Paper

Effect of urethral infusion of atracurium besylate on manual bladder expression in dogs and cats with spinal cord injuries: a randomised trial

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The aim of this randomised trial was to assess the effect of urethral infusion of atracurium besylate in dogs and cats with signs of urinary retention secondary to lesions affecting spinal cord segments T3–L3. Eighteen dogs and six cats with urinary retention were examined and scored before treatment on the degree of difficulty of inducing bladder emptying by manual bladder compression. Animals were subsequently treated in a blinded fashion by the same operator with urethral infusion of 2–4 ml of either a solution of 0.5 mg/ml of atracurium (treatment group) or placebo (control group) and, after five minutes, a second attempt was made to induce bladder emptying by manual compression and a post-treatment score assigned. Pretreatment scores did not differ between the treatment and control groups (5.6±0.8 v 6.2±0.7, respectively; P=0.22); however, post-treatment scores were significantly lower in the treatment group compared with the control group (2.9±0.4 v 5.9±0.3; P<0.05). Urethral infusion of atracurium facilitates manual bladder expression in dogs and cats with urinary retention secondary to spinal cord injuries. No side effects were recognised.

Introduction

Neurological causes of urinary bladder dysfunction are divided into upper motor neuron (UMN) dysfunction, associated with spinal lesions between the brainstem and the L7 spinal cord segment, and lower motor neuron dysfunction, associated with lesions affecting the sacral spinal segments, pudendal nerve or pelvic nerves (Dewey 2008). UMN lesions induce urinary retention because of loss of voluntary contraction of the detrusor muscle and hypertonic contraction of the urethral sphincter (Lane 2000, Coates and Kerl 2007, Dewey 2008). Urinary retention with high intravesical pressure may result in vesico-ureteral reflux, renal injury and secondary urinary tract infection (Osborne and others 1996, Lane 2000). Relief of urinary retention is therefore an important part of the management of spinal patients.

Treatment of urinary retention requires treatment of the primary spinal lesion and pharmacological induction of bladder voiding, intermittent or indwelling catheterisation or pudendal neurotomy (Gookin and Bunch 1996, Lane 2000, Coates and Kerl 2007). Intermittent or indwelling catheterisation may be problematic and increases the risk of urinary infection (Lees 1996, Lane 2000, Bubenik and others 2007). Experimental techniques to relieve urinary retention, such as the stimulation of the sacral nerves or pudendal nerve afferents (Boggs and others 2005, Woock and others 2008, Yoo and others 2008), have not yet been used in clinical veterinary practice.

Pharmacological treatments of urinary retention promote bladder voiding by promoting relaxation of the smooth or striated urethral muscles. Several classes of drugs have been used for this purpose, including parasympathomimetic agents, α-adrenergic blocking drugs, and central and peripheral muscle relaxants (Gookin and Bunch 1996, Lane 2000, Dewey 2008). The clinical responses to these drugs are variable and side effects have been observed at therapeutic doses (Mawby and others 1991, Barsanti and others 1996, Lane 2000). In humans, bladder voiding may be aided by injection of botulinum A toxin into the striated urethral sphincter (Kuo 2003, Frenkl and Rackley 2005, Smith and others 2005); however, there are no veterinary data about this technique.

Atracurium besylate is a curare derivative that acts as a neuromuscular blocking agent by antagonising acetylcholine at the nicotinic receptors in the neuromuscular junction and therefore inducing paralysis of striated muscles (Martinez and Keegan 2007). Atracurium, which is chemically stable in saline solution (Pramar and others 1996), has been used successfully in cats via intraurethral administration for the clinical management of urethral plugs (Galluzzi and others 2012). Muscle weakness or any other side effect related to atracurium administration was not detected in that study.

The aim of this study was to assess the ability of urethral infusion of atracurium besylate to induce manual bladder voiding in dogs and cats with signs of urinary retention due to spinal cord injuries.

