CONTROL ISSUES
Phenylpropanolamine, which has been shown to improve continence in dogs with USMI, is approved as a chewable tablet in the U.S.

FOCUS ON

Phenylpropanolamine for Urinary Incontinence

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Urethral sphincter mechanism incompetence (USMI) is the most common cause of urinary incontinence in spayed female dogs.[1] Studies have estimated the prevalence of USMI in dogs to be between 5.1% and 20%, with large-breed dogs being predisposed.[1-3] While the pathophysiology of USMI is multifactorial, medical management is often directed at increasing urethral tone with drugs such as α-adrenergic agents or estrogen derivatives.

Proin (PRN Pharmacal, prnpharmacal.com) is the only veterinary Food and Drug Administration (FDA)-approved phenylpropanolamine hydrochloride medication marketed in the United States to treat urinary incontinence due to hypotonicity of the urethral sphincter. Proin chewable tablets were first approved by the FDA in 2011, and an extended-release formulation, Proin ER, was approved in 2019.[4-6] In Europe and Canada a liquid formulation of phenylpropanolamine, Propalin (Vetoquinol, vetoquinol.ca), is available. Formulations that are no longer commercially available include Uriflex-PT, Uricon, Cystolamine, and Proin Drops.

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MECHANISM OF ACTION

Phenylpropanolamine is a sympathomimetic amine that indirectly stimulates the α_1- adrenergic receptors (and, to a lesser extent, β-receptors) by causing release of norepinephrine, leading to constriction of the smooth muscle internal urethral sphincter.[7,8] It is also thought to prolong its effect by inhibiting norepinephrine reuptake at the synaptic junction.[7] Phenylpropanolamine may have decreased efficacy in patients on long-term therapy owing to either depletion of norepinephrine stores or desensitization of the α-adrenergic receptors.[7-9]

DOSING

The recommended labeled dose for Proin is 2 mg/kg PO q12h, to be dosed to the nearest half-tablet.[6] Proin is commercially available in 25-, 50-, and 75-mg

tablets. The recommended dose of Proin ER is 2 to 4 mg/kg PO q24h (to be given with food).[10] Proin ER is available in 18-, 38-, 74-, and 145-mg tablets. It is not labeled for use in dogs weighing less than 10 pounds.[10] Owing to a lack of safety and efficacy studies, using Proin ER tablets and Proin chewable tablets interchangeably is not recommended, nor is the use of Proin in pregnant or lactating animals.[10]

EFFICACY

Phenylpropanolamine has been found to be efficacious at controlling incontinence secondary to USMI in several studies. In one study, phenylpropanolamine was found to be effective at controlling unconscious urination in 85.7% of dogs treated with 1 mg/kg PO q8h.[11] Studies funded by a manufacturer (Pegasus Laboratories Inc.) showed a significant reduction in urinary incontinence at 2 mg/kg PO q12h compared with placebo, with 91.3% of owners reporting satisfactory urinary continence by day 30 and 98.1% at day 180. However, during short-term efficacy studies, no significant improvement was noted in incontinent male dogs when accounting for a sex effect.[4] In a manufacturer-funded study with 107 dogs, there was no significant difference in efficacy between standard-release Proin tablets and Proin ER.

Analysis of urethral pressure profiles has shown that phenylpropanolamine causes a significant increase in urethral resistance compared with controls.[8] Similarly, a study measuring urethral pressure profiles and continence scores of incontinent dogs with USMI showed that phenylpropanolamine was significantly more effective than its analog, pseudoephedrine, at increasing maximum urethral closure pressure and functional area as well as continence score.[1]

PHARMACOKINETICS

Phenylpropanolamine has an excellent bioavailability for both controlled-release and immediate-release formulations (93.7% and 98%, respectively) in dogs.[12] Maximal concentrations (C_{max}) are reached 2 hours after administration, with a half-life of 3 to 4 hours for the immediate-release formulation.[8,12] Phenylpropanolamine absorption in the controlled-release formulation is biphasic, with a rapid initial absorption phase followed by a second slower absorption phase that continues for up to 16 hours.[12] Pharmacokinetic studies of Proin ER showed a slightly higher C_{max} than Proin; however, overall drug exposure (area under the curve) was less.[5] Phenylpropanolamine is primarily excreted unchanged by the kidneys.[12]

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SAFETY AND ADVERSE EFFECTS

Manufacturer-reported side effects include weight loss of >5%, vomiting, hypertension, anorexia, proteinuria, and anxiety/behavior change, including aggression.[4] In the authors' experience, therapy with estrogen-based products, such as estriol (Incurin; Merck Animal Health, merck-animal-health-usa.com), is preferable for patients with known behavioral concerns.

