

Evaluation of once daily dose of phenylpropanolamine in the treatment of urethral sphincter mechanism incompetence in spayed bitches

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Summary: The aim of this study was to evaluate the efficacy and long term safety of once daily administration of phenylpropanolamine (PPA) in the treatment of urethral sphincter mechanism incompetence (USMI) in spayed bitches in comparison to three times daily administrations. For this purpose, 22 spayed bitches suffering from USMI received either PPA at the dose rate of 1.5 mg/kg, body weight (BW) once daily (group I, n=11) or 1.5 mg/kg three times daily (group II, n=11) by oral administration. Clinical efficacy was determined by using a scoring system based on analysing the frequency and the amount of unconscious urination on d 7, 14 and 28. There was no significant difference ($p>0.05$) between the clinical response observed on d 7, 14 and 28 of treatment in group I and II. Eight dogs (72.7%) in each group were continent on d 28. The side effects observed were mild and transient. Phenylpropanolamine therapy was continued in 13 dogs that became continent after 28 d and the dogs were followed up for 12 months. None of the dogs showed symptoms of urinary incontinence except for 2 bitches that became refractory to PPA treatment in group II. Phenylpropanolamine was combined with estriol for 14 d (1 mg/dog PO) in dogs in which PPA therapy was inefficient or unsatisfactory on d 28 and in dogs that became refractory to PPA treatment. A total of 8 dogs were treated with estriol PPA combination. Five (62.5%) bitches were continent on 14th d of estriol PPA combination treatment. In one bitch (12.5%) urinary incontinence improved. In conclusion, once daily administration of PPA at a dose of 1.5 mg/kg, BW is effective in treatment of USMI in spayed bitches and it offers a cheap and convenient treatment option. In addition, recurrence of incontinence can be observed during long term administration of PPA and combination of PPA with estriol is effective in dogs in which PPA therapy alone is unsatisfactory and in dogs that become refractory to PPA treatment.

Key words: Estriol, phenylpropanolamine, spayed bitch, urethral sphincter mechanism incompetence.

Kısırlaştırılmış dişi köpeklerde üretral sfinkter mekanizması yetersizliğinin tedavisinde günlük tek doz fenilpropanolamin uygulamasının değerlendirilmesi

Özet: Bu çalışmanın amacı, kısırlaştırılmış dişi köpeklerde üretral sfinkter mekanizması yetersizliğinin (urethral sphincter mechanism incompetence, USMI) tedavisinde günde tek doz fenilpropanolamin (phenylpropanolamine, PPA) uygulamasının uzun dönem etkinlik ve güvenilirliğinin günde üç doz uygulama ile karşılaştırılarak araştırılmasıdır. Bu maksatla, USMI teşhisi konan 22 kısırlaştırılmış dişi köpeğe günde tek doz 1,5 mg/kg, vücut ağırlığı, per os (grup I, n=11) veya günde üç doz 1,5 mg/kg, vücut ağırlığı, per os (grup II, n=11) PPA uygulandı. Tedavinin klinik etkinliği 7, 14 ve 28. günlerde istemsiz ürünasyonun frekans ve miktarının ölçülmesine dayalı bir derecelendirme sistemi kullanılarak belirlendi. Tedavinin ilk 28 günü sonunda her iki grupta 8'er köpekte (%72,7) semptomlar tamamen ortadan kalktı. Gruplar arasında tedavinin 7, 14 ve 28. günlerinde klinik yanıt bakımından bir farklılık gözlenmezken ($p>0,05$), hafif ve geçici yan etkiler gözlemlendi. Tedavinin ilk 28 günü sonunda idrar kaçırma şikayeti ortadan kalkan 13 köpekte tedaviye devam edildi ve köpekler toplam 12 ay süreyle izlendi. Bu süreçte grup II'de PPA tedavisine dirençli hale gelen 2 köpek dışında idrar kaçırma şikayeti ile karşılaşılmadı. Fenilpropanolamin tedavisinin başarısız olduğu veya istenilen düzeyde etkili olmadığı köpekler ve PPA tedavisine dirençli hale gelen köpeklerde PPA 14 gün süreyle östriol (1 mg/kg, per os) ile kombine edildi. Fenilpropanolamin östriol kombinasyonu tedavisine alınan toplam 8 köpekten 5'inde (%62,5) tedavi sonunda idrar tutamama semptomları ortadan kalkarken, 1 köpekte (%12,5) semptomlar azaldı. Sonuç olarak, kısırlaştırılmış dişi köpeklerde üretral sfinkter mekanizması yetersizliği tedavisinde PPA'nın günde bir 1,5 mg/kg vücut ağırlığı dozunda uygulanması etkili olmakta, ucuz ve pratik bir tedavi seçeneği sunmaktadır. Ayrıca, uzun dönem PPA tedavisi sırasında idrar tutamama tekrarlayabilmekte ve PPA östriol kombinasyonu, PPA tedavisinin tatmin edici yanıt vermediği köpeklerde etkili olmaktadır.

