

Evaluation of phenylpropanolamine in the treatment of urethral sphincter mechanism incompetence in the bitch

In a multicentre, blinded, placebo-controlled trial, 50 dogs were treated for 28 days with either phenylpropanolamine or a placebo control. Each was given at a dose of one drop per 2 kg orally three times daily, equivalent to 1 mg/kg three times daily of phenylpropanolamine. Dogs that presented with clinical signs consistent with urinary sphincter mechanism incontinence were included in the study. They were examined on three occasions by the investigating veterinary surgeon. The frequency and volume of unconscious urination were scored by veterinary surgeons according to a pre-established scoring system. Phenylpropanolamine proved to be more effective than the placebo in regard to several parameters. At day 28, 85.7 per cent of phenylpropanolamine-treated cases had no episodes of unconscious urination compared with 33.3 per cent of placebo-treated cases. This was statistically significant. Few, mild side effects were seen in either group.

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INTRODUCTION

Urinary incontinence is defined as the involuntary passage of urine. The most commonly diagnosed cause of urinary incontinence in the adult female neutered dog is urethral sphincter mechanism incompetence (USMI) (Holt 1985, 1990). Although the relationship between ovariohysterectomy and this condition is unclear, the condition is agreed to be associated with decreased urethral tone (Richter and Ling 1985). For this reason sympathomimetic agents have been widely used to manage this condition. Their mode of action is by direct stimulation of the smooth muscle of the internal urethral sphincter, thus leading to increased sphincter tone and subsequent alleviation of urinary incontinence.

Phenylpropanolamine is a sympathomimetic drug that is licensed in the UK for the long-term management of USMI in the female dog. Although this drug has been used widely for many years in practice, it has not previously been assessed in a placebo-controlled, blinded trial. The aim of this

study was to evaluate the safety and efficacy of phenylpropanolamine in the treatment of USMI compared with a placebo in field conditions.

MATERIALS AND METHODS

Experimental design

Two parallel groups of female dogs presenting with signs of USMI were compared in an international, multicentre, blinded, placebo-controlled trial. Each animal received either a 5 per cent solution of phenylpropanolamine hydrochloride in sorbitol syrup (Propalin Syrup; Vétoquinol UK) or sorbitol syrup alone.

Selection of animals

Fifty female dogs were selected from trial sites in the UK, Belgium and France. Nineteen different centres took part in the study. The investigating veterinary surgeons were chosen on the basis that they were interested in participating in clinical trial work and had a high number of small animal cases in the clinic. Female neutered dogs were included if they were diagnosed as suffering from urinary incontinence as evidenced by unconscious urination, particularly where the history suggested an underlying USMI associated with ovariohysterectomy.

Animals that presented with inappropriate urination that was under conscious control were excluded from the trial. Specifically, the following conditions were excluded:

- Overt urinary tract infections, such as cystitis. Cases of cystitis not suspected upon clinical examination or from the clinical history, but which were subsequently detected upon urinalysis (occult infection), were included but required concomitant therapy;
- Polydipsia or polyuria associated with renal failure, hepatic insufficiency, diabetes or any other metabolic disorder;
- Behavioural causes of inappropriate urination.

Animals less than one year old or which had been ovariohysterectomised within the previous six months were not included.

Clinical examination

Clinical examination assessed general signs (ie, rectal temperature, body condition, heart rate, mucosal colour and capillary refill time) and urinary-specific signs (ie, bladder size [small, half full, full], urine leakage [yes/no] and vulval appearance for urine scalding).

The degree of unconscious urination was assessed in two ways. 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 these 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.

Clinical examination and assessment of unconscious urination were carried out on day 0 (day of entry onto the trial), day 7 and day 28. The owners monitored side effects on a daily basis. They were required to note the presence or absence of the following clinical signs: loose stools, liquid diarrhoea, vomiting, anorexia, lethargy, depression, abnormal behaviour, seizures, and discomfort on administration of treatment or afterwards. The veterinary surgeons were also required to question the owners as to the presence of any side effects at each examination.

