Dose Determination and Efficacy of Remotely Delivered Norgestomet Implants on Contraception of White-Tailed Deer

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Management of overabundant wildlife populations using contraceptives is being considered with increasing frequency in many localities. A wide array of effective contraceptives is needed to meet a variety of management objectives. Therefore, we evaluated the synthetic progestin norgestomet for its efficacy and its minimum effective dose in free-ranging white-tailed deer (Odocoileus virginianus). We evaluated two doses of norgestomet implants (14 and 42 mg) at a site in southern Connecticut during 1992–1995. Four doses (14, 21, 28, 42 mg) of norgestomet implants were tested at a site in northern Indiana during 1993–1996. The effectiveness of norgestomet implants in preventing pregnancy was similar for the 42 mg (92%), 28 mg (100%), and 21 mg (100%) doses. There was a significant decline in efficacy using the 14 mg (48%) dose. It appears that 21 mg is approximately the lowest dose that consistently prevents reproduction in adult white-tailed deer of various sizes and ages. Norgestomet implants show promise as a highly effective contraceptive agent that is safe to treated animals and secondary consumers and simple to deliver remotely. Zoo Biol 16:31–37, 1997.

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INTRODUCTION

The demand for safe, effective contraceptive agents for use in captive and free-ranging wildlife populations continues to increase [Curtis et al., 1995; Warren, 1995]. The usefulness of a contraceptive agent is determined by several factors, including efficacy, cost, ease of delivery, and absence of harmful effects on target or nontarget species. The efficacy of reproductive inhibitors for use in several vertebrate

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species has been reviewed thoroughly [Kirpatrick and Turner, 1985; Kirkpatrick et al., 1990; Plotka and Seal, 1989; Turner et al., 1992]. Costs of contraceptives vary considerably but usually are a minor component when choosing among contraceptives. Delivery mechanisms also are evolving rapidly, allowing for efficient, safe administration of contraceptive agents [DeNicola et al., 1996]. Much of the information regarding harmful effects is lacking, but, once determined, negative effects may limit the usefulness of a contraceptive agent. Therefore, the more diverse the selection of effective agents, the greater the probability that a suitable agent will be available for each situation.

There is no ideal, universally applicable contraceptive agent available [Garrott, 1995]. Each management situation is unique and requires different contraceptive attributes to achieve optimal results. For example, surgically implanted steroidal agents may have value when the goal is long-term management of animals that are easily captured with minimal stress. Remotely delivered immunocontraceptives are effective at reducing reproductive rates in a wide variety of species, but they also have limitations.

A high level of efficacy and reversibility are valuable attributes of a contraceptive agent to be used on rare or highly valued species maintained in zoos. Temporary reproductive control also is needed where genetic considerations dictate that all animals in the population have an opportunity to breed during their life. Jacobsen et al. [1995] demonstrated 100% efficacy and reversibility by the following breeding season in a captive herd of black-tailed deer (Odocoileus hemionus columbianus) treated with remotely delivered noriestomet implants. Our primary objective was to evaluate noriestomet implant efficacy on white-tailed deer, because it has been tested on only one wildlife species. A second objective was to determine the minimal dose necessary to prevent pregnancy in white-tailed deer.

**METHODS**

**Study Sites**

We evaluated noriestomet implants on two enclosed, unhunted deer herds, one in southern Connecticut and the other in northern Indiana. The Connecticut enclosure was 1.76 km² of predominantly wooded habitat, and deer were habituated to humans [Swihart et al., 1995]. All deer at the Connecticut site had been previously captured, marked with ear tags, and fitted with radio collars to facilitate identification and to ensure that treated deer could be located for later observation. Supplemental feed (12% protein commercial horse feed) was provided at the Connecticut site to ensure that does would be maintained on a good nutritional plane.

The Indiana site was 10 km² and composed primarily of open herbaceous vegetation. Some deer had been captured previously and marked with ear tags, whereas others were treated and ear-tagged at the time of capture.