Anahtar sözcükler: Fenilpropanolamin, kısırlaştırılmış dişi köpek, östriol, üretral sfinkter mekanizması yetersizliği.

Introduction

Urinary incontinence is one of the most common complications of ovariohysterectomy in dogs and it is reported that the incidence of urinary incontinence after ovariohysterectomy may reach up to 20% (3). The underlying mechanism is usually insufficient closure of the urethra and urinary incontinence after spaying is called urethral sphincter mechanism incompetence (15). Clinical signs of USMI, such as urine leakage during sleep or periods of excitement, may develop as long as 10 years after spaying. Medium to large breed dogs are affected (3). Several aetiologies have been proposed to explain this multifactorial condition, such as decreased urethral tone, caudal displacement of the bladder, a shorter urethra, hormonal deficiency, or obesity (12).

Medical treatment of USMI is the method of choice and should always precede surgical therapy. Estrogens, gonadotropin-releasing hormone (GnRH) depot analogues and tricyclic antidepressant agents may be used (21). However, alpha (α) agonist phenylpropanolamine (PPA) is currently the first line therapy (6). Alpha-adrenergic agonists improve the urethral closure pressure by stimulation of the α -receptors of the smooth urethral musculature (4). The treatment with α -adrenergic agonists results in continence in 74-97 % of incontinent bitches (3, 22, 23).

The current recommended dosage and rate of administration of PPA for the treatment of USMI in the dog is 1-1.5 mg/kg, BW every 8 or 12 h. It is usually suggested that the dog must remain on this medication for the rest of its life (22). However, a decrease in urethral response associated with recurrence of incontinence can be observed after a prolonged administration of PPA and it is proposed that desensitization of urethral α -adrenergic receptors may occur in dogs treated multiple times daily with PPA or in dogs receiving prolonged treatment (23). In a study in continent Beagle bitches, single daily administrations of PPA appeared to increase urethral pressure more than multiple daily administrations. Authors recommended the use of PPA at a dosage of 1.5 mg/kg, PO, every 24 h for treatment of dogs with USMI and pointed out the need for clinical studies including incontinent dogs to confirm the efficacy (8). The importance of clinical trials comparing the long term clinical efficacy of single vs. multiple administration of PPA in dogs suffering from USMI was further stressed in a recent study in which urethral resistance was significantly increased after 1 week of once daily administration, but not after three times daily administrations (19).

The aim of this study was to evaluate the efficacy and the long term safety of once daily administration of 1.5 mg/kg, BW PPA in the treatment of USMI in spayed bitches in comparison to three times daily administrations of 1.5 mg/kg, BW in field conditions.

Materials and Methods

Animal experimentation was approved by the respective local authority (Local Ethics Committee on Animal Experiments of Ankara University, Ankara, Turkey; Approval no: 2011-123-483).