Laboratory examinations

A blood sample was taken from each dog prior to inclusion in the trial and routine biochemistry and haematology were performed. If the results showed an abnormality that resulted in the dog meeting one of the exclusion criteria, the animal was removed from the trial at day 7 and was not included in the statistical analysis. In addition, a urine sample was taken from each dog and the following analysis was performed: deposit microscopy for the presence of crystals, tumour cells, red blood cells, white blood cells or epithelial cells; routine culture for the presence of bacteria; examination for urine pH,

protein and glucose; and measurement of specific gravity.

Dogs displaying occult urinary tract infection were allowed to be included in the trial within certain limits. Dogs with a positive urine culture were dealt with in one of two ways: where there was sparse bacterial growth and less than five white blood cells per high power field, the culture was not considered to be significant and no treatment was required; where there was moderate to high bacterial growth or more than five white blood cells per high power field, the dog was required to start a 10-day course of oral clavulanate potentiated amoxicillin (Synulox; Pfizer) at 12.5 mg/kg twice daily.

Treatments

The products were labelled A and B, and an envelope containing the letter A or B was assigned at random to each case pack to determine which product each recruited animal would receive. The randomisation list was kept at Vétquinol UK Ltd, thus keeping the owner and the veterinary surgeon blinded as to which product was used. The two products used were phenylpropanolamine hydrochloride (Propalin Syrup) and sorbitol syrup as the placebo. Both were given at a rate of one drop per 2 kg three times daily by oral administration in food over a four-week period. This was equivalent to a dose of 1 mg/kg of phenylpropanolamine hydrochloride. No other medication was allowed during the course of the study except, as specified, where an occult urinary tract infection was detected on urinalysis.

Assessment criteria

The primary criterion for analysis was the frequency of unconscious urination at day 28. Secondary criteria analysed included the frequency and amount of unconscious urination at day 7, the amount of urine produced during periods of incontinence at day 7 and day 28, and the degree of vulval scalding and bladder size at day 28. The frequency and type of side effects were also analysed for both groups.

Statistical analysis

For the main criterion, a Fisher's exact test was performed at the 5 per cent one-sided significance level.

The H₀ hypothesis to be tested was:

$$\pi_{\text{Phenylpropanolamine}} = \pi_{\text{Placebo}}$$

Against the H₁ alternative hypothesis:

$$\pi_{\text{Phenylpropanolamine}} > \pi_{\text{Placebo}}$$

Where:

$\pi_{\text{Phenylpropanolamine}}$ = frequency of dogs having no involuntary micturition under phenylpropanolamine

π_{Placebo} = frequency of dogs having no involuntary micturition under placebo

The sample size was planned before the study to achieve 80 per cent power (ie, chance of rejecting H₀ if the H₁ hypothesis was true). Baseline data were checked through a descriptive approach.

The other analyses (secondary variables, safety criteria) were based on the methods described below:

- The Fisher's exact test for qualitative variables in the form of 2 × 2 tables;
- The likelihood ratio chi-squared test for qualitative variables in the form of 2 × n tables (with n > 2), or alternatively the Fisher's exact test when expected frequencies were too low;
- The Student's *t* test for the comparison of group means, or alternatively the Wilcoxon's test when normality and/or homoscedasticity could not be realistic for the variable under analysis.

All the tests for secondary variables and safety criteria were performed at the 5 per cent two-sided significance threshold. The statistical analysis was performed using the SAS/STAT software, version 6.12.

RESULTS

All criteria were equally balanced between the two treatment groups on day 0. A description of the animals is provided in

Table 1. Comparison of the treatment groups at day 0

Variables		Phenylpropanolamine group	Placebo group
Age (mean)		9.2 years	10.1 years
SD		3.2 years	2.7 years
Weight (mean)		23.4 kg	24.5 kg
SD		12.1 kg	12.4 kg
Time since neutering (mean)		6.6 years	7.5 years
SD		3.9 years	3.5 years
Body condition (n=32)	Underweight	0.0% (n=0)	5.6% (n=1)
	Normal	50.0% (n=7)	72.2% (n=13)
	Obese	50.0% (n=7)	22.2% (n=4)
Frequency of unconscious urination (n=32)	Once a day	35.7% (n=5)	50.0% (n=9)
	More than once a day	64.3% (n=9)	50.0% (n=9)
Amount of urine during periods of incontinence (n=32)	Small amount	35.7% (n=5)	33.3% (n=6)
	Large amount	64.3% (n=9)	66.7% (n=12)

Table 1. A total of 25 dogs were included for analysis in the phenylpropanolamine group and 25 dogs in the placebo group.

