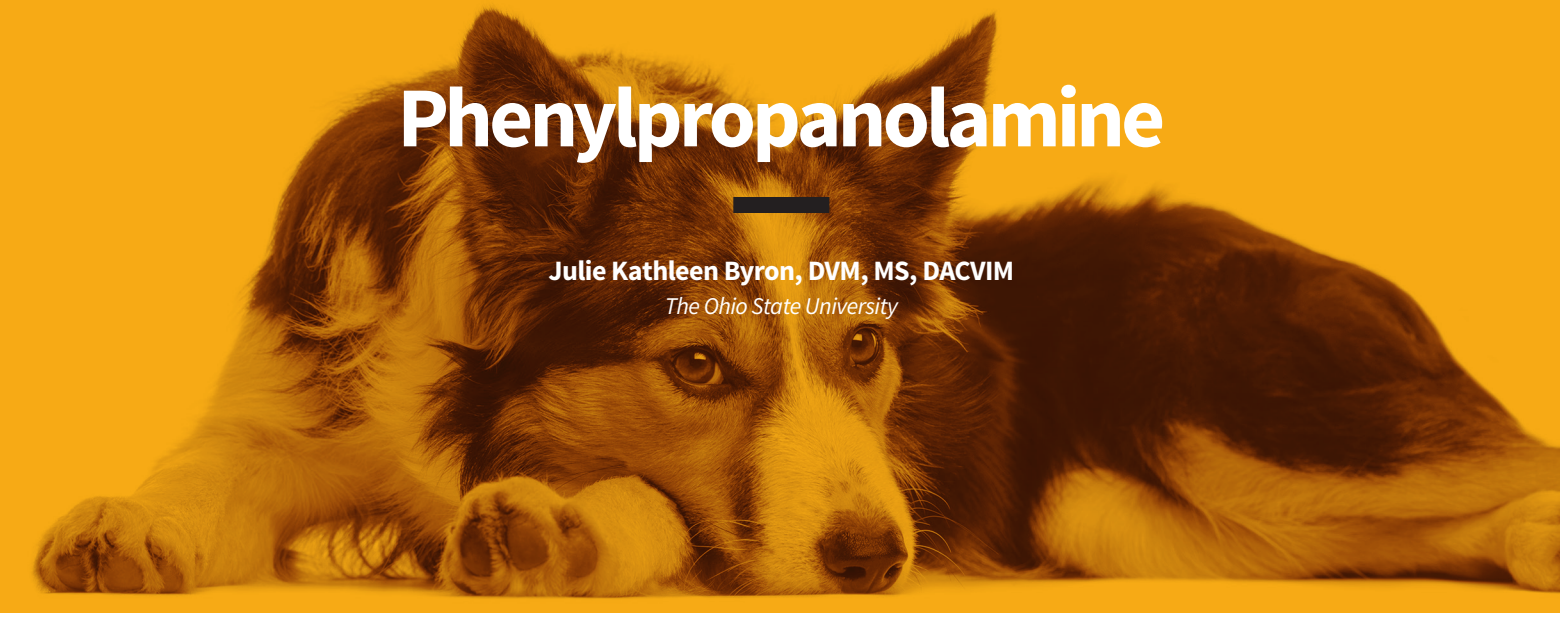

Phenylpropanolamine

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Phenylpropanolamine is an α_1-adrenergic agonist used to increase smooth muscle tone in the urethra of dogs with urethral sphincter mechanism incompetence (USMI). It is widely available in approved veterinary products and is often the first-line choice for treatment of urinary incontinence secondary to USMI.[1] Phenylpropanolamine is well tolerated, but specific adverse effects make it less appropriate in some patients, particularly those with or at risk for hypertension.

