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Dose-dependent effects of tamsulosin on the ejaculation and semen quality in bucks

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Abstract: The objective of this study was to investigate the effect of tamsulosin (TAM) dosages on ejaculation and semen quality. Two sets of Latin square experiment design were applied to 6 bucks receiving normal saline (CON), TAM 134.8 nM/kg (LTAM), or 269.7 (HTAM) nM/kg at 1-week intervals. Semen collection, libido, and ejaculatory scoring were undertaken at 3, 6, 9, 12, and 24 h after injection. Heart rate and body temperature were measured before administration and at 30 min, and before semen collection. The results showed that libido score and heart rate were not affected by treatments. Ejaculatory suppression was observed in both TAM groups. The percentage of ejaculatory suppression was 91.7% by 3 h for both TAM dosages and gradually diminished. Ejaculatory recovery in all bucks was observed by 12 h. Ejaculatory suppression remained unchanged between LTAM and HTAM, but HTAM caused more anejaculation by 6 h ($P < 0.05$). Some semen parameters of both TAM groups were significantly different from the CON group from 6 to 12 h; however, the values returned to being similar by 24 h. Both TAM dosages had temporary effects on ejaculatory suppression and semen quality, and the effective period was dose-dependent.

Key words: Alpha adrenoceptor antagonist, tamsulosin, buck, semen, ejaculation

1. Introduction

Temporary inhibition of ejaculation while sustaining normal sexual behavior might be a useful tool in controlling animal populations or heat detection in a herd. Tamsulosin (TAM), an alpha adrenoceptor antagonist, has been routinely used to treat benign prostatic hyperplasia in humans and adversely suppresses ejaculation in men (1,2) and bucks (3). This drug could also prove efficacious as a temporary contraception choice in animals, but sufficient information seems lacking in this field.

TAM, known as (-)-(R)-5-[2-[[2-(o-ethoxyphenoxy) ethyl]amino]propyl]-2-methoxybenzenesulfonamide monohydrochloride, has a high affinity for alpha-1 adrenoceptors in the human prostate gland and aorta (4–6) and induces smooth muscle relaxation in the prostate, bladder neck, and urethra. It was shown to decrease male urogenital tract contractions in dogs (7) and rats (8). Moreover, TAM adversely affects the expulsion phase during ejaculation in rats (9) and markedly reduces semen volume in men (1). Furthermore, an inhibitory effect on ejaculation while maintaining normal sexual desire was reported in bucks (3).

Interestingly, varying alpha adrenoceptor antagonist dosages affect sexual activity, as observed with alpha-2 adrenoceptor antagonists (such as yohimbine, rauwolscine, and idazoxan). Low-dose yohimbine (2.0 µg/kg) may stimulate sexual activity in rats, while a high dose (8.0 µg/kg) suppressed the activity (10). Rauwolscine and idazoxan also show dose-dependent effects on sexual response and ejaculated semen volume (11). Low doses of rauwolscine (0.1 and 0.3 mg/kg) markedly increased the ejaculated semen volume; however, high doses (1.0 and 2.0 mg/kg) decreased the ejaculated semen volume while markedly inhibiting the penile erection and pelvic thrusting behavior in dogs (11). TAM causes a dose-dependent effect on suppression of the intraurethral pressure with negligible effects on the arterial blood pressure effects in dogs (12). However, the effect of various TAM dosages, for example, on ejaculatory suppression and semen quality, has not been investigated in bucks.

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Bucks have a distinctly high libido, making them a suitable model for assessing the effects of various factors (drugs) on sexual suppression. Therefore, the dose-related effects of TAM on some reproductive parameters (libido, ejaculation, and semen quality) were investigated herein using a goat model.

2. Materials and methods

2.1. Animals and trials

The protocol was approved by the Animal Usage and Ethics Committee of Kasetsart University (ID No. ACKU 02156). Six cross-breed bucks (aged 1–3 years, weighing 27–65 kg) were evaluated. Animals were kept in a single pen and separated from female goats. They were confirmed to have a good libido, normal ejaculating ability (via an artificial vagina, AV), and normal semen quality

This experiment was designed as a 3 × 3 Latin square. Each buck was administered a single dose of 0.09% NaCl (normal saline, CON), TAM 134.8 nM/kg (60 μg/kg, LTAM), or TAM 269.7 nM/kg (120 μg/kg, HTAM) intramuscularly at 1-week intervals (Table 1). Since this protocol was performed twice, each treatment group comprised 12 trials in total.