Animal selection: Twenty-two spayed bitches diagnosed as suffering from USMI were used in the study. The dogs were selected after using exclusion criteria reported by Scott et al. (22) with minor modifications. Specifically, the following conditions were excluded; overt urinary tract infections (cases of cystitis not suspected upon clinical examination or from the clinical history, but which were subsequently detected upon urinalysis, were included after antibiotic therapy), polydipsia or polyuria associated with renal failure, hepatic insufficiency, diabetes or any other metabolic disorder, behavioural causes of inappropriate urination and animals less than one year old or which had been ovariohysterectomised within the previous six months (mo).

For this purpose, history of the animals (breed, age, weight, time after ovariohysterectomy, pre-existing medical conditions), clinical examination and laboratory examinations were used. In clinical examination rectal temperature, body condition, heart rate, mucosal colour and capillary refill time were assessed. Transabdominal ultrasonography was performed in order to rule out anatomical abnormalities of the urinary tract. Cephalic blood sample was taken from each dog and was used in routine biochemistry and haematology. If the results showed an abnormality that resulted in the dog meeting one of the exclusion criteria, the animal was not included in the study. A sterile urine sample was obtained via cystocentesis for urinalysis and bacteriological culture. Dogs included in the study showed no signs of lower urinary tract disease or infection and no abnormalities were detected on urinalysis. Body condition of the dogs was scored by a single investigator using a previously described nine-point scale which depends on visual inspection and palpation (17).

Scoring of urinary incontinence: The degree of unconscious urination was scored on day 0 for the evaluation of treatment outcomes. The frequency of unconscious urination and the amount of urine produced during unconscious urination were considered. The frequency of incontinence was scored as follows: 0=no unconscious urination, 1=once a day or less, 2=more than once a day. The amount of urine produced during periods of unconscious urination was assessed as follows: 1=small amounts of urine passed without control (drops), 2=large volumes of urine passed without control so that the ground where the bitch had been lying was obviously wet.

Treatments: Each dog was randomly allocated to one of two groups and received either PPA at the dose

rate of 1.5 mg/kg once daily (group I, n=11) or 1.5 mg/kg three times daily (group II, n=11) by oral administration in food for 28 d. Treatment was continued for 12 months in dogs which became continent after 28 d. Phenylpropanolamine was combined with estriol for 14 d (1 mg/dog PO) in dogs in which PPA therapy was inefficient or unsatisfactory on d 28 and in dogs that became refractory to PPA treatment at any time. No other treatment was permitted during the course of the study. Adverse effects of each treatment were monitored by both the veterinary surgeon and the owners of the animals. The owners were informed about possible side effects.

Assessment criteria: The frequency and the amount of unconscious urination were analysed on d 7, 14, 28 and once a month for a total period of 12 mo in PPA groups. In order to claim efficacy, treatment had to result in an improvement in the unconscious leaking of urine by the animal, as evidenced by a decrease in the frequency of unconscious urination and a decrease in the amount of urine produced during unconscious urination compared to urinary incontinence score on d 0. Accordingly, the response to the treatment was defined as a cure (continent), an improvement (better total score) or a no improvement (no change in total score). The same criteria were used for dogs that received PPA and estriol combination on d 0, 7 and 14 of the therapy.

Statistical analysis: Fisher's exact test was performed in comparison of clinical response and the number of side effects observed in group I and II. The statistical significance was set at $p < 0.05$. SPSS 14.0 program was used for data analysis.

Results

In 3 dogs, we were unable to finish the follow-up period of 12 mo. However, clinical data for the first 28 d of treatment in these 3 dogs were included in statistical analysis.

