

Effect of intraurethral administration of atracurium besylate in male cats with urethral plugs

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OBJECTIVE: To evaluate the effect of intraurethral administration of atracurium besylate for urinary obstruction resulting from urethral plugs in male cats.

METHODS: Forty-five male cats were divided into the treatment group (n=25), in which 4 mL atracurium besylate solution (0.5 mg/mL) was injected into the urethral lumen, and the control group (n=20), treated with saline. All cats were then submitted to retrograde flushing until the removal of the occlusion was obtained.

RESULTS: The percentage of cats in which the plug was removed at the first attempt was significantly ($P<0.05$) higher in the treatment group (64%) than in the control group (15%). Moreover, the mean (\pm SD) time required for the removal of the urethral obstruction was significantly shorter in the treatment group than in the control group (21.1 \pm 16.2 seconds versus 235.2 \pm 132.4 seconds; $P<0.001$).

CLINICAL SIGNIFICANCE: The results of this study indicate that in adult male cats with urethral plugs, urethral administration of atracurium besylate increases the proportion of animals in which the obstruction is removed at the first attempt and reduces the time required to remove the urethral plugs.

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INTRODUCTION

Obstruction of the lower urinary tract is a common disorder in male cats. According to Kruger and others (1991), urethral plugs are the most common cause of urinary tract obstruction (59%), followed by idiopathic obstruction (29%) and then by uroliths (12%). Barsanti and others (1996) found urethral plugs and idiopathic obstruction to be equally responsible for urethral occlusion (42%), while a more recent study (Gerber and others 2005) reported a considerably lower percentage of urethral plugs compared to uroliths or idiopathic obstructions. Other less-frequent causes of urethral obstruction are neoplasms, stenosis, abscesses and cysts.

Urethral plugs are more likely to occur in the postprostatic/penile tract of the urethra because of the smaller diameter of the lumen in this region (Wang and others 1999, Filippich 2006). Inflammation of the bladder and urinary crystals appear to play important roles in the formation of urethral plugs (Osborne and others 1996a, Hostutler and others 2005). The composition of

plugs is indeed predominantly a mixture of matrix made by proteins and epithelial/blood cells plus a variable amount of mineral crystals (mainly struvite) (Osborne and others 1996b). Urethral plugs rapidly lead to severe distension of the bladder and subsequently to postrenal azotaemia. In the absence of effective treatment, affected cats usually die within three to six days (Bartges and others 1996).

The most commonly employed procedure to remove urethral plugs in order to enable bladder voiding is retrograde flushing (Bernard 1984, Osborne and others 1996c, Walker 2009). Pharmacological management may facilitate removal of the urethral obstruction (Straeter-Knowlen and others 1995) and may reduce urethral damage, which could afterwards lead to complications or to a recurrence of the obstruction (Corgozinho and others 2007). Intravenously (iv) administered smooth and striated muscle relaxants, including acepromazine, phenoxybenzamine, prazosin, dantrolene and diazepam, have been studied for their ability to relax the urethral musculature, to aid relief of the obstruction and to prevent recurrences (Mawby and others 1990, Frenier and others 1992, Straeter-Knowlen and others

1994, Marks and others 1996). However, because these systemic treatments generally have side effects and their effectiveness is limited, they are not suitable for routine clinical practice (Lane 1995, 2000, Gaskell 2007). While the centrally acting muscle relaxant diazepam did not induce a significant pressure decrease in any of the urethral segments in anaesthetised, healthy, sexually entire male cats, dantrolene sodium, a direct-acting skeletal muscle relaxant, was effective in promoting a significant decrease in intraurethral pressure of the postprostatic/penile regions in clinically healthy cats and cats with urethral obstruction (Straeter-Knowlton and others 1994, 1995). Intravenously administered succinylcholine, a depolarising neuromuscular blocking drug, has also been studied and was effective in reducing urethral pressure in healthy anaesthetised cats (Straeter-Knowlton and others 1994). However, succinylcholine causes respiratory paralysis and is not, therefore, used for clinical applications in obstructed cats (Straeter-Knowlton and others 1994). Nevertheless, these observations indicate that skeletal muscle relaxants might be helpful for pharmacological management of lower urinary tract disorders in male cats.

Atracurium besylate (AB) is a curare derivative employed in humans and tested in cats (Coker and others 1981, Sutherland and others 1983) to obtain optimal muscle relaxation during surgery. AB acts as a neuromuscular blocking agent by antagonising acetylcholine at the nicotinic receptors in the neuromuscular junction and, therefore, induces paralysis of striated muscle (Coker and others 1981, Sutherland and others 1983). The metabolism of AB does not depend on renal or liver function, but AB is quickly inactivated by plasma esterases or by spontaneous degradation (Neill and Chapple 1982). AB can, therefore, be used in cats with liver or kidney failure without an increase of its effects (Bowman 2006, Martinez and Keegan 2007).

