disease.

-**Serotonin receptor inhibition:-** may be beneficial for feline "asthma." Cyproheptadine is the only drug in this category currently thought to be beneficial.

-Cyclosporine is an immunosuppressant drug:- but has been shown to be beneficial in experimental models of feline bronchial disease “asthma.”

Mast cell stabilizers:- are used in human medicine to treat allergic asthma. These cromones, cromoglycate and nedocromil, prevent the release of inflammatory mediators from mast cells by inhibiting the influx of calcium.

COUGH SUPPRESSION ;

Cough suppression and normalization of other respiratory reflexes. Sneezing and reverse sneezing, coughing, and airway narrowing reflexes that result in laryngospasm and bronchospasm are reflexes that are part of the normal pulmonary defenses and should not be suppressed unless they are excessive or debilitating.
1. Antitussives decrease the severity and frequency of coughing.

a. Peripherally acting antitussives include anti-inflammatory drugs, mucolytics, and bronchodilators.

b. Central acting opioid and nonopioid drugs reduce the sensitivity of the cough center to afferent stimuli. The opioid cough suppressants may cause sedation, nausea, and constipation. Like 1-Codeine antitussive and analgesic effect .

2- Hydrocodone—commonly used in the dog. More potent antitussive than codeine.

3-Butorphanol—100× more effective as an antitussive than codeine. Can be given orally or parenterally to dogs and cats. It has a short duration analgesia but longer sedative effect and minimal respiratory depression with a half-life of 1.7 hours.

4- Dextromethorphan is a semisynthetic opioid that is found in many over-thecounter human cough preparations but its efficacy in animals is not documented.

BRONCHIAL DILATION

Bronchodilators are common treatments for airway disease. The horse benefits the most from these drugs.

-Parasympathetic system—provides innervation to the entire tracheobronchial tree. These cholinergic nerves arise in the brain stem and course through the vagus nerve to synapse in local ganglia within the walls of the alveoli. From these ganglia, postganglionic fibers travel to airway smooth muscle and submuscosal glands. Ganglionic transmission is mediated by acetylcholine via neuronal nicotinic receptors, whereas smooth muscle contraction is mediated by acetylcholine via muscarinic receptors. M3 muscarinic receptor subtypes mediate airway smooth muscle constriction, plus vasodilation and mucus secretion.

Anticholinergic drugs will cause bronchodilation even in the normal healthy animal. like 1-Atropine—injectable 2. Glycopyrrolate—injectable 3- Ipratropium.

-Response to the adrenergic nervous system primarily involves the activation of β2-adrenoreceptors that are distributed throughout the lung in all species. The α1-receptors mediate airway muscle contraction ,The α2-receptors are inhibitory to cholinergic nerves and are responsible for a decrease in acetylcholine release.

- Adrenergic agonists a. Nonselective (α+β1+β2) agents may be used for the acute treatment of bronchoconstriction.

(1) Epinephrine (2) Ephedrine (3) Isoproterenol .

β2-Selective agonists produce fewer undesirable α- and β1-effects. 1-Terbutaline—orally or parenterally for severe bronchoconstriction in cats.

(2) Isoetharine—has been aerosolized and used in small animals. (3) Albuterol—has been aerosolized and used in horses and small animals.

Methylxanthines have been used for many years in veterinary medicine as a bronchodilator.

1. Mechanism of action. Methylxanthines are phosphodiesterase inhibitors, which induce bronchodilation by blocking the degradation of cAMP by phosphodiesterase in airway smooth muscle cells and inhibition of light chain myosin kinase. The increase of cAMP levels in mast cells inhibits the release of histamine and other autacoids, for example, leukotrienes which may reduce ongoing bronchoconstriction.

The increase of cAMP levels in the chromaffin cells of the adrenal medulla promotes the release of catecholamines which bronchodilate by stimulating noninnervated β2-receptors in the lung.

The other benefits of the methylxanthines are increased mucociliary clearance, improvement in diaphragmatic contractility, decreased pulmonary artery pressure, increased CNS sensitivity to CO2, and stabilization of mast cells.

In addition, methylxanthines are adenosine receptor antagonists. Adenosine receptors are coupled to Gi/o protein, which mediate the decrease in cAMP formation by inhibiting adenylyl cyclase.

Theophylline a. Therapeutic uses. Theophylline is administered orally. It is used primarily to induce bronchodilation for the treatment of obstructive small airway diseases.

Adverse effects (1) Side effects in dogs and cats include nausea and vomiting, restlessness, increased gastric acid secretion, diarrhea, polyphagia, polydipsia, and polyuria.

(2) Side effects in horses include nervousness, excitability (auditory, tactile, and visual), tremors, diaphoresis, tachycardia, and ataxia. Seizures or cardiac arrhythmias may occur in severe cases. other drugs that may inhibit hepatic CYP450 enzymes (e.g., cimetidine and fluoroquinolones) because their concurrent administration may elevate plasma levels of theophylline.

Sildenafil decreases pulmonary hypertension. Pulmonary artery blood pressure may elevate due to an increase in vascular resistance.

Mechanism of action. Sildenafil decreases pulmonary arterial pressure by inducing potent relaxation of arterial smooth muscle. Cyclic GMP is a potent vascular smooth muscle relaxant; sildenafil increases cyclic GMP levels in vascular smooth muscle cells, which is due to its inhibition of degradation of cyclic GMP by phosphodiesterase .

stimulate the peripheral chemoreceptors and the central respiratory center.

Doxapram hydrochloride is an analeptic and a centrally acting respiratory stimulant that also increases the sensitivity of the peripheral chemoreceptors located in the carotid bodies. When injected IV to dogs, the respiratory rate and tidal volume (minute ventilation) increase.

EXOGENOUS SURFACTANT:-

can be administered directly into the respiratory tract of foals or calves that are born prematurely and show signs of respiratory distress.

Surfactant is normally produced by the alveolar type II cells and is a complex mixture of phospholipids and protein. Surfactant is necessary in the alveoli to reduce the surface tension during inspiration and stabilizes alveoli during the resting phase after expiration.

Animals born prematurely may lack surfactant production, and breathing requires an increase in effort and work. One treatment option is to inject exogenous surfactant into the lungs. Several products for human use are derived from animals.

A. Beractant is lipid extract of bovine lung with synthetic lipids.

B. Calfactant is a lipid extract of calf lung lavage fluid.