



5th International Symposium on  
Non-Surgical Contraceptive Methods of Pet Population Control  
June 22, 2013, Portland, Oregon, U.S.

Slow release GnRH agonist implants- mode of action and their use as a contraceptive for dogs and cats

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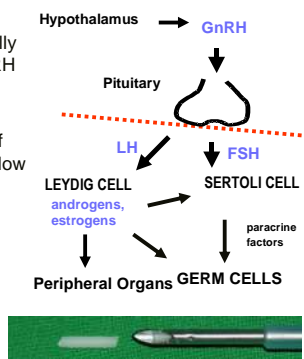
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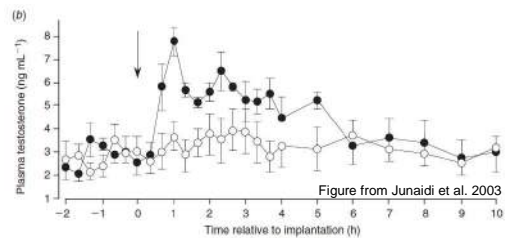
## Principle of Downregulation

- Secretion of GnRH physiologically pulsatile => upregulation of GnRH receptors
- A higher and constant release of GnRH, e.g. by application of a slow release GnRH-implant, causes downregulation of the pituitary GnRH-receptors
- Efficacy is proven in male and female dog, cat and ferret



## Use in male dogs

- Initial changes in testosterone concentrations:



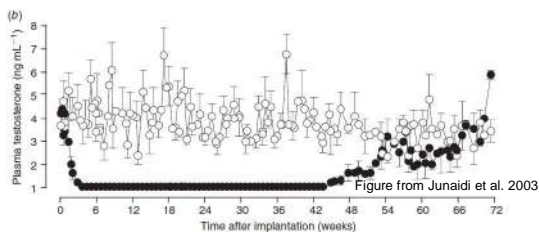
- stimulation after 40 min
- peak after 60 min

Junaidi et al. 2003



## Use in male dogs

- Long-term basal testosterone concentrations:



- basal T after 21-27 days

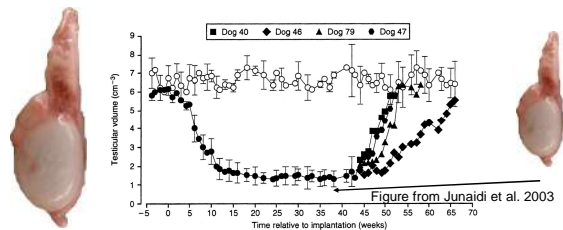
Junaidi et al. 2003



## Use in male dogs

- Further changes as a consequence of testosterone withdrawal:

- significant decrease of testicular size to 35% of initial size after 14 weeks
- significant decrease of prostate volume



Junaidi et al. 2003, 2007, 2009; Goericke-Pesch et al. 2009; Romagnoli et al. 2012

### Use in male dogs

**Further changes as a consequence of testosterone withdrawal:**

- changes in semen quality: initial decrease in semen concentration and motility and increase in pathomorphology (Junaidi et al. 2003) **BUT** initial increase in semen quality post treatment (Romagnoli et al. 2012)

Figure from Junaidi et al. 2003

Junaidi et al. 2003

### Use in male dogs

**Further changes as a consequence of testosterone withdrawal:**

- no ejaculates to be obtained after 42 days (Junaidi et al. 2003), complete sterility on days 23-84 (23, 40, 51, 60, 70, 84) (Romagnoli et al. 2012)
- histological arrest of spermatogenesis on spermatogonia/spermatocytes

Riesenbeck et al. 2002; Junaidi et al. 2003; Goericke-Pesch et al. 2009

### Use in male dogs

**All effects are fully reversible:**

- testosterone increase, back to normal
- increase of testicular and prostate volume
- normal semen parameters and recovery of spermatogenesis