Safety studies performed by the manufacturer showed that dosing at up to 5 times the recommended dose for 6 months resulted in hypertension; however, the mean arterial pressure was not significantly different than that in the ideal dosing group and no evidence of target organ damage was noted at necropsy.[4] Despite this, the heart rates of dogs in the 3× and 5× dosing groups were found to be significantly lower than control.[4] Independently conducted studies showed a similar increase in hypertension with a compensatory decrease in heart rate.[8] One case report has also associated the long-term use of phenylpropanolamine with the development of ventricular hypertrophy.[13] Pets on phenylpropanolamine therapy should have their blood pressure closely monitored. If significant hypertension is noted, therapy with an alternative agent should be considered.

In addition to hypertension, dogs in the 3× and 5× manufacturer safety dosing groups were found to have significant elevations in platelet counts, alanine aminotransferase (ALT), and lactate dehydrogenase.[4] Similarly, short-term dosing of phenylpropanolamine at 10× the recommended dose for 21 days resulted in hypertension, bradycardia, vomiting, leukocytosis, thrombocytosis, and elevations in ALT.

An increased risk of hypertension has been documented in patients receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), reserpine, or tricyclic antidepressants.[7]

While not reported in companion animal species, the use of sympathomimetic drugs, including phenylpropanolamine, has been associated with birth defects in people, rabbits, and chickens.[14,15] Safety studies in this population of companion animals are lacking; therefore, therapy with phenylpropanolamine should be avoided in pregnant or lactating bitches.

Several drug interactions are possible. An increased risk of hypertension has been documented in patients receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), reserpine, or tricyclic antidepressants.[7] Phenylpropanolamine should not be given within 2 weeks of a patient receiving a monoamine oxidase inhibitor such as amitraz.[7] Finally, anesthesia with halothane is associated with an increased risk of arrhythmias and should be avoided.[7]

PHENYLPROPANOLAMINE VERSUS ESTROGEN

In addition to phenylpropanolamine, estrogen or estrogen derivatives such as estriol and diethylstilbestrol (DES) are commonly used for dogs with USMI. One study showed that sympathomimetic drugs (pseudoephedrine) were more effective at controlling urinary incontinence than DES (82.4% versus 64.5%).[16] However, more recent studies of estriol have shown reported efficacies between 83% and 89.8%, similar to that of phenylpropanolamine.[17,18]

Prior to its discontinuation in humans, combined therapy with phenylpropanolamine and estrogen derivatives was found to be synergistic, with increases in maximum urethral closure and reductions in leakage episodes.[19-21] One recent study in healthy beagles without USMI showed no improvement in maximum urethral pressure or closure pressure when phenylpropanolamine was added to estriol.[22] However, as there are likely differences in the functional urodynamics of unaffected animals and dogs with USMI, additional studies are warranted. In the authors' experience, dogs affected with USMI that do not respond to phenylpropanolamine may respond to estriol or vice versa, and in some cases combination therapy is warranted.

CONCLUSION

Phenylpropanolamine is effective at improving continence in dogs with USMI. Generally, therapy with phenylpropanolamine is safe; however, routine blood pressure monitoring should be performed to screen for hypertension, and special consideration should be taken before prescribing phenylpropanolamine to animals with behavioral concerns. Therapy with concurrent NSAIDs, reserpine, or tricyclic antidepressants may increase the risk of hypertension. If unacceptable hypertension is observed, therapy with an alternative agent should be considered. TVP

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References

1. Byron JK, March PA, Chew DJ, DiBartola SP. Effect of phenylpropanolamine and pseudoephedrine on the urethral pressure profile and continence scores of incontinent female dogs. *J Vet Intern Med.* 2007;21(1):47-53.
2. Forsee KM, Davis GJ, Mouat EE, et al. Evaluation of the prevalence of urinary incontinence in spayed female dogs: 566 cases (2003-2008). *JAVMA.* 2013;242(7):959-962.
3. Arnold S. Urinary incontinence in castrated bitches. Part 1: significance, clinical aspects and etiopathogenesis [in German]. *Schweiz Arch Tierheilkd.* 1997;139(6):271-276.

