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Changes in blood pressure following escalating doses of phenylpropanolamine and a suggested protocol for monitoring

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Abstract — This prospective, cross-over, blinded study evaluated the effect of various doses of phenylpropanolamine (PPA) on blood pressure in dogs. Dogs were randomized to receive a placebo or 1 of 3 dosages of immediate release PPA, q12h for 7 days [1 mg/kg body weight (BW), 2 mg/kg BW, or 4 mg/kg BW] in a cross-over design. Blood pressure was recorded every 2 h, for 12 h, on days 1 and 7. There were significant increases in systolic, diastolic, and mean blood pressure following administration of PPA at 2 mg/kg BW and 4 mg/kg BW. A significant decrease in heart rate was also noted at all PPA dosages, but not in the placebo. Administration of PPA was associated with a dose response increase in blood pressure. Dosages of up to 2 mg/kg BW should be considered safe in healthy dogs.

Résumé — Changements de la pression artérielle après des doses progressives de phénylpropanolamine et suggestion d'un protocole de surveillance. Cette étude prospective à l'insu et à plan d'étude croisée a évalué l'effet de diverses doses de phénylpropanolamine (PPA) sur la pression artérielle des chiens. Les chiens ont reçu au hasard un placebo ou 1 de 3 doses de PPA à action immédiate, q12h pendant 7 jours (1 mg/kg de poids corporel [PC], 2 mg/kg PC ou 4 mg/kg PC) dans un plan d'étude croisé. La pression artérielle a été consignée toutes les 2 h, pendant 12 h, aux jours 1 et 7. Il n'y a pas eu de hausses significatives de la pression artérielle systolique et diastolique ni de la pression artérielle moyenne après l'administration de PPA à 2 mg/kg PC et à 4 mg/kg PC. Une baisse significative de la fréquence cardiaque a aussi été notée dans toutes les doses de PPA, mais non avec le placebo. L'administration de PPA a été associée à une hausse de la pression artérielle en fonction de la dose. Des doses jusqu'à 2 mg/kg PC devraient être considérées sûres chez des chiens en santé.

(Traduit par Isabelle Vallières)

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Introduction

Urethral sphincter mechanism incompetence (USMI) has been reported in as many as 20% of female dogs after ovariohysterectomy (1). The pathophysiology of UMSI is complex, but, more than 90% of dogs with UMSI are neutered (2). Estrogen deficiency was considered the most common cause for the decreased urethral closure pressure following ovariohysterectomy; however, only 65% of dogs with UMSI respond to estrogen administration (3,4), suggesting that other factors influence urethral tone following ovariohysterectomy (5–7).

Treatment for USMI can include estrogen compounds or sympathomimetic amines, such as phenylpropanolamine (PPA). It has been suggested that PPA causes norepinephrine release (8), but also inhibits norepinephrine reuptake by nerve endings (9). A variety of side effects of PPA have been reported in humans including hypertension (10); the drug was withdrawn for use in humans in 2003 by the US FDA. However, PPA is still prescribed regularly and considered effective for dogs with USMI (11). Side effects are also reported in dogs, including hypertension and tachycardia (11–16).

Although the effects of PPA on blood pressure have been studied, the methods for assessing blood pressure varied among studies and data are conflicting. One study did not find a change in systolic blood pressure after PPA administration; however, the timing at which the measurements were assessed was not clear (11). Conversely, systolic blood pressure was significantly elevated in a small group (n = 3) of healthy dogs receiving 1.5 mg/kg body weight (BW) of PPA twice daily. Mean arterial pressure, measured within 2 to 5 h after PPA administration, was also significantly higher from baseline (n = 5 dogs) and heart rates were significantly lower during that 14-day study (12). Higher doses of PPA and the effects these may have on serial hemodynamic measurements have not been reported for the dog.

The objectives of this study were to evaluate the effect of various doses of PPA on serial systolic, diastolic and mean blood pressures using an oscillometric blood pressure device, as well

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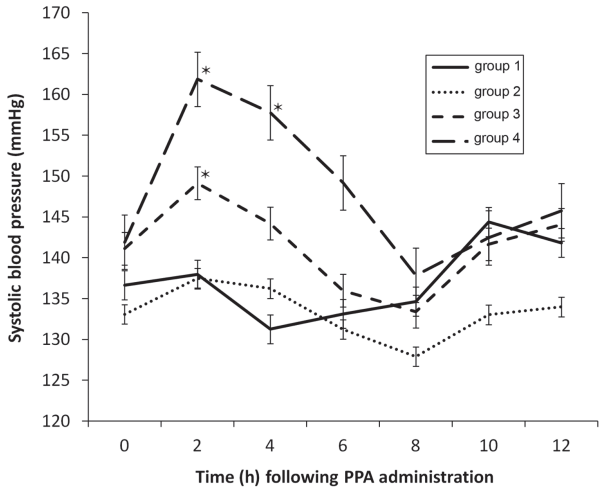