The aim of the present study was to evaluate the effect of intraurethral administration of the neuromuscular blocking agent AB on the resolution of urinary obstruction due to urethral plugs in male cats.

MATERIALS AND METHODS

The present prospective study was conducted in a non-blinded fashion between January 2008 and July 2010 on two groups of client-owned male cats brought to the "Veterinary Clinic Castellano" (RE, Italy) with clinical signs of urinary retention. The study was performed in compliance with the requirements of Local Ethics Committee and informed consent was obtained from the owners before the participation of their cats in the study.

A diagnosis of urethral obstruction was made by the medical history of the animals (presence of anuria or stranguria lasting one to four days), physical examination (palpation of the bladder) and detection of urethral obstruction by urethral catheterisation. Urethral plugs were diagnosed when traces of a plug were detected after the withdrawal of the urinary catheter. Survey radiographs and ultrasonography were also used in order to

exclude the presence of uroliths. Cats with obstruction located at the tip of the penis were not included in this study because of the impossibility of performing intraurethral irrigation. Only the cats in which the obstruction was located in the postprostatic/penile urethra, i.e. when the plug could be reached by a 32-mm-length catheter, were included in the study. The reason for this was to exclude the animals with obstruction in the urethral segment with prevalent smooth muscle control. All enrolled cats had urinary retention with total absence of bladder emptying and the cats that had been obstructed or catheterised before (recurrent cases) were excluded.

None of the cats received any drugs for at least 24 hours before the treatment. The cats (n=45) were divided into 2 groups in alternating order; the treatment group (n=25), treated with AB, consisted of 19 neutered and 6 entire male cats, while the control group (n=20), not treated with AB, consisted of 13 neutered and 7 entire male cats.

Simple physical restraint was sufficient to perform the procedure in three cats in the treatment group and in one cat in the control group, as they were cooperative or had sensorial depression; all the other animals were premedicated with acepromazine (0.025 mg/kg) and butorphanol (0.2 mg/kg), and anaesthetised with propofol (2 mg/kg) and isoflurane.

Drugs

For the preparation of the intraurethral solution, 0.2 mL of AB (Tracrium, 10 mg/mL, Glaxo SmithKline, San Polo di Torrile, Parma, Italy) was diluted in 3.8 mL of 0.9% sodium chloride to obtain a final volume of 4 mL with a 0.5 mg/mL concentration of AB. The concentration of AB was established empirically, as this is, to the authors' knowledge, the first work concerning local intraurethral administration of this compound. The concentration of the AB solution (0.5 mg/mL) was the same used in a previous study to improve local peribulbar anaesthesia for ophthalmic surgery in humans (Küçükayavuz and Arici 2002).

Treatment procedure

The cats were placed in a lateral recumbency and, after disinfection of the sheath, the penis was extruded and a sterile, iv polytetrafluoroethylene catheter of 3 F × 32 mm (Delta Ven 1[®]), previously lubricated with Luan[®], was carefully introduced into the urethra. A 5-mL syringe containing either AB or saline solution was attached to the catheter and a steady, gentle pressure was exerted on the syringe plunger for 5 minutes while the urethral orifice was pressed with two fingers to prevent leakage of the solution. Then, the syringe was removed and a retrograde flushing with saline was performed for a maximum of 20 seconds. This 20-second period refers only to the total time of flushing and does not include "downtime" such as the time required to reload the syringe.

If the obstruction was not removed by the first attempt, the entire procedure (5 minutes treatment and subsequent flushing) was immediately repeated until the urethral plug was removed (Fig 1). The times of retrograde flushing were recorded with a chronometer and then summed to obtain the overall time required to remove the obstruction.

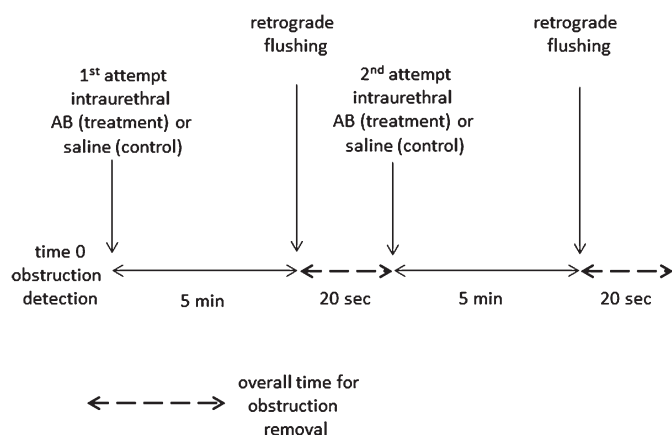


FIG 1. Treatment procedure. Each attempt was composed by a 5-minute intraurethral administration of atracurium besylate (treatment group) or saline (control group), followed by a 20-second retrograde flushing with saline. The overall time of retrograde flushing needed to remove the obstruction was recorded

