Veterinary Bioscience: Digestive System

LECTURE 14
THE VOMITING REFLEX AND APPROACH TO ANTIEMETIC THERAPY

LECTURER

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INTENDED LEARNING OUTCOMES

At the end of this lecture, you should be able to:

- Describe the sequence of events in the vomiting reflex, the nerve pathways, neurotransmitters and receptors involved in the vomiting reflex.
- Explain how vomiting differs from regurgitation.
- Describe the mechanism of action of classes of peripherally acting and centrally acting emetics, in particular dopamine antagonists, neurokinin-1 antagonists and 5HT3 antagonists, antihistamines, phenothiazines and anticholinergics and explain how understanding of their mechanism of action and the cause of vomiting can assist in rational selection of an appropriate anti-emetic.

KEY WORDS

Vomiting centre, vomitus, brain stem, chemoreceptor trigger zone, CTZ, vestibular apparatus, semi-circular canals, emetic, anti-emetic, apomorphine, metoclopramide, cisapride, phenothiazine, anti histamine, H1 receptor, dopamine receptor antagonist, neurokinin-1 receptor antagonist, 5HT3 antagonist, acepromazine, maropitant, ondansetron, prokinetic, anti-spasmodic.

LECTURE OVERVIEW

The mechanics of vomiting

Vomiting is a complex reflex event, coordinated by the vomiting centre in the brain stem (medulla). It is not reverse peristalsis; the stomach, oesophagus, gastro-oesophageal sphincter and pyloric sphincter are all relaxed. Not all mammals can vomit: dogs and cats vomit readily.

Once stimulated, the vomiting reflex involves a predictable sequence of mechanical events. Preceding vomiting there is salivation, increased heart rate, and pallor. Vomiting commences with deep inspiration and closure of glottis, that is followed by contraction of the diaphragm and abdominal muscles leading to

increased intra-abdominal pressure. With concomitant relaxation of the stomach and its sphincters, gastric content is forced into the oesophagus. Increased pressure leads to relaxation of the pharyngo-oesophageal sphincter and passage of vomitus into the mouth.

Regurgitation is different from vomiting

Regurgitation involves a reverse peristaltic wave in the oesophagus. It generally occurs shortly after eating and is not preceded by salivation, increased HR and so on. In contrast to vomitus, regurgitated material is generally undigested or poorly digested.

Control mechanisms in the vomiting reflex

There are many and diverse stimuli to the vomiting reflex- unpleasant sights and smells, processed at the level of the cerebral cortex may stimulate vomiting. Abnormal motion, sensed by the semicircular canals of the vestibular apparatus, as well as a range of stimuli from visceral organs- distension, inflammation, intense pain, can all stimulate vomiting. In addition, blood borne toxins and chemicals can directly stimulate vomiting.

The vomiting centre in the brain stem (medulla) receives afferent input from cortical, visceral and vestibular receptors. In addition, in close proximity to and in communication with the vomiting centre in the medulla is a discrete area known as the chemoreceptor trigger zone (CTZ). In this region, the normally tight blood-brain barrier is more permeable, allowing contact between blood borne toxins and neurons. Blood borne toxins thereby stimulate vomiting via activation of the CTZ and hence the vomiting centre.

A number of different neurotransmitters are involved in the different elements of the vomiting reflex. In the vomiting centre, the predominant neuroreceptors are for acetylcholine, neurokinin1 and 5 hydroxytryptamine (5HT), in the vestibular apparatus for histamine. In the CTZ dopamine, 5HT and neurokinin 1 receptors are important and, in the periphery, 5HT and acetylcholine.

Why is this important? Because when the neurotransmitters and their receptors in the vomiting pathway are identified, it is possible to develop drugs that target and block these receptors, thereby blocking the vomiting reflex.