Descriptive data: Descriptive data of the bitches included in the study is given in Table 1. Mean age of the bitches was 6.05 ± 2.30 years. The mean length of time between ovariohysterectomy and inclusion of bitches in the trial was 2.80 ± 1.43 years. Average weight and body condition score of the animals were 28.68 ± 7.8 kg and 5.95 ± 1.40 , respectively. Thirteen breeds of animals were included in the study. Among them, there were more than one animal from Boxer (5/22), German Shepherd (4/22) and Golden Retriever (3/22) breeds.

Clinical efficiency: Frequency of unconscious urination in group I and group II on d 0, 7, 14 and 28 of therapy is provided in Table 2. In group I, on d 0, one bitch had frequency score of 1 whereas the frequency score

Table 1. Descriptive data of the bitches included in the study.
Tablo 1. Çalışmada kullanılan köpeklere ait tanımlayıcı veriler.

No	Breed	Group I				No	Breed	Group II			
		Age (y)	Weight (kg)	BCS	OVH-USMI Interval (y)			Age (y)	Weight (kg)	BCS	OVH-USMI Interval (y)
1	Doberman Pinscher	3,8	33	6	1,2	1	Golden Retriever	4,6	37	8	2,1
2	Boxer	8,0	27	5	5,0	2	Boxer	3,8	22	4	1,3
3	Boxer	9,2	28	6	3,8	3	German Shepherd	7,5	36	8	1,7
4	Boxer	5,0	21	4	1,8	4	Turkish Shepherd	11,0	43	7	6,0
5	Golden Retriever	2,3	27	6	0,9	5	Golden Retriever	6,0	25	5	3,0
6	Dalmatian	4,0	25	6	2,2	6	German Shepherd	6,3	27	4	3,3
7	German Shepherd	6,3	30	6	4,3	7	Siberian Husky	3,5	24	5	2,3
8	Boxer	7,0	23	5	3,0	8	Pointer	9,7	23	5	2,0
9	Rottweiler	5,8	44	7	5,2	9	Mixed	5,5	25	6	3,5
10	Irish Setter	9,1	29	7	3,4	10	Labrador Retriever	6,3	38	9	3,3
11	German Shepherd	6,0	33	7	1,1	11	Staffordshire Bull Terrier	3,0	11	5	1,3
Mean		6.0	29.1	5.9	2.9			6.1	28.3	6.0	2.7

y: years, BCS: Body condition score, OVH: ovariohysterectomy, USMI: uretral sphincter mechanism incompetence

Table 2. Frequency of unconscious urination in group I and group II on days 0, 7, 14 and 28 of phenylpropanolamine therapy.
Tablo 2. Fenilpropanolamin tedavisinin 0, 7, 14 ve 28. günlerinde grup I ve grup II'de belirlenen istemsiz ürünasyon sıklığı.

	Day 0		Day 7		Day 14		Day28	
	Group I (n=11)	Group II (n=11)	Group I (n=11)	Group II (n=11)	Group I (n=11)	Group II (n=11)	Group I (n=11)	Group II (n=11)
No unconscious urination	-	-	6 (54.5 %)	5 (45.5 %)	7 (63.6 %)	8 (72.7 %)	8 (72.7 %)	8 (72.7 %)
Once a day or less	1 (9.9. %)	3 (27.3 %)	-	2 (18.2 %)	1 (9.9. %)	2 (18.2 %)	-	2 (18.2 %)
More than once	10 (90.9 %)	8 (72.7 %)	5 (45.5 %)	4 (36.4 %)	3 (27.3 %)	1 (9.9. %)	3 (27.3 %)	1 (9.9. %)

Table 3. The amount of urine produced during unconscious urination at day 0, 7, 14 and 28 of phenylpropanolamine therapy in group I and II.

Tablo 3. Grup I ve grup II'de fenilpropanolamin tedavisinin 0, 7, 14 ve 28. günlerinde belirlenen istemsiz ürünasyon sırasında üretilen idrar miktarları.