MECHANISM OF ACTION

- Phenylpropanolamine is a synthetic sympathomimetic amine that acts primarily at α receptors with some β effect, as well as in the CNS.[2]
  - Although the drug's effect on continence has been thought to come primarily from the stimulation of α receptors in urethral smooth muscle, there is evidence that phenylpropanolamine also stimulates β receptors in the bladder, leading to increased detrusor relaxation and lower bladder pressures during the storage phase of micturition (see ***Physiology of Micturition***).[3]

CLINICAL APPLICATIONS & EFFICACY

- Phenylpropanolamine is primarily used to increase urethral tone in spayed dogs with acquired urinary incontinence secondary to USMI.
  - Studies have shown resolution or improvement of incontinence in 85% to 90% of female dogs with USMI.[4]
- Phenylpropanolamine can also be used in cats, but there is little evidence of its efficacy.
  - Anecdotal evidence suggests that many cats with urinary incontinence have underlying urogenital malformations and that the incidence of USMI is likely low.
- Dosages up to 2 mg/kg PO q8-12h are considered safe in patients without comorbidities that can predispose to hypertension or in patients that are vulnerable to negative effects of increased cardiac preload (eg, mitral valve insufficiency).
  - Otherwise healthy dogs receiving higher doses are at risk for clinically significant elevations in blood pressure.[5]
- There is anecdotal evidence that phenylpropanolamine may become less effective over time in some patients and require dose escalation.

USMI = urethral sphincter mechanism incompetence

- This may be due to downregulation of adrenergic receptors, but this is unproven.
- When maximum doses are reached, an estrogen (eg, estriol, diethylstilbestrol) can be added to improve continence.

- There has been speculation that phenylpropanolamine and estrogens have a synergistic effect.
  - Only one study of this effect has been performed and did not support this theory[6]; however, further studies should be conducted to evaluate the interaction of these drugs.
- Anecdotally, patients with intolerance to higher doses of phenylpropanolamine may be maintained on lower doses with the addition of an estrogen (eg, diethylstilbestrol, estriol) at a standard dose.

MONITORING & ADVERSE EFFECTS

- The nonspecific nature of phenylpropanolamine can lead to potential for adverse effects from stimulation of the sympathetic nervous system, including hypertension, agitation, sleeplessness, and decreased appetite.[7]
  - Most adverse effects are mitigated by decreasing the dose or discontinuing use of phenylpropanolamine.
- A recent study showed that dogs receiving standard oral doses of 1 and 2 mg/kg q12h experienced increases in systolic, diastolic, and mean blood pressure, as well as compensatory decreases in heart rate.[5]
  - Of note, changes were not outside normal parameters and therefore are unlikely to be clinically significant.
- Phenylpropanolamine should be used with caution in patients with hypertension, with diseases predisposed to hypertension (eg, hyperadrenocorticism, chronic kidney disease, pheochromocytoma, hyperthyroidism), or with conditions sensitive to increased cardiac preload.
  - Blood pressure should be monitored 2 hours postadministration (at the time of maximal blood levels and smooth muscle effect) and can be evaluated after a single dose.[5,8]
  - The author recommends initial blood pressure measurement and twice-yearly rechecks in healthy patients and monitoring every 3 to 4 months in patients at risk for hypertension.

PHYSIOLOGY OF MICTURITION

Storage Phase

During the normal storage phase, stretch receptors in the bladder wall send afferent signals along the pelvic nerve, which activate a reflex arc through the hypogastric nerve to the urethra. Norepinephrine is released by postganglionic neurons to activate β-adrenergic receptors in the bladder wall, allowing for relaxation and continued filling. Norepinephrine also stimulates α_1-adrenergic receptors in the urethra and causes contraction of the circular and longitudinal smooth muscle surrounding the urethra, thus preventing urine leakage.

In addition to smooth muscle tone, the somatic-mediated contraction of the striated muscle surrounding the urethra is also important for maintenance of continence. With sudden increases in abdominal pressure, afferent signals travel up the pelvic nerve and initiate efferent signals down the pudendal nerve, releasing acetylcholine and activating nicotinic cholinergic receptors, thus causing contraction of the striated muscle.

Voiding Phase

During initiation of voiding, stretch receptors send afferent signals along the pelvic nerve and cranial to the pontine micturition center. Signals from the cerebral cortex and the hypothalamus are processed to determine if the situation is appropriate for initiation of micturition; if so, signals are sent down the pelvic nerve, leading to release of acetylcholine at the postganglionic parasympathetic neurons. Acetylcholine binds to receptors and stimulates bladder smooth muscle contraction. At the same time, inhibitory signals are sent to the sympathetic reflexes, and the urethra relaxes, allowing for normal emptying.

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