Drugs that stimulate vomiting - centrally and peripherally acting emetics

Sometimes veterinarians actually want to stimulate vomiting- for example when the stomach needs to be emptied of toxic or irritant ingesta. Two types of drugs are used for this purpose- peripherally acting compounds, such as washing soda, that stimulate the vomiting reflex via receptors and afferent pathways from the gastric mucosa, and centrally acting compounds such as apomorphine, that is absorbed from the stomach to the bloodstream, and stimulates the CTZ and hence the vomiting centre.

Classes of drugs that inhibit vomiting - anti-emetics

A class of drugs is a group of drugs that shares a common mechanism of action. Because there are multiple causes (stimuli) for vomiting, involving various neural pathways and neurotransmitters and receptors, a number of different classes of drugs are used to treat vomiting. It is important to recognize too, that when anti-emetics are used, they are generally being used to alleviate a sign of disease - not the disease itself. (for example, if vomiting is due to increased blood urea levels as a consequence of kidney disease, the anti-emetic has no effect on blood urea levels or on the progress of the renal disease. The following are the classes of anti-emetics most commonly used in veterinary medicine; a prototypical drug in each class has been included.

Neurokinin-1 receptor antagonists for example maropitant are the newest class of veterinary anti-emetic. These drugs target NK1 receptors in both the CTZ and the vomiting centre and are effective antiemetics.

Dopamine receptor antagonists for example metoclopramide, domperidone. These drugs act by antagonizing dopamine at the CTZ. Metoclopramide also promotes the release of and increases the sensitivity of visceral smooth muscle to acetyl choline, which results in: increased tone of the lower oesophageal sphincter, increased strength of oesophageal contraction, increased gastric antral contraction, relaxation of pylorus, increased smooth muscle contraction in the duodenum. Often nausea and vomiting are related to delayed gastric emptying. These actions increase gastric emptying and small intestinal activity without altering gastric or intestinal secretion or absorption. Significant side effects relate to dopamine's other roles as a CNS neurotransmitter, and range from hyperactivity to depression, disorientation and frenzy.

5HT3 antagonists for example ondansetron (three times daily); dolasetron (once daily). These are very effective antiemetics, that have been used extensively in cancer chemotherapy in humans. They are thought to have a central action on the CTZ, probably also act through antagonism of peripheral 5HT-3 receptors.

Anti-histamines for example promethazine. These are effective in treatment of vomiting associated with middle ear infections or motion sickness (there are histamine receptors in semicircular canals). Their most significant side effect is sedation (which is not necessarily a bad thing for a car sick puppy!)

Phenothiazines for example prochlorperazine. We will meet this class of drugs again as pre-anaesthetic sedatives. These drugs act at multiple receptors, blocking the CTZ at low doses, through dopamine receptors, and the vomiting centre at higher doses, through muscarinic acetylcholine (ACh) receptors. They also block peripheral dopamine receptors in the stomach. AS they have a number of side effects, there are better classes of drugs available.

Drugs that modify gastrointestinal motility

Prokinetics, that normalize gastrointestinal activity and antispasmodics that reduce activity are sometimes used in the treatment of vomiting. Drugs that are prokinetics include metoclopramide (discussed above) and cisapride, that increase levels of the parasympathetic neurotransmitter acetylcholine in the synaptic cleft, and myenteric plexus.

Most antispasmodics are antagonists of acetylcholine at parasympathetic receptors, for example hyoscine. Anticholinergics reduce gastrointestinal motility, which can act as stimulus to further vomiting. Overuse can result in atony and predispose to absorption of endotoxins through damaged mucosa. Whilst they are included in a number of formulations for treatment of vomiting, their use is not recommended.

FURTHER READING

Sherwood, L. *Human Physiology from Cells to Systems* 8th Edition 2013 Ch 16

Cunningham's *Textbook of Veterinary Physiology* 6th Ed Elsevier 2020 Ch 27 & 28

Maddison J, Page S and Church D *Small Animal Clinical Pharmacology* 2nd Ed 2008

Riviere JE, & Papich MG *Veterinary Pharmacology & Therapeutics* 10th Edn 2018 Wiley Blackwell (ebook)

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