2.2. Solution preparation

TAM and dimethyl sulfoxide (DMSO, TAM solvent) were purchased from Sigma-Aldrich (St. Louis, MO, USA). TAM (50 mg) was dissolved in DMSO (1 mL) to generate a concentrated stock solution, and then it was diluted with additional DMSO (200 μL) prior to administration. Normal saline (200 μL) was administered during the control trial.

2.3. Libido scoring and semen collection

Semen was collected via an AV with a natural female in estrus to trigger mating behavior at 3, 6, 9, 12, and 24 h following drug administration. Libido was scored as described by Frydrychova et al. (13) as shown in Table 2, but with some modification. Each buck had chances to copulate once or twice within 10–20 min. In the first attempt, if no semen was found in the AV collecting tube after thrusting, the male with ejaculatory suppression was allowed to have the second chance of mounting within 10 min.

2.4. Ejaculatory scoring

Ejaculation was classified into three groups: anejaculation, incomplete ejaculation, and complete ejaculation. Anejaculation was defined as the lack of semen in the AV collecting tube. Incomplete ejaculation was defined as a collected semen volume that included spermatozoa but was less than 0.1 mL and complete ejaculation as semen volume of at least 0.1 mL containing spermatozoa. Ejaculation was scored as follows: 0 (anejaculation), 1 (incomplete ejaculation), or 2 (complete ejaculation).

Table 1. Sequence of soluble injection in each week and buck groups.

Buck group (n)	Time points (weeks)		
	Week 1	Week 2	Week 3
Group 1 (n = 2)	CON	LTAM	HTAM
Group 2 (n = 2)	LTAM	HTAM	CON
Group 3 (n = 2)	HTAM	CON	LTAM

Table 2. Libido score characterization.

Score	Evaluation	Characterization of libido
0	No jumping	No thrusting or copulation, no sexual interest.
1	Inconvenient	Little sexual interest, prolonged thrusting and copulation, more than 10 min for ejaculation.
2	Substandard	Little sexual interest, several times following out jump, longer time to thrusting and copulation, duration of face contact until ejaculation between 5 and 10 min.
3	Standard	Moderate sexual interest, using incentive to thrust and copulate, duration of face contact until ejaculation between 3 and 5 min.
4	Very good	Great sexual interest, longer searching reflex with consecutive copulation, duration of face contact until ejaculation between 1 and 3 min.
5	Excellent	Intense sexual interest, copulation immediately after face contact, duration of jump until ejaculation within 1 min.

2.5. Semen quality assessment

The semen volume, mass spermatozoal movement score, percentages of motile and live spermatozoa, spermatozoal concentration, total spermatozoa per ejaculate, and seminal alkaline phosphatase (ALP) concentration were measured to assess the semen quality.

Semen volume was measured using automatic pipettes. Mass spermatozoal movement was scored from 0 (immotile) to 5 (high), and the percentage of motile spermatozoa was measured immediately following collection using light microscopy. Spermatozoal concentration was estimated by hemocytometer. The percentage of live spermatozoa was based on the hypoosmotic swelling test (14). Seminal ALP was analyzed using the Reflotron dry chemistry method (Roche, Mannheim, Germany).

2.6. Heart rate and temperature measurement

Heart rate and body temperature were measured at 30 min before drug administration and before each semen collection.

2.7. Statistical analyses

The data from semen volume, percentages of motile and live sperm, sperm concentration, total sperm, ALP, heart rate, and body temperature were analyzed using analysis of variance for Latin square experimental designs using SPSS 17. Libido score, ejaculation score, number of ejaculatory characteristics, and mass spermatozoal movement score were examined by chi-square test. Mean values were considered statistically significantly different at $P < 0.05$. All values except the number of ejaculations are shown as the mean and standard error of the mean (mean ± SEM).