	Day 0		Day 7		Day 14		Day 28	
	Group I (n=11)	Group II (n=11)	Group I (n=11)	Group II (n=11)	Group I (n=11)	Group II (n=11)	Group I (n=11)	Group II (n=11)
No urine	-	-	6 (54.5 %)	5 (45.5 %)	7 (63.6 %)	8 (72.7 %)	8 (72.7 %)	8 (72.7 %)
Small amounts of urine	4 (36.4 %)	3 (27.3 %)	4 (36.4 %)	5 (45.5 %)	3 (27.3 %)	2 (18.2 %)	2 (18.2 %)	3 (27.3 %)
Large amounts of urine	7 (63.6 %)	8 (72.7 %)	1 (9.9. %)	1 (.9. %)	1 (9.9. %)	1 (9.9. %)	1 (9.9. %)	-

Table 4. Clinical response to once daily (group I) and three times daily (group II) phenylpropanolamine administrations on day 7, 14 and 28 of therapy.

Tablo 4. Günde bir (grup I) ve günde üç (grup II) fenilpropanolamin uygulamasının 7, 14 ve 28 günlerinde belirlenen klinik yanıt.

Day	Day 7			Day 14			Day28		
	Group I (n=11)	Group II (n=11)	P value	Group I (n=11)	Group II (n=11)	P value	Group I (n=11)	Group II (n=11)	P value
Cure	6 (54.5 %)	5 (45.5 %)	p>0.05	7 (63.6 %)	8 (72.7 %)	p>0.05	8 (72.7 %)	8 (72.7 %)	p>0.05
Improvement	2 (18.2 %)	4 (36.4 %)	p>0.05	1 (9.9. %)	2 (18.2 %)	p>0.05	-	2 (18.2 %)	p>0.05
No response	3 (27.3 %)	2 (18.2 %)	p>0.05	3 (27.3 %)	1 (9.9. %)	p>0.05	3 (27.3 %)	1 (9.9. %)	p>0.05

Table 5. Number of adverse effects during the first 28 days of phenylpropanolamine treatment.

Tablo 5. İlk 28 günlük fenilpropanolamin tedavisinde gözlenen yan etki sayısı.

Adverse effect	Group I (n=11)	Group II (n=11)	P
Diarrhoea	3	5	p>0.05
Vomiting	3	6	p>0.05
Decreased appetite	2	6	p>0.05
Others	1	3	p>0.05

was 2 in the other 10 bitches. The frequency of unconscious urination showed no change in 5 of 10 score 2 bitches on 7th d of treatment. In contrast, remaining 5 bitches and the only score 1 bitch on d 0 were out of urinary incontinence on d 7. One of 5 score 2 bitches became continent and another one showed improvement on d 14. There was no improvement in the remaining 3 bitches in terms of frequency and amount of unconscious urination until d 28. The only bitch that was scored 1 on d 14 was continent on d 28.

In group II, there were 3 score 1 bitches and 8 score 2 bitches at the beginning of the trial. Two of score 1 bitches were continent on d 7 while the other dog became continent on d 14. Of 8 the score 2 bitches, 3 became continent, one showed improvement and 4 showed no change in first 7 d of the trial. The only bitch that had improved unconscious urination frequency on d 7 was continent on the examination on d 14. One of 4 bitches that had unchanged frequency of unconscious urination in the first week became continent in second week. Two of these 4 bitches were scored 1 on d 14 and the score remained unchanged until d 28. In the remaining bitch, frequency of unconscious urination was not improved.

The amount of urine produced at d 0, 7, 14 and 28 in group I and II is given in Table 3. In group I, 4 bitches were unconsciously urinating small amounts (score 1) of urine and 7 bitches were unconsciously urinating large amounts (score 2) of urine at d 0. Two of the 4 score 1 bitches were out of urinary incontinence at d 7 and 14, respectively. In contrast, in the other 2 bitches amount of urine produced was not changed in 28 d. Six of 7 score 2 bitches became continent within 28 d. The amount of urine produced was not changed in one dog.