Primary criterion

The main criterion for efficacy was the frequency of unconscious urination at day 28. In the phenylpropanolamine group, 85.71 per cent of dogs scored 0 (none) compared to 33.3 per cent of the placebo group. In addition, 14.29 per cent scored 1 (up to once daily) compared with 27.78 per cent of the placebo group. No cases in the phenylpropanolamine group were recorded

as a failure, whereas 38.89 per cent of the placebo group fell into this category (Fig 1). The results were statistically significant (Fisher's exact test) with $P=0.012$.

Secondary criteria

The frequency of unconscious urination at day 7 was examined. In the phenylpropanolamine group, 55 per cent of dogs scored 0, with 30 per cent scoring 1 and 15 per cent scoring 2. In the placebo group, 26.32 per cent of dogs scored 0, with 42.11 per cent scoring 1 and 31.58 per cent scoring 2.

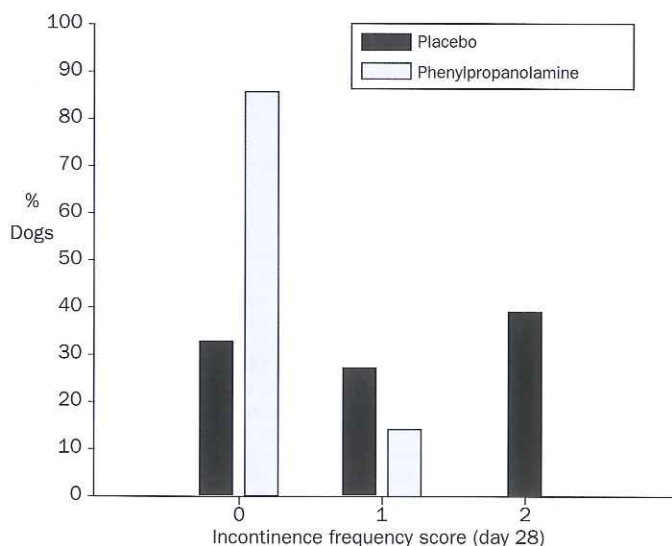


FIG 1. Frequency of unconscious urination at day 28

The amount of urine produced at day 7 was also analysed. Fifty-five per cent of the phenylpropanolamine group had a score of 0 compared with 26.32 per cent of the placebo group. The amount of urine produced at day 28 was also assessed for both groups. For this criterion, 85.71 per cent of the phenylpropanolamine group scored 0, compared with 33.33 per cent of the placebo group.

The progression of the scores for vulval scalding and bladder size was more favourable in the phenylpropanolamine group than in the placebo group. There were no failure cases in the phenylpropanolamine group.

Frequency of side effects

There was no significant difference between the reported side effects in the phenylpropanolamine group compared to the placebo group (Table 2). Side effects noted tended to be mild, transient and infrequent.

DISCUSSION

USMI is a commonly diagnosed cause of urinary incontinence in the adult bitch, particularly in the neutered female (Arnold and others 1989, Holt 1990). Previous papers have discussed the use of α -adrenergic agonists in treating this condition in dogs (Richter and Ling 1985, White and Pomeroy 1989). Phenylpropanolamine is one such agent that works by stimulating the receptors of the smooth muscle to increase tone. It has been demonstrated to increase maximal urethral closure pressure in cases of sphincter mechanism incompetence (Richter and Ling 1985). In this

Table 2. Number of occurrences of adverse events as recorded on a daily basis by owners

	Phenylpropanolamine group	Placebo group
Diarrhoea	12	7
Vomiting	8	3
Others	16	11

NB Several side effects could be noted in the same animal

study, phenylpropanolamine was compared with a placebo, against which it performed well.