Figure from Junaidi et al. 2003

Riesenbeck et al. 2002; Junaidi et al. 2003; Goericke-Pesch et al. 2009

### Use in male dogs

**Further indications**

- androgen-related disorders:
  - benign hyperplasia of the prostate,
  - adenomas of the hepatoid glands
- treatment of behavioural problems (hypersexuality, aggressiveness) => identify dogs where castration may not be beneficial
- alopecia X

Riesenbeck et al. 2002; Goericke-Pesch et al., 2010; de Gier et al. 2012

### Use in tom cats

**Initial changes in testosterone concentrations:**

5 of 10 toms basal T after 20 days

9 of 10 toms basal T after 11 weeks

Goericke-Pesch et al. 2011

### Use in tom cats

**Long-term changes in testosterone concentrations:**

**T<0.1 ng/mL over > 15 months in all toms**

Goericke-Pesch et al. 2011

**Use in tom cats**

As a consequence of testosterone withdrawal significant decrease of testicular volume:

Week	Volume (%)
1	100
4	75
8	55
12	40
16	45
20	40
24	40
28	35
32	30
36	25

Goericke-Pesch et al. 2011

**Use in tom cats**

As a consequence of testosterone withdrawal a loss of penile spines was observed:

Goericke-Pesch et al. 2011, Novotny et al. 2012

**Use in tom cats**

Further changes as a consequence of testosterone withdrawal:

- initially increased sexual behaviour in 8/10 cats
- afterwards significantly decreased sexual behaviour from week 11/16 on
- no more urine marking
- temporary infertility: TSC ↓, motility ↓
- but: highly variable testicular histology

Goericke-Pesch et al. 2011, Ackermann et al. 2012, Novotny et al. 2012

Figure from Ackermann et al. 2012 (middle and right)

**Use in tom cats**

Full reversibility regarding all effects induced:

- rapid testosterone increase

mean duration of efficacy:  $551.9 \pm 90.1$  days; high variability

Goericke-Pesch et al. 2014

**Use in adult queens**

**Reversible contraception and suppression of estrus:**

- initial estrus induction possible: increase in fecal E2, clinical estrous signs
  - 10/10 Munson et al.
  - 20/21 Toydemir et al.
  - 4/10 Ackermann et al., 1 ovulated, 3/6 without estrous signs, but ovulation
  - Significantly lower E2 after combined megestrol acetate treatment, but also estrus induction 6/7.
- induction of ovulation (100% in estrus, 40%) possible
- induced estrus may be fertile!
- possible influence on luteal function (early P4 decrease)

Munson et al. 2001, Rubion et al. 2006, Goericke-Pesch et al. 2010, Toydemir et al. 2012, Ackermann et al. 2012

**Use in adult queens**

- estrus during treatment possible (after 138 and 155 days, resp.)
- variable duration of efficacy (4.7 mg: 483 – 1025 days, 1x > 1102 days;  $680.4 \pm 62.0$  days; 6 mg: 7.5 – 14 months; 9.4 mg: >18 months)
- reversibility of effects induced
  - estrus and ovulation induction possible
  - naturally occurring estrus
  - reversible infertility => 7/8 conceived in the first post-treatment estrus, 1/8 conceived in the third estrus
  - litter size 1-5 kittens ( $3.3 \pm 1.5$  kittens)

Munson et al. 2001, Rubion et al. 2006, Goericke-Pesch et al. 2010, Toydemir et al. 2012, Ackermann et al. 2012



## Conclusions

### **Male dog/Tom:**

- reversible downregulation of endocrine and germinative testicular function
- tom: high variability of the onset of endocrine downregulation, of the duration of efficacy and of the degree of germinative downregulation

### **Queen:**

- initial estrus induction possible
- (short/long-term) suppression of estrus
- full reversibility regarding estrus and fertility

**For short-term treatment: treatment into umbilical area instead of neck.  
Repeated treatments possible for long-term/permanent contraception.**

**GnRH agonist implants offer a suitable alternative for contraception in male dogs and male and female cats!**



**Thank you for your attention!**