Materials and methods

Animals

The study was conducted between January 2010 and July 2012 using client-owned dogs and cats brought to the Veterinary Clinic Castellarano (Reggio Emilia, Italy). The study was

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performed in compliance with institutional guidelines for research on animals. Informed consent was obtained from owners before enrolling their pet in the study. Animals were eligible for inclusion if they had a history and clinical signs compatible with acute spinal cord injury localised to the T3–L3 spinal segments and had signs of urinary retention. In all cases manual bladder expression was impossible or extremely difficult. Physical causes of urethral obstruction were excluded by ability to catheterise the bladder without difficulty. Cats that were particularly aggressive were not included. Cats were sedated with ketamine (6 mg/kg) and midazolam (0.2 mg/kg) intramuscularly.

The present study is a randomised controlled clinical study in which the animals that were eligible for the experiment were randomly distributes in two parallel groups: treated and control (placebo) group. The allocation ratio was 1:1. The administration of the solution with or without atracurium was done in a blinded fashion. The treatment allocation utilised in the study in the randomisation process was as follows: an assistant prepared the solution (with or without atracurium) based on the progressive number of the clinical record (even for atracurium, odd for placebo). In this way the operator was blinded to the contents of the solution used.

Bladder palpation and infusion of atracurium besylate

Apart from the preparation of the solution (with or without atracurium), all the experimental procedures were done by the same operator. Firm pressure over the bladder was applied for up to 60 seconds in order to obtain a stream of urine. Based on the difficulty of obtaining a stream of urine, a score from 0 to 7 was assigned (Table 1). Bladder palpation was performed immediately before and five minutes after urethral infusion.

Infusion of atracurium besylate was achieved by the utilisation of a Sovereign (Medtronic-Covidien, USA) polypropylene bladder catheter (5-8-10 French) for male dogs, a Foley Surgivet (Smiths Medicals, USA) in silicone (8 French) for bitches and a Buster (Kruuse, Denmark) urinary catheter in polyethylene without stylet (3 French) for all cats. After the animal had been placed in lateral recumbency, the catheter was lubricated (lidocaine 1 per cent gel) and placed 0.8–2 cm inside the urethra, according to the size of the patient. A 5 ml syringe (Omnifix Luer Lock) connected to the catheter was used to administer a saline solution containing atracurium besylate (treatment group) or saline alone (control group). The urethral infusion was made up using 0.2 ml of Tracrium (10 mg/ml atracurium besylate, GlaxoSmithKline) diluted in 3.8 ml of 0.9 per cent sodium chloride to obtain a final volume of 4 ml with a 0.5 mg/ml concentration of atracurium. The volume of solution administered was 2 ml for all cats and dogs weighing less than 10 kg, 3 ml for dogs weighing 10–20 kg and 4 ml for dogs weighing over 20 kg. In male animals, the urethral orifice was manually occluded to avoid retrograde losses of the solution. The catheter was kept in place for five minutes after infusion.

Statistical analysis

All data are expressed as mean±sd and were analysed by multiple regressions, with the score for difficulty as the dependent variable and group (treatment v control), sexual status (neutered v intact), weight and age as independent variables. The non-parametric Mann-Whitney U-test was used to compare variables between groups. The level of statistical significance in the hypothesis tests was set at $P<0.05$. Analyses were performed using commercially available software (SPSS, V.10.0, IBM).