4. U.S. Food and Drug Administration. Proin chewable tablets. Freedom of Information Summary. NADA 141-324. August 4, 2011. animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/881. Accessed October 2020.
5. U.S. Food and Drug Administration Center for Veterinary Medicine. FDA approves PROIN ER tablets for controlling urinary incontinence in dogs. April 1, 2019. fda.gov/animal-veterinary/cvm-updates/fda-approves-proin-er-tablets-controlling-urinary-incontinence-dogs. Accessed October 2020.
6. PRN Pharmacal. PROIN® chewable tablets. prnpharmacal.com/products/urinary-health/proin-chewable-tablets. Accessed October 2020.
7. Plumb DC. *Plumb's Veterinary Drug Handbook: Pocket*. 9th ed. Hoboken, NJ: Wiley-Blackwell; 2018.
8. Noël S, Cambier C, Baert K, et al. Combined pharmacokinetic and urodynamic study of the effects of oral administration of phenylpropanolamine in female beagle dogs. *Vet J.* 2010;184(2):201-207.
9. Collins S, Caron MG, Lefkowitz RJ. Regulation of adrenergic receptor responsiveness through modulation of receptor gene expression. *Annu Rev Physiol.* 1991;53:497-508.
10. PRN Pharmacal. PROIN ER™. prnpharmacal.com/products/urinary-health/proin-er. Accessed October 2020.
11. Scott L, Leddy M, Bernay F, Davot JL. Evaluation of phenylpropanolamine in the treatment of urethral sphincter mechanism incompetence in the bitch. *J Small Anim Pract.* 2002;43(11):493-496.
12. Hussain MA, Aungst BJ, Lam G, Shefter E. Phenylpropanolamine pharmacokinetics in dogs after intravenous, oral, and oral controlled-release doses. *Biopharm Drug Dispos.* 1987;8(5):497-505.
13. Hanson KR, Ware WA. Myocardial hypertrophy associated with long-term phenylpropanolamine use in a dog. *JAVMA.* 2018;253(11):1452-1459.
14. Gilbert-Barness E, Drut RM. Association of sympathomimetic drugs with malformations. *Vet Hum Toxicol* 2000;42(3):168-171.
15. Yau WP, Mitchell AA, Lin KJ, et al. Use of decongestants during pregnancy and the risk of birth defects. *Am J Epidemiol.* 2013;178(2):198-208.
16. Nendick PA, Clark WT. Medical therapy of urinary incontinence in ovariectomised bitches: a comparison of the effectiveness of diethylstilboestrol and pseudoephedrine. *Aust Vet J.* 1987;64(4):117-118.
17. Mandigers RJ, Nell T. Treatment of bitches with acquired urinary incontinence with oestriol. *Vet Rec.* 2001;149(25):764-767.
18. U.S. Food and Drug Administration. Incurin. Freedom of Information Summary. NADA 141-325. July 25, 2011. animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/882. Accessed October 2020.
19. Ahlström K, Sandahl B, Sjöberg B, et al. Effect of combined treatment with phenylpropanolamine and estriol, compared with estriol treatment alone, in postmenopausal women with stress urinary incontinence. *Gynecol Obstet Invest.* 1990;30(1):37-43.
20. Kinn AC, Lindskog M. Estrogens and phenylpropanolamine in combination for stress urinary incontinence in postmenopausal women. *Urology.* 1988;32(2):273-280.
21. Beisland HO, Fossberg E, Moer A, Sander S. Urethral sphincteric insufficiency in postmenopausal females: treatment with phenylpropanolamine and estriol separately and in combination. A urodynamic and clinical evaluation. *Urol Int.* 1984;39(4):211-216.
22. Hamaide AJ, Grand JG, Farnir F, et al. Urodynamic and morphologic changes in the lower portion of the urogenital tract after administration of estriol alone and in combination with phenylpropanolamine in sexually intact and spayed female dogs. *Am J Vet Res.* 2006;67(5):901-908.