Statistical analysis

All data were expressed as mean \pm SD and analysed by multiple regressions, with time (in seconds) of retrograde flushing as the dependent variable and group (treatment versus control), sexual status (neutered versus entire), weight and age as independent variables. The non-parametric Mann-Whitney *U*-test was used for variable comparisons between groups. The chi-square test was used to compare the number of animals that responded or not to the treatment after the first attempt. The level of statistical significance was set at $P < 0.05$. Analyses were performed by a commercial software programme (SPSS, version 10.0, IBM).

RESULTS

The breeds of cats were domestic shorthair (22 treated and 15 controls), domestic longhair (3 treated and 3 controls), Chartreux (1 control) and Maine coon (1 control). The mean age of the cats in the treatment group was 4.50 ± 3.2 years and their mean weight was 5.59 ± 2.2 kg. The corresponding values for the controls were 4.45 ± 2.5 years and 5.85 ± 1.4 kg (Table 1).

There was no significant difference in age or weight between the treatment and control group and neither age nor weight of the animals affected the time required for plug removal in a significant fashion (Table 1).

In the treatment group, the urethral plugs were removed at the first attempt in 16 cats (64%), $P < 0.05$, and in the remaining 9 at the second attempt (36%). By contrast, in the control group, the urethral plugs were removed at the first attempt only in 3 cats (15%), whereas in the other 17 more than one treatment was needed (Table 1). The overall time required for the removal of the urethral plug was significantly shorter ($P < 0.001$) in the treatment group compared with the control group (20.7 ± 16.2 seconds versus 235.2 ± 132.4 seconds, respectively) (Table 1).

Sexual status (neutered or entire) did not influence the time for plug removal in the treatment group (21.8 ± 22.0 and 25.3 ± 11.6 seconds for neutered and entire cats, respectively, $P = 0.39$), but

Table 1. Means \pm SD of age, weight, percentage of subjects responding to the first treatment, and overall time required to remove the urethral obstruction in AB- and saline-treated cat groups

	Age (years)	Weight (kg)	Response at first attempt (%)	Overall time for plug removal (seconds)
AB	4.50 ± 2.5	5.59 ± 2.2	64*	$20.7 \pm 16.2^{**}$
Saline	4.45 ± 2.5	5.85 ± 1.4	15	235.2 ± 132.4

AB Atracurium besylate
* $P < 0.05$ versus saline; ** $P < 0.001$ versus saline

amongst the cats in the control group, the plugs were removed more quickly in neutered compared to entire animals (139.1 ± 144.7 seconds versus 376.8 ± 278.1 , respectively, $P < 0.05$).

DISCUSSION

In clinical practice, the most commonly used procedure to remove urethral plugs in male cats in order to re-establish bladder voiding is retrograde flushing. This technique is not devoid of risks as the catheter could damage the urethra and the subsequent inflammation may lead to a relapse of the occlusion caused by muscle spasm and/or oedema of periurethral tissues (Corgozinho and others 2007). Urethral plugs occur more frequently in the postprostatic/penile urethra because of the smaller diameter of the urethral lumen in this tract (Hostutler and others 2005, Filippich 2006). Since this portion of the urethra is under predominant control by striated muscle cells (Wang and others 1999), the neuromuscular blocker AB, given intraurethrally, was used to see if it could improve the removal of the obstruction, by a relaxing action on urethral musculature.

There are currently no reports of urinary diseases associated with the presence of urethral plugs in men, so very little can be learned from human studies that might prove helpful for this disorder in cats. In the human genitourinary tract, urethral calculi are fairly uncommon, accounting for only 1% of all urinary calculi (Hemal and Sharma 1991). Symptomatic calculi that fail to be expelled spontaneously require management by methods such as flush-back treatment, endoscopic extraction or extracorporeal shock wave lithotripsy (Gerber 1981, Al-Ansari and others 2005).

