Neutersol: A Clinical Perspective

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THE PRODUCT

Neutersol is zinc gluconate neutralized by arginine to a pH of 7. The product was the result of over 20 years of research and development by the University of Missouri, Center of Reproductive Science. The product concentration is 13.1 mg of zinc per ml. and has no preservatives. It is an aqueous and syringe able solution which may be kept at controlled room temperature (59-86 F).

Initial FDA approval was based on a study of 224 male puppies 3 to 10 months of age. The initial indication and approval was for that age group. Custom dosing calipers are supplied with 2 ml vials of product. Measuring each testicle at the widest point determines which of six dosing levels (0.2 ml to 1.0 ml) is used.

Insuring that the animal is properly restrained, each testicle is measured with the calipers. While a surgical scrub is not necessary, it is desirable to remove excess dirt from the scrotum with mild surgical soap. The amount of product determined by measurement is drawn into a 1cc insulin syringe with a 28 gauge, ½ inch needle. The intratesticular injection is done at the dorsal cranial portion of the testis, beside the head of the epididymis at a moderately slow pace. Technique is very important to safe and effective sterilization. It is important that the product is not injected into the scrotum or intradermally.

Efficacy in the field trial was shown to be 99.6% (223 of 224 dogs) with the one unsuccessful dog thought to have been under dosed. While having a very low sperm count, this dog did not meet the criteria. Evidence of efficacy was based on semen analysis, clinical observations, and microscopic observations. Clinical observation showed a significant reduction in testicular measurements in treated

versus controls. While testicular atrophy is variable and not an indicator of efficacy, a 77% decrease was seen in treated versus the controls. Microscopic observation showed atrophy of seminiferous tubules, non-functional testes and absence of sperm. Prostate weights were reduced an average of 52% when measured 24 months after injection. Measured 24 months after injection, testosterone blood levels showed a significant reduction with some as high as 52%.

Adverse events were recorded for the 270 dogs injected for the field trial. Reactions upon injection were limited to 6 dogs (2.2%) vocalizing and I dog (0.4%) kicking. The highest incident of local reactions was scrotal pain upon palpation which was noticed in 17 (6.3%) of the dogs. There were 3 (1.1%) incidents of scrotal irritation, 2 (0.7%) biting and licking, 2 (0.7%) scrotal swelling, 2 (0.7%) scrotal irritations and dermatitis, and a single incident (0.04%) of scrotal ulceration, scrotal infection, dry scrotal skin, scrotal bruising, preputial swelling and scrotal sore. General reactions included 17 (6.3%) dogs with neutrophilia, 12 (4.4%) with vomiting, 11 (4.1%) anorexia, 6 (2.2%) lethargy, 5 (1.9%) diarrhea and 2 (0.7%) leukocytosis.

THE ORGANIZATION

The Spay-Neuter Assistance Program, Inc. (SNAP) has a mission “to prevent the suffering and death of cats and dogs due to overpopulation, especially in low-income areas”. Since 1994, SNAP has helped 441,059 dogs and cats with 40,223 being helped in the last fiscal year (July 1, 2007 through June 30, 2008).

As with the introduction of any medical procedure resulting from technological advances, the use of Neutersol generated many questions both in the veterinary medical and animal welfare communities. In keeping with our mission and with a goal of ending dog and cat overpopulation, the veterinary medical team at SNAP carefully reviewed the use and effects of Neutersol. At the SNAP surgery clinic in October of 2003, we injected several shelter puppies with Neutersol. We were impressed with the increased operating efficiencies achieved by utilizing Neutersol. These included the reduction of veterinarian and staff time, reduction of facilities, equipment, drugs and supplies required for traditional neutering. We

recognized that the utilization of Neutersol eliminated the risks of general anesthesia as well as some of the stress of the dogs and their guardians.

Following our initial use of Neutersol, we decided to develop protocols for its use and investigate how the product might be used to reduce the overpopulation of dogs. First, we identified those dogs where Neutersol would not be used to include:

1. Undescended testicle (cryptorchid)
2. Pre-existing scrotal irritation or dermatitis
3. A disease or malformation of the testicle
4. A history of allergic reaction of any of the components of the drug
5. Testicular width less than 10 mm or greater than 27 mm

We established procedural guidelines to include a sedation chart utilizing Diazepam and Ketamine. We included all Neutersol labeling guidelines and instructions. We included pain medication in the protocol. It further included that each dog sterilized with Neutersol would be identified by tattooing an approximately one inch “N” on the left inner ear.