Figure 1. Changes in systolic blood pressure over the 12 h following PPA administration in the 4 study groups: placebo group (Group 1), 1 mg/kg BW group (Group 2), 2 mg/kg BW group (Group 3), 4 mg/kg BW group (Group 4). The asterisks represent significant change compared to the baseline (prior to drug/placebo administration).

as the effect on the heart rate in dogs at various time points following the administration of PPA.

Materials and methods

Animals

This study was approved by the Institutional Animal Care and Use Committee at the School of Veterinary Medicine, the Hebrew University of Jerusalem, Israel. Eight beagle dogs (4 castrated males and 4 spayed females) were evaluated. All dogs were determined to be healthy based on history, normal physical examination, and the absence of abnormalities on a complete blood cell count, serum biochemical analysis, urinalysis, and urine culture.

Study design

This was a prospective, crossover, masked study. Each of the 8 dogs received a placebo or immediate release formulation of PPA, every 12 h for 1 wk. In each study week, dogs received either placebo (Group 1) or 1 of 3 dosages of PPA: 1 mg/kg BW PPA (Group 2), 2 mg/kg BW (group 3), and 4 mg/kg BW (Group 4) in a random order with a washout period of 2 wk before a change was made to the next designated treatment. Capsules were prepared individually based on the dogs' body weight, which was maintained throughout the study period.

Blood pressure measurement

Blood pressure measurements were obtained on days 1 and 7. Blood pressure was measured in all dogs just prior to receiving the PPA or placebo (baseline) as well as 2, 4, 6, 8, 10 and 12 h (± 15 min) following each PPA or placebo drug administration. Blood pressure was obtained by a single trained technician, who was blinded to the PPA dose, using an oscillometric blood pressure device (Cardell 9405; CAS Medical, Brantford, Connecticut, USA), and was classified according to guidelines previously set (17). Blood pressure measurements were obtained in the dogs' natural environment to minimize stress that may have been associated with the procedure. Five minutes of adjustment were allowed for each dog prior to initiation of the measurement. At each time point the blood pressure was recorded as an average of 10 sequential measurements that had $< 10\%$ differences among them and after outliers were removed. Blood pressure was also evaluated after 7 d of the prescribed dose of PPA (or placebo) for each of the dogs at the same time points described.

Statistical analysis

Descriptive statistics were used to calculate the mean and standard deviation of the systolic, diastolic, and mean blood pressure, and the heart rate. The Shapiro-Wilk test was used to assess the normality of distribution of continuous parameters. Repeated measures analysis of variance (ANOVA) was used to assess the changes in blood pressure measurement over time and to assess the differences in systolic, diastolic, and mean blood pressure and the heart rate among the different dosages of PPA as well as any interactions. When changes over time were observed, paired samples Student *t*-test was used to assess the differences between different time points (i.e., baseline compared with subsequent time points) within each group. $P \leq 0.05$ was considered statistically significant. All calculations were performed using statistical software (SPSS 17.0 for Windows, SPSS, Chicago, Illinois, USA).

Results

Animals

The mean age and body weight of the dogs were 11.7 ± 3.5 y and 7 ± 1.5 kg, respectively.

Blood pressure evaluation

When comparing the baseline heart rate and blood pressure parameters, that were obtained just prior to the placebo or PPA administration, there were no statistically significant differences between days 1 and 7. Also, when assessing the cumulative effect of PPA administration by using repeated measures ANOVA, there were no statistically significant differences in the changes in blood pressure or heart rate between the days. Therefore, unless indicated otherwise, results refer to blood pressure measurements on day 1.

Systolic blood pressure

There was a statistically significant increase in systolic blood pressure following PPA administration during the 12 h after PPA administration ($P = 0.021$) and significant differences among Groups ($P = 0.05$), but no interaction was noted ($P = 0.06$) (Figure 1). The primary differences were apparent 2 h after PPA administration for dogs in Groups 3 and 4 (Figure 1; Table 1).