In this trial the mean weight of dogs was just less than 25 kg. This corresponds to previous data, suggesting a strong correlation between bodyweight and the incidence of incontinence (Arnold 1992, Holt and Thrusfield 1993). The diagnosis of USMI was made on the basis of careful history taking and examination of the clinical signs. Typically, dogs with this condition can present with a history of urinary incontinence that is often observed during sleep or at other times when the bitch is relaxed. Micturition and the frequency of micturition are normal. Careful history taking was important in excluding behavioural causes of inappropriate urination. Animals were excluded until six months after neutering to rule out iatrogenic-induced incontinence. Similarly, young dogs were excluded to help rule out undiagnosed ectopic ureters. It has been reported that not all cases of ectopic ureters will present with the typical signs (Holt and others 1982). The omission of radiographic studies was not considered to weaken the study as this reflects what is usually done in the field; if anything, it would bias the results against the product if the incorrect diagnosis was made.

As part of the screening process blood and urine samples were obtained for each dog to rule out false presentations of incontinence due to polyuria and polydipsia. Initially all dogs showing bacterial growth on urine culture were excluded. Following rejection of a high number of dogs that had no obvious clinical signs of cystitis, but yet had bacterial growth on urine culture, an amendment was written to allow dogs with occult infection to be included in the study within certain parameters. It has been recognised that USMI can predispose a dog to urinary tract infection, and the animal may thus remain incontinent after successful antibacterial treatment (Arnold 1992). In a previous study, antibiotic therapy of urinary tract infection did not affect the degree of incontinence at all (Holt 1985). Therefore, the inclusion of dogs with

occult urinary tract infections was not considered to weaken the results of this study.

In order to enter the trial, both treatment groups had to have a minimum score of 1 for frequency and volume of unconscious urination. The phenylpropanolamine group had slightly poorer incontinence scores overall, but this difference was not statistically significant.

The main criterion for analysis was the frequency of involuntary urination at day 28. In the phenylpropanolamine-treated group, the majority of dogs showed no signs of incontinence. In addition, no dogs were classed as failures at this stage. It is interesting to note that a third of the dogs in the placebo group were reported as showing no signs of incontinence either. This may be partly explained by the intermittent nature of this condition. In addition, a placebo effect is likely to have been playing a part on the owners' assessment of the dogs on a daily basis and their subsequent reports to the veterinary surgeon. This underlies the importance of having a control group. A large percentage failed in the placebo group and the differences between the groups at day 28 were statistically significant ($P < 0.05$). The excellent primary criteria results were supported by the results of the secondary analysis; even at day 7, the results in the phenylpropanolamine group were favourable, demonstrating the rapid onset of action. This speed of action is important in a practice situation, as dealing with urinary incontinence can frequently be distressing for the owner, and a quick resolution of clinical signs is required. It should be pointed out that, at day 7, there were still dogs in the group classed as failures.

The analysis of the secondary criteria confirmed that phenylpropanolamine was superior to the placebo. The amount of urine passed during incontinent periods and vulval scalding both decreased over time. This would be expected as urethral sphincter tone increased. The safety of phenylpropanolamine was proven to be acceptable. There were slightly more incidences of adverse reactions reported on

a daily basis by the owners for the phenylpropanolamine group compared with the placebo group. Each reported incidence was recorded as a suspected adverse reaction even though, in several cases, the owners linked the presenting clinical sign to another change in the dog's routine and did not in fact relate it to the product given. Overall, there was no statistically significant difference between the incidences of adverse reactions between the two groups.

It is acknowledged that, although this trial was undertaken over a 28-day period, phenylpropanolamine is intended for life-long management of USMI. Further work should be undertaken to confirm efficacy and safety over a prolonged period of time.

Conclusions

In this 28-day trial, phenylpropanolamine given orally at a dose of 1 mg/kg three times daily demonstrated superior efficacy over the placebo treatment in the control of USMI in the neutered bitch.

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