In addition to the established protocol, we developed certificates of chemical sterilization, consent forms for injectable chemical sterilization, tattooing guidelines and Neutersol after care instructions. SNAP then began to seek funding support to hold public Neutersol clinic events.

THE MEXICO STUDY

In the late fall of 2003, SNAP became aware of a study to evaluate Neutersol as a chemical sterilant in sexually mature male dogs. The program was initiated with the participation of the Mexican Government and several humane organizations in Mexico. Carlos F. Esquivel Lacroix, DVM served as program director and Hugh Wheir, DVM served as a monitor for the Center of Reproductive Science and Technology, University of Missouri-Columbia. The data was collected according to the protocol the Center designed to obtain FDA approval for use of Neutersol in sexually mature dogs.

The same parameters and criteria as used in the original trials were used and 54 owned dogs were selected for the trial. All dogs were retained for observation with their owners and veterinarians from the Public Health Department and Veterinary College visited them during the investigation. The visits were every 24 hours during the first week and then 1, 2, 4 and 6 months after injection.

The injection of dogs was carried out from November 12, 2003 (first dog injected) to January 24, 2004 (last dog injected). The injected dogs were followed until July 24, 2004. One dog developed an ulcer after injection and was castrated. The remaining 53 dogs were followed for the remainder of the study and had no abnormalities on physical examination after injection (every 24 hours during week one and then 1, 2, 4 and 6 months). The study showed that Neutersol was safe and effective for sexually mature dogs. The Center of Reproductive Science and Technology sent summary information to SNAP and informed us that the data was being submitted to the FDA for its approval process. Based upon this study and knowing that testicles do not change at ten months, SNAP made the decision to expand the use of Neutersol to include sexually mature dogs. The consent for sterilization form was changed to state, “I understand that, although the approval of the injectable sterilant was for male dogs from three to ten months of age, SNAP utilizes such product in dogs of all ages”.

THE EVENTS

After securing financial support for Neutersol from PETsMART Charities and Halliburton Foundation, SNAP began to plan public events for the its use. From our work with shelter puppies, we knew that we could deliver safe, effective, irreversible sterilization to large numbers of male dogs for the following reasons:

1. The injection of Neutersol does not require specialized facilities, equipment or supplies
2. Since general anesthesia was not required, the sterilization procedures was greatly shortened
3. A team of one veterinarian and two technicians could average 10-12 procedures per hour.

SNAP's first event was held on August 7, 2004 in Albuquerque, New Mexico with support from Hooter's Restaurant and the local Harley Davidson dealership. It was marketed as "Hooters for Neuters" in the restaurant parking lot with waitresses and bikers helping as volunteers. Our New Mexico Mobile Clinic team sterilized forty-seven (47) dogs and it was noted that a high percentage were owned by individuals that would not castrate their dogs. Clients seemed very pleased that they could stay with their dogs and observe the entire process. Over the next four months, the New Mexico team did events in Grants, NM, Valencia, NM, Deming, NM, and Albuquerque, NM for a total of 249 dogs. As per an agreement with the Navajo Nation, no animals over ten months of age were injected on their lands.

SNAP's first event in Texas was held in Baytown, Texas on October 5, 2004 by the Houston teams. This event was used to train teams and improve event efficiencies. Prior to the check-in process, all dogs were examined to determine acceptance for sterilization with Neutersol. Computers were used for check-in and medical records. Multiple stations and teams were used for the procedures. A recovery area was designated with crates and volunteers to monitor the dogs. The event was held in a city park building but SNAP had one of our mobile units in the park for emergency use should it be needed. Seventy-five (75) dogs were sterilized at this event.

The Houston Mobile Clinic team then held events in Galveston, Texas (77 dogs), Katy, Texas (113 dogs), Houston, Texas (61 dogs), Austin, Texas (121 dogs) and Lake Jackson, Texas (66 dogs). A SNAP veterinarian traveled to Marshall, Texas on three occasions and injected 153 dogs. Additionally, 77 clients using our mobile clinic chose Neutersol as their preferred method of sterilization. This team did a total of 743 dogs.

The Houston Surgery Clinic team (stationary facility) injected 429 dogs when the owners chose this as the preferred method of sterilization. Unlike the clients utilizing the free services at events, these clients paid $35 for the procedure.