3. Results

3.1. Effect on libido

All bucks responded to the female goats. The mean libido score did not show any statistical difference ($P > 0.05$) between treatment groups and time periods (Table 3). In the first week, the ejaculated semen was missed during collection in one buck receiving normal saline (3 h); however, his libido score was included in the analyses.

3.2. Effect on ejaculation

In the CON group, complete ejaculation was achieved in all cases. Both anejaculation and incomplete ejaculation were observed in the LTAM and HTAM groups at 3 to 9 h after injection (Table 4). The distribution of ejaculatory suppression types was similar ($P > 0.05$) between the LTAM and HTAM treatments at each time period. At 3 h after injection, anejaculation was comparable following LTAM and HTAM at 33.3% and 50%, respectively. However, at 6 h after injection, a significantly higher ($P < 0.05$) rate of anejaculation was observed following HTAM than after LTAM and CON (50%, 0%, and 0%, respectively). In addition, incomplete ejaculation occurred in significantly ($P < 0.05$) more occasions following LTAM than following CON. The ejaculatory scores following LTAM and HTAM were significantly lower ($P < 0.05$) than that of CON at 3 h after injection, and the score remained significantly lower following HTAM through 6 h after injection. The ejaculatory suppression and ejaculatory scores were similar ($P > 0.05$) between the groups at 9 h after injection.

3.3. Effect on semen quality

Considering the lack of data for the CON group, a comparative analysis between the groups was not performed. Collected semen volume following incomplete and complete ejaculation in all groups is summarized in Table 5. The semen volume for incomplete ejaculation showed no significant difference ($P > 0.05$) between the LTAM and HTAM groups. However, the semen volume for complete ejaculation was quite similar between the groups at all periods except those of 12 h after injection, which had a significantly higher volume in the LTAM group than in the CON group ($P < 0.05$).

The remaining comparisons of semen quality comparisons following the complete ejaculation are summarized in Table 6. Seminal ALP concentrations were similar between the groups at all periods. However, the percentage of sperm motility was significantly lower in the HTAM group than those in the CON and LTAM groups at 6 h ($P < 0.05$). The percentage of live sperm was significantly lower in the HTAM group than those in the CON at 9 h ($P < 0.05$). The sperm concentration and

Table 3. Libido scores between 3 and 24 h after injection of normal saline (CON), tamsulosin 134.8 nM/kg (LTAM), and tamsulosin 269.7 nM/kg (HTAM) (mean ± SEM).

Group	n	Libido score (per hour, h)				
		3 h	6 h	9 h	12 h	24 h
CON	12	5.0	5.0	4.9 ± 0.1	4.9 ± 0.1	5.0
LTAM	12	5.0	4.9 ± 0.1	4.9 ± 0.1	4.9 ± 0.1	4.9 ± 0.1
HTAM	12	5.0	5.0	5.0	4.8 ± 0.1	4.9 ± 0.1

Table 4. Numbers of anejaculation, incomplete ejaculation, and complete ejaculation at 3–24 h after injection of normal saline (CON), tamsulosin 134.8 nM/kg (LTAM), and tamsulosin 269.7 nM/kg (HTAM).

Hour (h)	Group	n	Complete ejaculation (%)	Ejaculatory suppression**			Ejaculatory score
				Incomplete ejaculation (%)	Anejaculation (%)	Total (%)	
3 h	CON	11*	11^{b} (100)	0^{a} (0)	0^{a} (0)	0^{a} (0)	22^{b}
	LTAM	12	1^{a} (8.3)	7^{b} (58.3)	4^{b} (33.3)	11^{b} (91.7)	9^{a}
	HTAM	12	1^{a} (8.3)	5^{b} (41.7)	6^{b} (50)	11^{b} (91.7)	7^{a}
6 h	CON	12	12^{b} (100)	0^{a} (0)	0^{a} (0)	0^{a} (0)	24^{b}
	LTAM	12	6^{a} (50)	6^{b} (50)	0^{a} (0)	6^{b} (50)	18^{ab}
	HTAM	12	4^{a} (33.3)	2^{ab} (16.7)	6^{b} (50)	8^{b} (66.7)	10^{a}
9 h	CON	12	12 (100)	0 (0)	0 (0)	0 (0)	24
	LTAM	12	11 (91.7)	1 (8.3)	0 (0)	1 (8.3)	23
	HTAM	12	9 (75)	3 (25)	0 (0)	3 (25)	21
12 h	CON	12	12 (100)	0 (0)	0 (0)	0 (0)	24
	LTAM	12	12 (100)	0 (0)	0 (0)	0 (0)	24
	HTAM	12	12 (100)	0 (0)	0 (0)	0 (0)	24
24 h	CON	12	12 (100)	0 (0)	0 (0)	0 (0)	24
	LTAM	12	12 (100)	0 (0)	0 (0)	0 (0)	24
	HTAM	12	12 (100)	0 (0)	0 (0)	0 (0)	24