Muscle-relaxing drugs have already been tested in the cat for their effects on urethral tone. Previous experiments suggest that only drugs acting directly on striated muscle are effective in reducing the pressure in the postprostatic/penile segment of the urethra in cats. Indeed, acepromazine, xylazine, alpha-adrenergic antagonists such as phenoxybenzamine and prazosin or the calcium-channel blocker nifedipine were effective only at preprostatic or prostatic level (Mawby and others 1990, Frenier and others 1992, Marks and others 1996), whereas the efficacy of diazepam was controversial (Mawby and others 1990, Straeter-Knowlen and others 1994). Conversely, the ryanodine-receptor antagonist, dantrolene, and neuromuscular blocker succinylcholine succeeded in reducing the tone of the postprostatic/penile tract (Straeter-Knowlen and others 1994, 1995). The efficacy of

these compounds appears to be limited, though, and Straeter-Knowlen and others (1995) doubted the real utility of such treatment in urethral obstruction in cats. Another major issue is represented by the necessity of administering these drugs systemically, thus bearing side effects, the relevance of which could seriously hinder a putative beneficial activity.

The results of our study indicate that intraurethral administration of AB can be useful in the removal of urethral plugs causing urethral obstruction in male cats. Indeed, following treatment with AB, the urethral plugs were removed at the first attempt in a significantly higher number of cats (64%), compared to saline-treated cats (15%). Altogether, the overall time required for the removal of the urethral plugs was significantly shorter in the treated group with respect to control patients. This could be clinically relevant because it would allow reducing the damage to the urethra caused by flush-back treatment and by the presence of the catheter in the urethral lumen (Corgozinho and others 2007).

This is the first evidence of an efficacy of intraurethral administration of a skeletal muscle relaxant in the management of urethral obstruction in male cats. The data are in accordance with the previous work in which AB, given iv, was effective in relieving distal urethral spasm in cats with experimentally induced cauda equina lesions (Flood and others 1990). This study suggests that AB is able to act directly on skeletal muscle to decrease urethral tone in the postprostatic/penile segment.

Curare derivatives, like AB, are usually employed iv to achieve total muscular relaxation for surgical procedures. To the present day, very little is known about the effects of topical administration of a curare derivate (Küçükyavuz and Arici 2002). Systemic administration of AB induces a paralysis of all skeletal muscles, with failure of spontaneous breathing and can cause dangerous side effects like hypotension and tachycardia (Mirakhor 1990). Non-depolarising neuromuscular blockers can also interact with other drugs, like inhalation anaesthetics, and antibacterial agents, like aminoglycosides and polymyxins (Ostergaard and others 1989, Dickens 1995).

Local administration of AB could be useful, because it minimises the risks of adverse effects. Indeed, muscle weakness or any other side effect related to AB administration was not detected in this study.

AB is chemically stable in 0.9% sodium chloride (Pramar and others 1996) but is characterised by a very low liposolubility, so only few molecules are normally able to cross the biological membranes (Neill and others 1983). However, the efficacy of AB observed in our study seems to suggest that, at the concentration used, enough drug was able to cross the urethral mucosa to induce at least a partial paralysis of the urethral muscle. The volume of AB solution used (4 mL) may have stretched the urethral mucosal surface to allow sufficient contact between the drug and the urothelium during the 5 minutes of administration. Urethral inflammation and associated disruption of the epithelial barrier may have further facilitated AB penetration and efficacy. However, further investigation will be required to better understand the real bioavailability of AB by intraurethral route.

An interesting observation of this study is that, in the control group, the time required to remove the urethral obstruction

was shorter in neutered cats than in sexually entire cats ($P < 0.05$). This observation is consistent with those of previous studies in which it was found that mean urethral pressure is generally lower in neutered cats than in sexually entire cats and, therefore, that less retrograde flushing would be required to remove the obstruction and/or the effect of AB would be less significant (Straeter-Knowlen and others 1995). A difference in time for removal of the obstruction between neutered and sexually entire animals was not observed in the treatment group, because the treatment already reduced the overall time for plug removal.

It would be enlightening in the future to assess the effects of AB in a larger number of entire cats affected by urethral plugs.

In the present work only one dose of AB was evaluated. It would be important to test higher and lower doses of this drug in further experiments, in order to assess the presence of a dose-dependent effect and to determine the optimal dose of AB to be used. It would also be interesting to assay the effects of other striated muscle relaxants by the intraurethral route and to use instruments for the measurement of bladder pressure. Bladder pressure could only be assessed subjectively and this could be a limitation of the study as it might have influenced how easy it is to flush the plug into the bladder. Another limitation is that it was not possible to assess precisely how long the cats had been obstructed before the treatment because they were client-owned cats and therefore not always under control.

In conclusion, the results of this study indicate that, in adult male cats, intraurethral administration of AB before retrograde flushing technique may facilitate the clinical management of urethral plugs by reducing the overall time needed to remove the obstruction.

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Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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