In group II, 3 bitches were scored 1 whereas 8 bitches were scored 2 at d 0. Two of score 1 bitches were continent on the examination at d 7. The amount of urine produced during unconscious urination showed no changes in the other bitch in 28 d. Of the 8 score 2 bitches, 3 became continent on d 7 and another 3 became continent on d 14. Remaining 2 bitches showed improvement which was observed on d 7 in one bitch and on d 28 in the other.

Clinical response to the treatment determined by changes in total incontinence score in group I and II is illustrated in Table 4. Three cases were recorded as a treatment failure in group I. There were no detectable changes in total incontinence score throughout 28 d in these cases. The number of continent bitches on d 7, 14 and 28 were 6 (54.5%), 7 (63.6%) and 8 (72.7%), respectively. None of the dogs were considered as an improvement on 28th d. Eight dogs (72.7%) in group II were continent on d 28 and incontinence were improved in 2 (18.2%) dogs. There was no response to treatment in one dog (9.9 %). There was no significant difference ($p>0.05$) between the clinical response observed on 7, 14 and 28 d of treatment in group I and II.

12 months of follow-up: Six dogs in group I and 7 dogs in group II in which 28 d of therapy was successful (cure) were followed up for 12 mo. None of the dogs showed symptoms of urinary incontinence except for 2 bitches in group II. Urinary incontinence was observed on about 4th and 7th mo of the treatment, respectively.

Adverse effects: The side effects observed were diarrhoea, vomiting, decreased appetite, aggression and apathy. The side effects were not life threatening and mild. They were recorded without preventing treatment continuation and resolved spontaneously. The number of animals showing side effects and the number of side effects observed were lower in group I than in group II. However, the difference in the prevalence of side effects was not significant ($p>0.05$, Table 5).

Estriol PPA combination treatment: Eight dogs were treated with estriol plus PPA. These included 3 no improvements in group I, one no improvement and 2 unsatisfactory responders in group II and 2 bitches that became refractory to PPA treatment. Previous dosage and the number of PPA administrations were not changed during combination with estriol. Four (50%) and 5 (62.5%) bitches were continent on 7th and 14th d of estriol plus PPA treatment, respectively. In one bitch (12.5%) urinary incontinence improved. In 2 bitches the medication did have no effect and the dogs underwent colposuspension.

Discussion and Conclusion

Traditionally, treatment of USMI in spayed female dogs has been to increase urethral sphincter tone with α -agonists. Phenylpropanolamine is the most frequently used α -agonist for this condition (6). Although the older substance ephedrine and its stereoisomer pseudoephedrine have been reported to be effective in treatment, lesser efficacy and owner perception of continence compared with PPA as well as the increased incidence of adverse effects make these compounds less satisfactory alternatives to PPA for the treatment of USMI in female dogs (5, 14).

Urethral sphincter mechanism incompetence is the main cause of acquired urinary incontinence cases in the spayed bitch and among female dogs with USMI, 90% are spayed (15). However, urinary incontinence in female dogs can also result from congenital or acquired physical defects, inflammatory conditions and physiological abnormalities (12). To rule out the other causes of urinary incontinence, animal selection criteria previously reported by Scott et al. (22) were used. The breed, age and weight of the bitches, time elapsed between ovariohysterectomy and the onset of incontinence and previous medical records were used in order to make a correct diagnosis. As it will be discussed later in this text, there appears a strong connection between body weight and the incidence of incontinence and some breeds show

a high incidence (3). Typically, dogs with USMI present with a history of urinary incontinence that is often observed during sleep or at other times when the bitch is relaxed. It is suggested that exclusion of animals until six mo after neutering as a means of ruling out iatrogenic-induced incontinence and exclusion of animals less than one year old helps eliminating juvenile incontinence which is usually related to congenital defects such as ectopic ureters (22). Additionally, transabdominal ultrasonography was performed in this study in order to rule out anatomical abnormalities of the urinary tract. We were unable to use other diagnostic screening examinations i.e. intravenous contrast urography, computerized tomography and urodynamic testing techniques such as urethral pressure profile due to lack of equipment. Unfortunately, these tests are likely underutilized in practice and are typically offered only in some universities or large referral centres. In practice the diagnosis of USMI in spayed bitches is established by ruling out other causes of incontinence (2). Therefore, the lack of specific techniques was not considered to weaken the study.