Diastolic blood pressure

There was a statistically significant increase in diastolic blood pressure during the 12 h after PPA administration ($P = 0.03$), and statistically significant difference among the groups

Table 1. Differences in systolic, diastolic, mean blood pressure, and heart rate between the baseline (prior to drug or placebo administration) and 2 h after drug or placebo administration. Numbers in parentheses represent the percent change from baseline

	Placebo (Group 1)	1 mg/kg BW (Group 2)	2 mg/kg BW (Group 3)	4 mg/kg BW (Group 4)
Systolic (mmHg)	1.3 (1%)	4.4 (5%)	8.0 (6%)*	20.0 (17%)*
Diastolic (mmHg)	−8.8 (10%)	6.3 (12%)	12.9 (14%)*	21.2 (23%)*
Mean (mmHg)	−2.7 (2%)	4.4 (7%)	11.9 (11%)*	19.6 (18%)*
Pulse (pulse/minute)	−3.5 (3%)	−22.2 (20%)*	−21.2 (19%)*	−37.1 (32%)*

* Significant difference ($P < 0.05$) compared to the baseline.

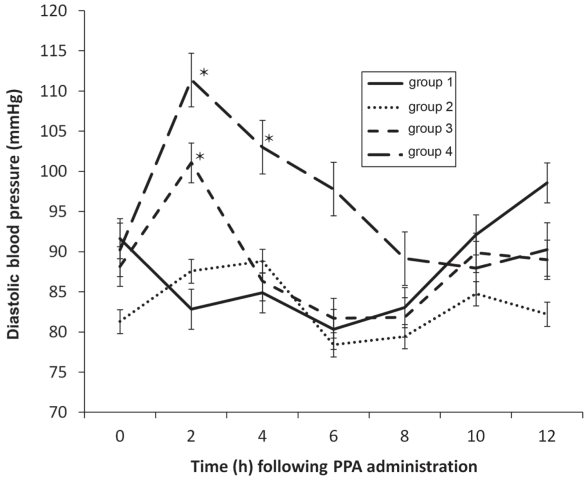

Figure 2. Changes in diastolic blood pressure over the 12 h following PPA administration in the 4 study groups: placebo group (Group 1), 1 mg/kg BW group (Group 2), 2 mg/kg BW group (Group 3), 4 mg/kg BW group (Group 4). The asterisks represent significant change compared to the baseline (prior to drug/placebo administration).

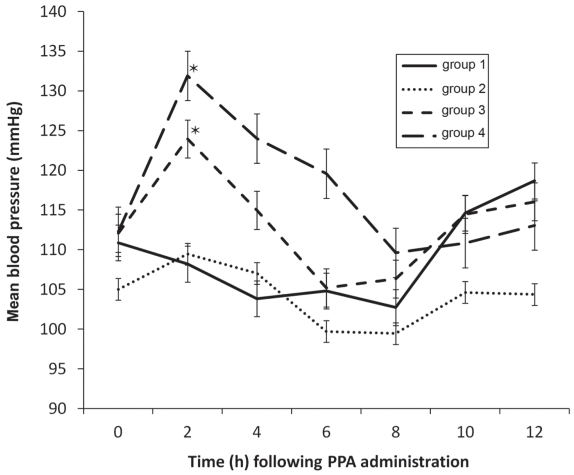

Figure 3. Changes in mean blood pressure over the 12 h following PPA administration in the 4 study groups: placebo group (Group 1), 1 mg/kg BW group (Group 2), 2 mg/kg BW group (Group 3), 4 mg/kg BW group (Group 4). The asterisks represent significant change compared to the baseline (prior to drug/placebo administration).

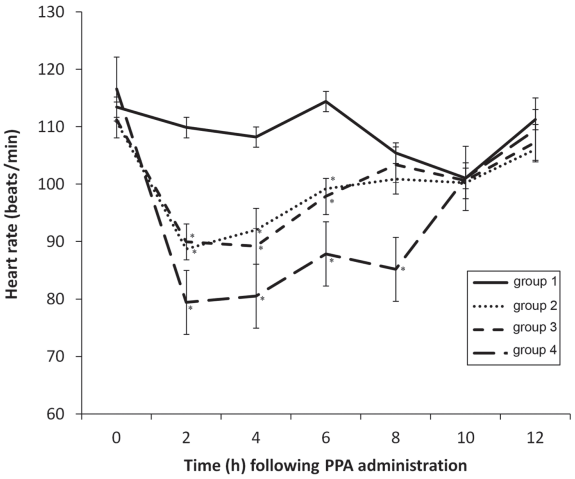

Figure 4. Changes in heart rate over the 12 h following PPA administration in the 4 study groups: placebo group (Group 1), 1 mg/kg BW group (Group 2), 2 mg/kg BW group (Group 3), 4 mg/kg BW group (Group 4). The asterisks represent significant change compared to the baseline (prior to drug/placebo administration).