The San Antonio team held their first event on November 13, 2004 at the Bexar County Humane Society/SPCA facility. The response was overwhelming with 254 owners checking in for the procedure. With

only two veterinary teams working, the lines and wait were very long. Additional Neutersol had to be brought over from Houston after the on-site supply was depleted. A few clients left due to the wait but, at the end of the day, 216 male dogs were injected. Each team averaged injecting 12 dogs per hour. A second event was held at the same facility in January of 2005 and another 101 dogs were sterilized.

By the spring of 2005, Addison Biological Laboratory had ceased production of Neutersol and SNAP could no longer obtain product. The last event was held in late April of 2005. In a nine month period from August 2004 through April 2005, SNAP had injected 1,738 male dogs with Neutersol.

AFTER CARE INSTRUCTIONS

Since SNAP was using a new product and technology, very thorough after care instructions were given to all owners of the dogs that were sterilized with Neutersol. They were told normal side effects:

1. Mild swelling of the testicles is expected
2. Dogs may vomit within a few minutes to four hours after the injection
3. Lethargy related to nausea in the first 24 hours
4. Sensitivity to testicular palpation in the first 24 hours

The clients were told that Neutersol may not kill sperm present at the time of injection and that they should keep their dog away from females in heat for at least 60 days.

The clients were instructed that to minimize the occurrence of post injection problems, such as scrotal irritation, inflammation or infection, it was important to closely monitor their dog's activity. They were instructed to take precautions necessary to prevent injury to the testicles and prevent their dog from licking or biting the scrotal area. They were instructed that for the first seven days after injection they should:

1. Restrict the dog's exercise to leash walking
2. Not allow the dog to run, jump or engage in play activity

3. Not allow the dog to lie on hard or wet surfaces
4. Not allow the dog to lick or bite the scrotal area

The clients were provided telephone numbers for both the appropriate program manager and the emergency pager number for their area. They were told to call the emergency number immediately if they noticed the dog licking or biting the scrotal area or if they saw signs of redness, discharge or broken skin in the scrotal area. For general questions about the product or the animal's condition, they were encouraged to call the program manager.

ADVERSE EVENTS

Of the 1,738 dogs injected with Neutersol, twelve (12) were seen by various veterinary clinics or emergency clinics. Seven (7) dogs seen by veterinary clinics required only minor care such as exams, pain medication, etc. The remaining five (5) dogs were determined by the examining veterinarian to require surgical treatment and received surgical castration or scrotal ablation. SNAP paid for or provided all after care services.

Case 1 was a 10 pound dog injected on November 13, 2004. The owner took the dog to her private veterinarian on November 20th. The veterinarian did an exam and dispensed antibiotics and prednisone. On November 24th, the owner returned to her veterinarian and the dog was castrated.

Case 2 was a four year old Beagle brought to an emergency clinic with an "open wound" six days after injection with Neutersol. The emergency clinic did a routine scrotal ablation and the dog went home the next day.

Case 3 was a 2 year old male Chihuahua that had been injected on December 7, 2004. The owner presented the dog at the SNAP Wellness Clinic where it was determined that both testicles were ulcerated and infected. A SNAP veterinarian performed a scrotal ablation on December 18, 2004.

Case 4 was a 2 and a half year old, forty pound dog that was injected on December 11, 2004. On December 23, 2004, the dog was presented to the SNAP Surgery Clinic with a scrotal ulcer, scrotal inflammation and swelling. The dog was treated with antibiotics and pain medication. The client was given an e-collar and encouraged to apply hydrotherapy (warm water spray on the scrotal area) daily. The dog returned on January 6, 2005 and a scrotal ablation surgery was done.

Case 5 was an eleven month old, 58 pound Blue Heeler that was injected on January 29, 2005. The dog was presented to an emergency clinic on February 2, 2005. The examining veterinarian described an opening into the scrotum as a result of an abscessed left testicle. The emergency clinic performed a scrotal ablation that evening.

Although case 5 was only eleven months old, all five significant adverse events occurred in dogs older that the label approved ten months. While this may have significance, it is my opinion that proper technique is the critical factor. Any miss-injection or leakage of Neutersol will cause ulcers, necrosis and/or inflammation. When veterinarians are injecting 10-12 dogs per hour they must be very careful to not sacrifice technique for speed.

SUMMARY

In the search to find additional tools to use in reducing animal overpopulation, SNAP utilized Neutersol to sterilize 1,738 dogs in Texas and New Mexico in 2004 and 2005. The product was preferred to castration by some owners and proved to be an effective and efficient way of sterilizing male dogs. While there were no deaths related to Neutersol, there were five adverse events that required surgical correction.