*One buck in this treatment missed collection.
**Ejaculatory suppression = incomplete ejaculation + anejaculation.
[ab]Means having different superscripts at the same time points are significantly different at $P < 0.05$.

Table 5. Collectable semen volumes between 3 and 24 h after injection of normal saline (CON), tamsulosin 134.8 nM/kg (LTAM), and tamsulosin 269.7 nM/kg (HTAM) (mean ± SEM).

Hour (h)	Group	n	Semen volume (mL)	
			Complete ejaculation (n)	Incomplete ejaculation (n)
3 h	CON	11	0.517 ± 0.06 (11)	-
	LTAM	8	0.262 (1)	0.014 ± 0.004 (7)
	HTAM	6	0.17 (1)	0.018 ± 0.008 (5)
6 h	CON	12	0.401 ± 0.06 (12)	-
	LTAM	12	0.419 ± 0.106 (6)	0.029 ± 0.012 (6)
	HTAM	6	0.381 ± 0.128 (4)	0.015 ± 0.010 (2)
9 h	CON	12	0.456 ± 0.06 (12)	-
	LTAM	12	0.641 ± 0.075 (11)	0.01 (1)
	HTAM	12	0.637 ± 0.131 (9)	0.07 ± 0.001 (3)
12	CON	12	0.381 ± 0.03[a] (12)	-
	LTAM	12	0.706 ± 0.09[b] (12)	-
	HTAM	12	0.574 ± 0.08[ab] (12)	-
24 h	CON	12	0.465 ± 0.08 (12)	-
	LTAM	12	0.582 ± 0.07 (12)	-
	HTAM	12	0.559 ± 0.06 (12)	-

[ab]Means having different superscripts at the same time points are significantly different at $P < 0.05$.

Table 6. Semen quality following complete ejaculations between 3 and 24 h after injection of normal saline (CON), tamsulosin 134.8 nM/kg (LTAM), and tamsulosin 269.7 nM/kg (HTAM) (mean ± SEM).

