# Intravesical dosing in the female Sprague Dawley rat

SARAH GRAHAM CHENERY and ZAC TURNER

Labcorp Early Development Laboratories Limited

Correspondence: sarah.graham-chenery@labcorp.com and zac.turner@labcorp.com

## Introduction

The test article for this study was an antibiotic to treat urinary tract infections (UTIs), one of the top recurring infectious ailments of the elderly.

Whilst many UTIs respond well to antibiotics, it is not uncommon for them to resurface several months later, which is thought to be (amongst other reasons) due to infection of the bladder itself. Most treatments for UTIs involve oral administration of an antibiotic, which relies on systemic exposure to remove microbes within the bladder wall and urinary excretion of the antibiotic to remove microbes within the bladder. In clinical treatments for this test article, the urinary bladder will be catheterised and dose will be instilled; two hours later the patient will be allowed to urinate to remove residual dose. Because we cannot tell the animal not to urinate for a couple of hours, the animal was anaesthetised to facilitate catheterisation and then held under general anaesthesia for an hour after dose administration.

## Elements to consider

Females have a shorter urethra than males. This means bacteria are more likely to reach the bladder or kidneys and cause an infection. Therefore UTIs occur more frequently in females. Also, the anatomy of the female lends itself to this dosing route a lot easier than the anatomy of the male. In addition, the published papers on this model/route only refer to females.

The study consisted of 12 female Sprague Dawley rats, 6 control and 6 treated. Animal care and use was conducted in alignment with Animal Welfare regulatory requirements in an AAALAC accredited facility.

As the patients on the clinical trial will receive treatment once a week for 4 weeks, it was decided that the animals would receive treatment twice weekly for 4 weeks to give a safety margin, which is important as the objective of this study is to protect the first patients on the clinical trial.

Excessive salivation was seen on a similar (once weekly dosed) study at our Madison, WI (US) facility. Accordingly, discussions were held with the veterinary surgeon regarding holding the animals on their back headfirst on a slight downward incline of 10° on a purpose-made slope, which was slight enough to give the saliva a directional flow out of the body but not too much to cause issues, as well as reducing dose loss due to gravity. Subsequently no issues regarding salivation were observed throughout the duration of the study.

## Methods

We started the procedure by anaesthetising the animal in the animal room with a combination of 2.5% isoflurane and 3 litres per minute of oxygen. These measurements were deemed appropriate as the animals were subject to this procedure for 1 hour, twice a week for 4 weeks. Once the animal was satisfactorily anaesthetised, it was transferred to the surgery suite and placed in a supine position onto the 10° slope with the nose positioned in the breathing tube (Figure 1).

Viscotears were applied to both eyes to ensure they were kept hydrated during the procedure. A rectal thermometer was inserted with the aid of KY jelly, which was connected to a heat blanket as part of our routine observations. The thermometer was then secured to the tail using LeukoFix™ tape to ensure that it remained in

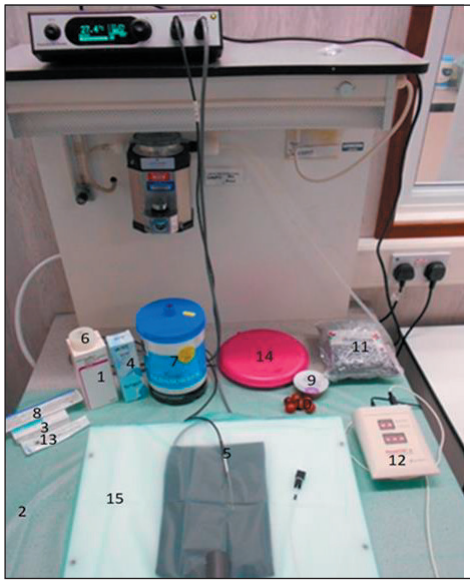


**Figure 1.** Anaesthesia workstation including dosing equipment.

place. A pulse oximeter was attached to the forepaw of the animal, which enabled monitoring of the heart rate and oxygen saturation. After the animal was prepared, the catheter was lubricated with Instillagel and placed into the urethra in the direction of the tail (Figure 2), then rotated upwards until the catheter was parallel with the tail.

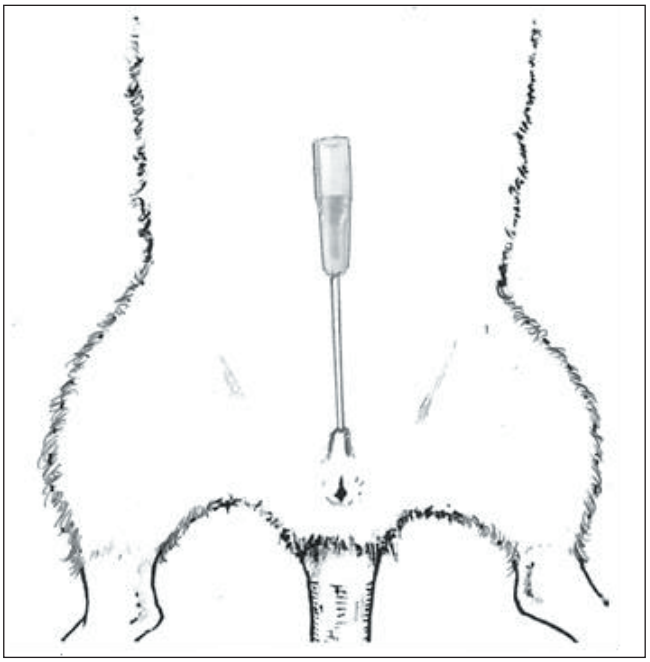

**Figure 2.** A22G x 1" soft Teflon intravenous administration catheter inserted into the external urethral orifice. Illustration by Duncan Patten of Labcorp.

## Observations

Observations were performed every 5 minutes to monitor the animal's heart rate, oxygen saturation, body temperature, isoflurane/oxygen rate, oral secretions as well as applying Viscotears and supplemental care as necessary.

After an hour of administration, the last set of observations were performed, the dose was withdrawn slowly back into the 1 ml syringe and the rectal thermometer was removed.

## Recovery

To aid recovery post-administration, we placed the animal into its own recovery cage, which was then put on top of a heat mat. Once the animal had recovered from the general anaesthetic, it was given post-operative recovery hydrogel, ¼ teaspoon of sunflower seeds and a grape. This enrichment was chosen to encourage the animal to eat and drink, to stay hydrated and for enjoyment purposes.

After four weeks of treatment the animals were sacrificed and subjected to necropsy examination and histopathology of the urinary tract (kidneys, ureters, urinary bladder and urethra).

## Results

There were no effects on organ weights; however there was a slight effect on bodyweight. This was not a response to the test article but was considered to be associated to the anaesthesia/dosing procedure, as during the first four days of the study the controls lost a mean of 3g and the test gained a mean of 1g.

There were some minor findings from the urinary bladder that came back in the toxicology report; one of them being some congestion for one control but no test animals. The other finding was isolated cases of focal areas of oedema (one control and two test animals). This was also considered to be associated with the administration procedure. There were no signs of adverse effects from the procedure seen post-dose or at dose site observations.

## Conclusions

This dose administration method was well tolerated by female Sprague Dawley rats, which were treated for 1 hour, twice a week for 4 weeks, with minimal irritation of the urinary bladder epithelium.

## Acknowledgements

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## References

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https://www.nhs.uk/conditions/urinary-tract-infections