($P = 0.05$) as well as an interaction ($P < 0.001$), indicating the differences over the time were dependent on the dose (Figure 2). Similar to systolic blood pressure measurements, the differences were most evident 2 h following PPA administration (Figure 2; Table 1).

Mean blood pressure

There was a statistically significant increase in mean arterial blood pressure during the 12 h after PPA administration ($P = 0.009$), a statistically significant difference among groups ($P = 0.04$) as well as an interaction ($P = 0.002$), indicating once again the differences over time were dose-dependent. Consistent with the changes in systolic and diastolic blood pressure, the most pronounced changes were documented 2 h after PPA administration (Figure 3; Table 1).

Heart rate

There were statistically significant decreases in heart rates during the 12 h after PPA administration ($P < 0.001$), there was a difference among groups ($P = 0.024$), and a statistically significant interaction ($P = 0.002$), indicating the changes documented were dependent on the dose of PPA administered. Heart rate was significantly lower 2 h after PPA administration on day 1 for dogs in all groups, except for those receiving the placebo

Table 2. Number of occasions on which severe hypertension was documented on day 1 among the different doses of PPA or placebo. The number of dogs in which these occasions of hypertension were documented is indicated in parentheses. The percentages are calculated as number of occasions on which severe hypertension was documented out of 56 measurements that were performed for each dose/placebo (i.e., 8 dogs, 7 measurements for each dog)

	Systolic (> 180 mmHg)	Diastolic (> 120 mmHg)	Mean (> 140 mmHg)
Group 1 (placebo)	0 (0 dogs), 0%	0 (0 dogs), 0%	1 (1 dog), 2%
Group 2 (1 mg/kg)	1 (1 dog), 2%	2 (1 dog), 4%	3 (2 dogs), 5%
Group 3 (2 mg/kg)	2 (2 dogs), 4%	3 (2 dogs), 5%	4 (2 dogs), 7%
Group 4 (4 mg/kg)	8 (2 dogs), 14%	7 (3 dogs), 13%	3 (2 dogs), 5%

(Figure 4). Consistent with the changes in blood pressure, the most pronounced changes in heart rate were noted 2 h following drug administration (Figure 4; Table 1)

Proportion of hypertension

The number of occasions on which severe hypertension was documented was low despite its increase with the PPA dose (Table 2).

Discussion

In this study, we documented hemodynamic changes in healthy dogs receiving dosages of PPA commonly prescribed for treatment of USMI. Administration of PPA was associated with a dose response increase in blood pressure and a dose response decrease in heart rate. The maximal increase in blood pressure occurred 2 h following PPA administration which corresponds to the time of maximal blood concentration (18,19). No cumulative effect was documented after 7 d of treatment. Therefore, monitoring blood pressure in dogs receiving this drug should commence 2 h after PPA administration. While not always significant, blood pressures (systolic, diastolic, and mean) were increased on day 1 for dogs in all groups, except those receiving the placebo. These data suggest that when clinically indicated, blood pressure monitoring can be assessed within 24 h after PPA administration.

Phenylpropanolamine is a non-selective α-agonist and therefore has the potential to increase systemic blood pressure due to an increase in total peripheral resistance (20). The drug can act indirectly by releasing norepinephrine at the adrenergic terminals and also has weak β-receptor agonist activity (21). Increases in systemic blood pressure will increase arterial stretch receptors, stimulate the vagus nerve, and decrease heart rate in order to maintain normal blood pressure. This is likely the reason that, in all groups except the placebo, the heart rate decreased by 20% to 32%.

The effect of PPA on blood pressure is inconsistent among different studies; however, many of the published studies in dogs evaluating the effects of PPA on hemodynamic parameters were performed on anesthetized animals following IV administration of PPA, which is not mimicing its administration in the clinic. Hemodynamic parameters documented in this study are different from some previous publications and are in agreement with others. The changes in blood pressure and heart rate in this study differ from another report (11), in which increase in blood pressure was not noted after PPA administration but the times at which the hemodynamic parameters were measured were not reported. Peak plasma concentrations of PPA are usually noted within 2 to 4 h after oral administration (19); therefore, if blood pressure is not evaluated at peak plasma PPA concentrations, a change in blood pressure may not be noted. In another study there was no change in mean arterial pressure 2 wk after oral PPA administration (1.5 mg/kg q8h) (22). Conversely, in a different study, significant increases in the mean and the diastolic blood pressures were documented, 7 and 14 d after administration of PPA, 1.5 mg/kg BW q8h, with no change in the systolic blood pressure (23). In a recent study evaluating the urodynamic and hemodynamic effects of 1.5 mg/kg BW PPA administration for 8 d every 8 or 24 h, there were increases in the systolic and the mean arterial pressures compared to the baseline values, but not in the diastolic blood pressure (18). However, these dogs had high baseline blood pressure measurements, and there were only 2 dogs in each study group.