Hour (h)	Group	n	Sperm motility (%)	Mass sperm movement score	Sperm concentration ($\times 10^9$ cells/mL)	Total sperm ($\times 10^9$ cells)	Live sperm (%)	ALP ($\times 10^4$ IU)
3 h	CON	11	87.3 ± 2.4	4.8 ± 0.1	4.1 ± 0.5	12.2 ± 1.3	34.8 ± 6.2	8.1 ± 1.8
	LTAM	1	95	5.0	5.6	16.9	27.5	11.1
	HTAM	1	50	3.0	2.4	7.1	9.5	2.4
6 h	CON	12	80 ± 3.1[b]	4.8 ± 0.1	3.9 ± 0.6	11.8 ± 1.9	36 ± 5.6	8.4 ± 2.2
	LTAM	6	75.0 ± 5.5[b]	4.5 ± 0.3	5.2 ± 1.4	15.5 ± 4.1	32.4 ± 7.4	17.8 ± 7.8
	HTAM	4	57.5 ± 9.5[a]	3.8 ± 0.8	4.9 ± 0.9	14.8 ± 2.6	27.5 ± 14.0	8.7 ± 1.9
9 h	CON	12	73.8 ± 8.3	4.3 ± 0.4	3.2 ± 0.4	9.7 ± 1.2	36.1 ± 4.5[b]	5.4 ± 0.6
	LTAM	11	73.2 ± 3.8	4.3 ± 0.4	4.8 ± 0.8	14.4 ± 2.4	28.5 ± 3.4[ab]	10.0 ± 3.1
	HTAM	9	76.7 ± 5.3	4.0 ± 0.4	4.2 ± 0.7	12.5 ± 2.2	18.8 ± 3.1[a]	6.0 ± 0.8
12 h	CON	12	75.8 ± 4.7	4.4 ± 0.3	3.0 ± 0.2[a]	8.8 ± 0.6[a]	37.8 ± 3.0	4.2 ± 0.5
	LTAM	12	57.5 ± 6.5	3.6 ± 0.4	4.2 ± 0.3[b]	12.6 ± 1.0[b]	31 ± 4.4	6.0 ± 0.9
	HTAM	12	57.9 ± 8.3	3.3 ± 0.4	4.6 ± 0.3[b]	13.8 ± 0.9[b]	27.9 ± 5.1	5.7 ± 0.8
24 h	CON	12	60.0 ± 7.3	3.7 ± 0.4	3.2 ± 0.3	9.6 ± 1.0	37.2 ± 4.7	4.3 ± 0.6
	LTAM	12	65.8 ± 5.9	3.6 ± 0.5	4.1 ± 0.3	12.2 ± 0.8	35.8 ± 3.0	4.5 ± 0.6
	HTAM	12	62.5 ± 6.0	3.1 ± 0.4	4.2 ± 0.6	12.5 ± 1.7	31.8 ± 4.6	5.3 ± 0.6

[ab]Means having different superscripts at the same time points are significantly different at $P < 0.05$.

total sperm measurements were significantly higher in the HTAM and LTAM groups than in the CON group at 12 h ($P < 0.05$). At 24 h after injection, none of the semen quality parameters between the groups had significant differences ($P > 0.05$).

3.4. Heart rate and temperature

The heart rate and body temperature were similar ($P > 0.05$) between the groups in all periods (Table 7).

4. Discussion

This study demonstrated clearly that both TAM dosages used (134.8 and 269.7 nM/kg) temporarily suppressed ejaculation in the buck with no side-effects on libido or body physiology (heart rate and body temperature). Moreover, TAM-induced suppression, particularly anejaculation, was dose-dependent.

Maintaining the dominant male's sexual behavior, as a temporary contraception, could prevent repeated mating by subordinate males. In this study, neither TAM dose affected the buck's libido, as similarly observed in our previous study using a 179.8 nM/kg (80 μg/kg) TAM dose (3). A potential dose-dependent effect on libido, similar to other alpha adrenoceptor antagonists (such as yohimbine, causing variable sexual activity in rats in a dose-dependent manner (10)), was a concern. However, the libido scores were similar in the LTAM and HTAM groups, which might indicate either that the selected dosages were incapable of producing an observable difference or that TAM had no dose-dependent effect on libido. Both TAM dosages used here (134.8 and 269.7 nM/kg) maintained the dominant buck's libido (i.e. the ability and desire to engage in normal copulation).

Both LTAM and HTAM dosages induced the greatest ejaculatory suppression (incomplete ejaculation and anejaculation) by 3 h after injection; thereafter, the effect gradually decreased until complete recovery by 12 h. Although ejaculatory suppression occurred at similar rates between the TAM groups, the number of anejaculation events was higher in the HTAM group than in the LTAM group by 6 h after injection. This indicates that the high TAM concentration was associated with greater ejaculatory suppression than the low TAM concentration. Increased

Table 7. Changes of heart rate and body temperature between 0 and 24 h after injection of normal saline (CON), tamsulosin 134.8 nM/kg (LTAM), and tamsulosin 269.7 nM/kg (HTAM) (mean ± SEM).