TABLE 1: Scale of difficulty in obtaining a urine stream

Score	Urine stream	Urine jet calibre
0	Constant	Large
1	Generally constant with few short breaks	Large
2	Generally constant with few short breaks	Medium–large
3	Mostly constant but with frequent short breaks	Medium
4	Not constant	Medium–small
5	Not constant	Small
6	Not constant	Very small
7	Absent or drop by drop	

Results

Eighteen dogs and six cats were enrolled and all the animals were included in the final analysis of the data. The treatment group (n=12) included four mixed breed dogs, two German shepherd dogs, one dachshund, one Argentine mastiff, one rottweiler and three domestic shorthair cats. The control group (n=12) included five mixed breed dogs, two German shepherd dogs, one labrador retriever, one English setter and three domestic shorthair cats. The treatment group included seven male dogs, two neutered female dogs and three neutered male cats. The control group included eight male dogs, one neutered female dog and three neutered male cats. The mean weight of the dogs in the treatment group was 25.7±13.7 kg while that of the dogs in the control group was 23.7±12.1 kg; the mean weight of the cats in the treatment group was 5.1±1.6 kg while the mean weight of the cats in the control group was 3.9±1.8 kg. The mean age of the dogs in the treatment group was 9.6±3.2 years, while that of the control group was 8.2±3.7 years. The corresponding values for the cats were 4.3±1.02 years and 4.8±1.3 years.

There were no significant differences in gender ratio, age or weight between treatment and control groups. The pretreatment scores of difficulty of manual bladder expression did not differ between the treatment and control groups (5.6±0.8 v 6.2±0.7, respectively; $P=0.22$). The post-treatment scores of difficulty of manual bladder expression were lower in the treatment group than in the control group (2.9±0.4 v 5.9±0.3, respectively; $P<0.05$). Within the treatment group, the score of difficulty of manual bladder expression decreased significantly between pretreatment and post-treatment (5.6±0.8 v 2.9±0.4, n=12; $P<0.001$), whereas the difference was not statistically significant in the control group (6.2±0.7 v 5.9±0.3, n=12; $P=0.21$).

Discussion

In this study, urethral infusion of atracurium was found to facilitate manual bladder expression in dogs and cats with urinary retention secondary to spinal cord injuries. This effect is consistent with counteraction of the increased urethral striated muscle tone observed in spinal patients. In dogs and cats there is no focal urethral sphincter because the whole urethra has muscle that contributes to sphincter activity (Stolzenburg and others 2002a, b). In female dogs, striated muscle is present around the middle and distal thirds of the urethra, with the distal part also surrounding the vagina (Stolzenburg and others 2006), whereas in male dogs, striated muscle surrounds the pelvic (membranous) urethra from the apex of the prostate to the bulb of the penis (Creed and Van Der Werf 2001). In male cats, the striated muscle surrounds the urethra from the part caudal to the prostate and includes the entire penile urethra (Wang and Bhadra 1999), while in female cats striated muscle is present only in the distal urethra (Lane 1995).

Manual expression of the bladder is a commonly used technique to induce bladder voiding and is associated with a lower incidence of urinary infection than indwelling catheters (Lees 1996, Coates and Kerl 2007). However, manual expression of the bladder can be difficult in patients with UMN spinal lesions and does not always enable voiding of urine (Lane 2000, Dewey 2008). Use of atracurium infusion should be considered by clinicians managing spinal patients, particularly if urinary retention is a problem. Urethral infusion of atracurium has also been found to facilitate the clinical management of urethral plugs in male cats (Galluzzi and others 2012).

Infusion of atracurium into the urethra did not produce any apparent muscle weakness or other side effects. Very little is

currently known about the effects of topical administration of a curare derivative (Kücükyavuz and Arici 2002). Atracurium is characterised by a very low liposolubility, so only few molecules are usually able to cross biological membranes (Neill and others 1983). However, the efficacy of atracurium observed in this study seems to suggest that, at the concentration used, enough drug was able to cross the urethral mucosa to induce at least partial paralysis of the urethral muscles. The volume of atracurium solution used appears sufficient to allow absorption of the drug across the urothelium within five minutes. However, further investigation will be required to better understand the real bioavailability of atracurium administered by the urethral route.

In conclusion, urethral infusion of atracurium facilitates manual bladder expression in dogs and cats with urinary retention secondary to spinal cord injuries and appears not to produce any side effects. Future studies will be necessary to evaluate the duration of action of atracurium infusion.

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Notes