Blood and urine samples were collected from each dog to rule out false presentations of incontinence due to other physiological abnormalities. In contrast to the study of Scott et al. (22) in which cases of cystitis detected only upon urinalysis were included but required concomitant antibiotic therapy, only dogs with normal urinalysis were included in this study. In dogs with occult infection cephalixin was given orally for 14 d and the dogs were included in the trial in case they have normal urinalysis on d 14. Cephalixin was the choice of treatment because it is bactericidal, acidic drug with a lowVd, and it is relatively nontoxic. It has excellent activity against *Staphylococci*, *Streptococci*, *E. coli*, *Proteus spp.*, and *Klebsiella spp.*, as well (11). However, vomiting and gastrointestinal disturbances may occur in dogs treated with cephalosporins. For the reason that adverse effects of PPA were of interest in the present study, simultaneous antibiotic and PPA therapy was avoided.

The mean length of time between ovariohysterectomy and the onset of incontinence (2.80 ± 1.43 years) in the current study was in accordance with the findings published in earlier reports. However, the age at onset of USMI (6.05 ± 2.30 years) was found higher. Previous work has suggested a median time to onset of USMI of 2.4-3 years after spaying with an approximate age at onset of USMI of 3-5 years (2, 5). The higher age at onset of USMI reported in the current study might be explained by the fact that neutering female dogs at early ages is not a common procedure in Turkey. The onset of incontinence has been reported to vary between immediately to more than 10 years after surgery and the urethral closure pressure for continent bitches drops significantly within 12 mo after surgery (2). The earliest

onset in the present study was 11 mo after surgery which might be considered as later than expected. However, it has to be kept in mind that the dogs that had been ovariohysterectomised within the previous six mo were not included in the current study.

In this trial the mean weight of the animals was 28.68 ± 7.81 kg. This is in agreement with previous studies suggesting a strong connection between body weight and the incidence of incontinence (1, 3). In one of these studies Arnold et al. (3) reported that of bitches with a body weight of less than 20 kg only 9.3% were incontinent whereas in bitches with a body weight of more than 20 kg the incidence was 30.9%. The mean body condition score (BCS) for dogs in the current study was 5.95 ± 1.40 , which refers overweight, and only 3 (13.6%) dogs had a BCS of <5 . To the author's knowledge, there is no study directly analysing the relationship between BCS and the incidence of urinary incontinence. However, it was reported that bitches that were overweight before spaying had 3.5 times more risk of developing the disease as compared with subjects that were not obese before and after surgery (1). Generally medium and large breeds are affected and some breeds are said to be particularly at risk of urinary continence. Boxers, German Shepherds and Golden Retrievers were predominated in this study. Among these breeds, Boxers and German Shepherds have been reported to be at high risk (3).

Eight bitches (72.7%) in both treatment groups became continent on d 28. These results are comparable to some previous success rates reported after administration of α -adrenergic agents (3, 21) but lower than results obtained in some studies (6, 22, 23). One of the reasons of lower success rates observed in the current study should be that the treatment was regarded as successful only in continent bitches not in bitches showing improvement. To the author's knowledge, single daily dose of PPA in the treatment of USMI in the bitch was clinically evaluated in only one retrospective study which reported that single daily dose of 1.5 mg/kg, BW of PPA was effective in 8/9 bitches (9). Different inclusion criteria used in different studies might contribute to discrepancy in results obtained as well.