In this study, blood pressure was monitored following a conventional starting dose of 1 mg/kg BW of PPA, and although the systolic, diastolic, and mean blood pressures increased, these changes were not significant compared with the placebo group. Therefore, this dosage of PPA should be considered safe when administered to healthy dogs, and is unlikely to be associated with clinically relevant hypertension; the effects these changes might have in dogs with concurrent diseases were not assessed in this study. There was a mild, short-lived increase in blood pressure when a dosage of 2 mg/kg BW of PPA was administered to dogs. This likely does not substantially increase the risk for end organ damage in healthy dogs; however, this dosage may be more concerning for dogs with renal disease or other co-morbidities associated with hypertension. The most apparent difference in blood pressure became evident when dogs received 4 mg/kg BW of PPA. While the authors do not recommend administering 4 mg/kg BW of PPA, we wanted to assess what effect higher doses may have on the baroreflex. At that dosage, it appeared the heart rate did not decrease to the extent needed to maintain normal blood pressure.

Phenylpropanolamine was administered twice daily in this study; increasing the frequency, which is often done clinically, might increase the abnormalities we documented. Furthermore, isolated incidents of severe hypertension were documented in all groups and were more common with higher dosages. These events, while likely to be of minimal clinical significance in healthy dogs, may pose a risk for dogs with mild or moderate hypertension, or for dogs with underlying disorders that could predispose to hypertension, such as chronic kidney disease (CKD).

In this study heart rate significantly decreased to maintain normal blood pressure in most dogs except for those in Group 4. These dogs had the most pronounced decrease in heart rate, but hypertension was still present after PPA administration, suggesting that this compensating decrease in heart rate was insufficient to negate the increase in blood pressure. In humans with CKD, the baroreceptor reflex described to maintain normal blood pressure is delayed, and hypertension is noted (24). Judicious use of PPA in dogs with cardiovascular diseases is also recommended because it may be associated with a significant decrease in heart rate. It is our recommendation that older dogs or dogs suspected of having CKD or cardiovascular disease should have their blood pressure evaluated prior to and during PPA administration. In these dogs alternative therapies for USMI such as estrogen compounds should be considered.

The isolated incidents of severe hypertension that were documented in this study could have been due to excitement, despite the acclimation period, and to normal variation. We also aimed to mimic the method used to monitor dogs for hypertension in the clinical setting, based on guidelines established by the American College of Veterinary Internal Medicine (17).

Despite the cumulative effect of PPA, twice daily PPA administration for 7 d did not have any influence on the blood pressure or the heart rate compared to the first day of drug administration. Since the drug is prescribed in most clinical cases for substantially longer period of times, conclusions regarding the influence of long-term administration of PPA should be drawn with caution.

There are several limitations to our study. First, blood pressure was not obtained using the gold standard, but rather using an oscillometric blood pressure device following standard guidelines as used by most practicing clinicians. This method correlated with the gold standard in dogs following phenylephrine administration (25). Second, despite the acclimation process, some dogs might have been excited, resulting in an overestimation of their blood pressure. Therefore, the risk for hypertension may be lower than we documented, if some of the dogs were falsely hypertensive. Finally, this study was performed on healthy beagle dogs, which do not represent the spectrum of breeds and disease status for which PPA may be prescribed.

In summary, after PPA administration there was a dose response increase in blood pressure which was maximal 2 h after drug administration, with an average increase in systolic blood pressure on day 1 of 5% in the dogs in Group 2, 6% for dogs in Group 3, and 17% for dogs in Group 4. Monitoring blood pressure in dogs receiving PPA should be done 2 h after PPA administration and can be completed as soon as 24 h after beginning the medication. The indirect oscillimetric device was easy to use, but required that dogs acclimatize to the procedure. We suggest PPA be used with caution and that blood pressure be monitored in dogs with co-morbidities that may predispose to hypertension. CVJ

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