Hour (h)	Group	Heart rate (bpm)	Temperature (°C)
0 h	CON	64.5 ± 4.5	38.72 ± 0.3
	LTAM	69.0 ± 3.3	38.67 ± 0.2
	HTAM	60.7 ± 5.8	38.61 ± 0.2
3 h	CON	80.0 ± 5.5	38.72 ± 0.3
	LTAM	85.0 ± 6.2	38.33 ± 0.3
	HTAM	89.2 ± 4.2	38.33 ± 0.3
6 h	CON	81.8 ± 6.1	39.11 ± 0.3
	LTAM	87.5 ± 3.2	39.00 ± 0.2
	HTAM	82.0 ± 4.8	39.00 ± 0.3
9 h	CON	85.0 ± 4.4	39.17 ± 0.2
	LTAM	86.5 ± 3.6	39.11 ± 0.2
	HTAM	86.8 ± 5.3	39.28 ± 0.2
12 h	CON	84.5 ± 4.9	39.28 ± 0.3
	LTAM	84.0 ± 3.5	39.06 ± 0.2
	HTAM	79.5 ± 5.0	39.22 ± 0.2
24 h	CON	74.8 ± 4.1	38.94 ± 0.4
	LTAM	70.8 ± 3.1	38.67 ± 0.2
	HTAM	73.5 ± 2.5	38.94 ± 0.1

intraurethral pressure in dogs (12) and salivary inhibition in rats (15) were both reported to occur in a dose-dependent manner with alpha-1 adrenoceptor antagonist. The dose-dependent effect of TAM on ejaculation demonstrated herein may indicate the involvement of the central nervous system. The possible sequence of TAM-induced ejaculatory suppression has been proposed previously (9,16). TAM may suppress ejaculation through its powerful affinity for 5-hydroxytryptamine 1A and dopamine 2-like receptors that are involved in the main regulation of ejaculation (9,16). This binding may lead to: 1) relaxation of urethral smooth muscles (7,17), 2) decrease of seminal vesicle pressure (8), and 3) reduction of the bulbospongiosus muscle contraction (9), collectively resulting in ejaculatory suppression in a dose-dependent manner.

Interestingly, once the TAM effect dissipated, the semen volume for complete ejaculation in the LTAM group was markedly higher than that in the CON group by 12 h after injection. An increased semen volume has not been previously reported for alpha-1 adrenoceptor antagonists. However, an elevated postejaculatory semen volume has been reported in dogs receiving low doses of alpha-2 adrenoceptor antagonists, such as rauwolscine and idazoxan (11), and the effect might also occur in animals receiving TAM. Alternatively, the repeated ejaculation events in bucks receiving normal saline might have caused a consistent or reduced semen volume (18,19), and therefore the importance of this remains unclear. Notably, by 24 h after injection, the semen volume remained similar between the groups.

The elevated semen volume may also explain the higher sperm concentration and total sperm in the LTAM and HTAM groups than in the CON group by 12 h after injection. As was the case with semen volume, both the sperm concentration and total sperm were similar between the groups by 24 h after injection.

The sperm motility at 6 h and live sperm percentages at 9 h were markedly lower in the HTAM group than in the CON or LTAM groups. This trend is consistent with our previous study, using 179.8 nM/kg TAM (3). TAM presumably alters the epididymal epithelial secretory and absorptive functions, or epididymal contraction, ultimately impairing spermatozoa viability as proposed by Kimsakulvech et al. (3). This effect was also dose-dependent, similar to previous reports investigating the salivary gland function (15).

Alterations in seminal ALP concentration may indicate epididymal blockage (20), but the concentrations used herein did not differ between groups. Potentially, TAM might inhibit all the reproductive tract's smooth muscle contraction. Heart rate and body temperature values remained unchanged and were similar between the groups over time, presumably indicating that the selected TAM dosages did not adversely affect cardiovascular and metabolic function in bucks.

In conclusion, the present study showed that TAM administered at 134.8 and 269.7 nM/kg dosages has temporary suppressive effects on ejaculation in bucks from 3 h to 9 h and led to altered semen quality up to 12 h after injection, both in a dose-dependent fashion. Moreover, the TAM effect was negligible at 24 h after injection. TAM did not affect the libido, allowing the male to remain actively dominant. Therefore, it was considered that TAM could be utilized as a temporary contraception of choice in males; nevertheless, further confirmation with future studies is warranted in animals of different species.

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