The results of the current study demonstrate the efficacy of once daily dose of PPA administration in treatment of USMI in spayed bitches. This treatment schedule offers a cheaper and more convenient alternative to multiple doses of PPA administrations. Administrations in every 8 h are hard to follow and restrictive for many dog owners and usually result in missing some doses and administration of inappropriate amounts of the drug.

Two dogs receiving multiple doses of PPA became refractory to treatment in the current study. Recurrence of incontinence associated with a decrease in urethral

response is observed after a prolonged administration of multiple doses PPA (23) and it has been proposed that desensitization of urethral α -adrenergic receptors may occur in dogs treated multiple times daily with PPA or in dogs receiving prolonged treatment (8). In accordance with the results of the current study, Claeys et al. (9) followed up 5 bitches on single daily PPA treatment for a mean of 20.8 mo and observed no recurrences. There are no adequate and well-controlled studies focusing on recurrence of incontinence during long term PPA administrations in dogs. However, it may be assumed that once daily administration of PPA is advantageous over multiple daily administrations in terms of preventing recurrences during PPA treatment.

The observed side effects and their severity were in accordance with previous reports (3, 6, 23). Three dogs in group I and 6 dogs in group II showed side effects. The number of side effects observed was also lower in group I than in group II as expected. However, the difference in the prevalence of side effects was not significant. The reason for this might be the small number of animals included in the study.

In humans, treatment with PPA sometimes causes hemodynamic side effects, such as an increase in blood pressure. Reported results in dogs are controversial. When PPA was used in dogs at the recommended dose an increase in blood pressure was not observed by (14). In contrast, a decrease in heart rate associated with an increased arterial pressure consecutive to PPA administrations was reported in some studies (8, 19, 20). Although arterial pressure was not measured in this study and arterial hypertension has not been reported clinically at recommended dosage in bitches, authors of this study share the previously reported concerns about cautious use of drugs that are capable of inducing tachycardia in animals receiving α -adrenergic agents (8, 9). In addition, serial blood pressure monitoring in dogs that are receiving α -adrenergic agents is recommended.

Estriol treatment in combination with PPA was effective in 62.5% of cases. In one dog (12.5%) incontinence improved. In female dogs with USMI, the success rate for complete urinary continence with administration of estriol is approximately 65% (18). Estriol, a naturally occurring estrogen, is currently the estrogenic substance of choice for treatment of female dogs. Estrogens indirectly increase the urethral closure pressure by sensitizing the α -receptors to endogenous and exogenous catecholamines (7) and it is reasonable to combine an α -adrenergic agent with estrogen to try to obtain a synergetic therapeutic effect. Administration of such drug combinations was reported to be superior to the administration of estriol alone in postmenopausal women (16). Investigations on the effectiveness of estrogen combined with an α -adrenergic agent in female dogs are rare. Creed (10) identified an increased urethral

functional profile length after administration of estrogens and phenylephrine in female dogs without urinary incontinence, however, this effect was not detected in incontinent females. In a previous study, we found that combination of ephedrine with estradiol benzoate was more effective than ephedrine alone in the treatment of USMI in spayed bitches (5). In the present study, most of the bitches became continent by the end of first week of estriol PPA combination. This is in accordance with results of a study reporting a significantly increased urodynamic values at d 7 of estriol plus PPA treatment (13). Recommended duration of estrogen treatment in USMI is 7-14 d and an improvement is usually noticed within a few days. However, clinical response can first be observed during second week of treatment as it was the case for one dog in the current study.

In conclusion, once daily administration of PPA at a dose of 1.5 mg/kg, BW is effective in treatment of USMI in spayed bitches and it offers a cheap and convenient treatment option. In addition, recurrence of incontinence can be observed during long term administration of PPA and combination of PPA with estriol is effective in dogs in which PPA therapy is unsatisfactory and in dogs that become refractory to PPA treatment.

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