**Norgestomet Implant Formulation**

Remote delivery projectiles, termed biobullets, are composed of a biocompatible outer casing of approximately 50% hydroxypropyl cellulose and 50% calcium carbonate. There is a silicone matrix rod impregnated with each of the four doses tested (14, 21, 28, 42 mg) contained within the biobullet casing [see Jacobsen et al., 1995]. Upon intramuscular administration, the outer casing dissolves after a few
hours. The remaining controlled release silicone implant then emits a daily dose of norgestomet for ≥6 months [Jacobsen et al., 1995]. Biobullets were manufactured by Antech Laboratories, Inc. (Savoy, IL 61874).

Norgestomet Delivery

In Connecticut we treated seven does with 42 mg norgestomet implants from 10–13 October 1992. Does ranged in age from 3.5–11.5 years. Does were aged using standard tooth wear criteria [Severinghaus, 1949]. An additional 18 does were treated with 42 mg norgestomet implants from 24 August to 3 October 1993. Does ranged in age from 2.5–10.5 years. We also treated 12 does with 14 mg norgestomet implants from 12–15 August 1994. Does ranged in age from 2.5–11.5 years.

Norgestomet was delivered using a remote delivery system and projectiles tested and calibrated by DeNicola et al. [1996]. We approached does in a vehicle and shot them in the hindquarters from distances <35 m. We used the same protocol to treat an additional 11 control does with placebo projectiles filled with lactose in 1992. Control does (n = 12) were not administered placebo projectiles in 1993–1994 because the contraceptive trials from the previous year showed no effect on stress or fertility due to placebo projectile delivery. Control does ranged in age from 2.5–8.5 years in 1992–1994. We determined treatment efficacy by observing whether does had mammary gland development or were accompanied by fawns in May and June following treatment.

In Indiana we treated 13 does with 42 mg norgestomet implants and 13 does with 28 mg norgestomet implants from 31 August to 11 September 1993. Does ranged in age from 3.5–7.5 years. Does were captured using darting techniques, ear-tagged, and then administered the projectiles impregnated with norgestomet in the center of the hindquarter from 3 m [DeNicola et al., 1996]. Twenty-six does captured previously served as controls. We determined treatment efficacy in May and June following treatment by observing from a vehicle the presence or absence of mammary gland development.

We also treated 11 does with 14 mg norgestomet implants from 15–20 October 1994 in Indiana. Does ranged in age from 2.5–7.5 years. We approached marked does in a vehicle and shot them in the hindquarters from distances <35 m. Treated does were euthanized in March 1995 to determine treatment efficacy by recording the presence or absence of fetuses. Control deer consisted of 19 does that had been marked before the trial and were euthanized the following August.

An additional 9 does were administered 21 mg norgestomet implants from 25 August to 3 September 1995 in Indiana. Does ranged in age from 1.5–6.5 years. Does were treated as described above for does administered 42 and 28 mg norgestomet implants in Indiana. Contraceptive results were collected by euthanizing treated does in March 1996 and recording the presence or absence of fetuses. Control deer consisted of 14 does that had been marked before the trial and were euthanized at the same time in March 1996. Data were analyzed using chi-square tests for homogeneity of proportions [Zar, 1984].

RESULTS

In Connecticut, one of the seven does treated with a 42 mg norgestomet implant in 1992 reproduced the following spring, and two of 18 does treated in 1993 repro-

<table>
<thead>
<tr>
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<th>Dose (mg)</th>
<th>Control</th>
<th>Treated</th>
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<tr>
<td>Indiana 1993</td>
<td>31 August to 11 September</td>
<td>42</td>
<td>25/26 (96%)</td>
</tr>
<tr>
<td></td>
<td>31 August to 11 September</td>
<td>28</td>
<td>25/26 (96%)</td>
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<td></td>
<td>15–20 October 1994</td>
<td>14</td>
<td>17/19 (89%)</td>
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<tr>
<td></td>
<td>25 August to 3 September 1995</td>
<td>21</td>
<td>13/14 (93%)</td>
</tr>
<tr>
<td>Connecticut 1992</td>
<td>10–13 October 1992</td>
<td>42</td>
<td>11/11 (100%)</td>
</tr>
<tr>
<td></td>
<td>Combined 1994</td>
<td>42</td>
<td>19/23 (83%)</td>
</tr>
<tr>
<td></td>
<td>12–15 August 1994</td>
<td>14</td>
<td>11/12 (92%)</td>
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<tr>
<td>Total</td>
<td></td>
<td>85/94 (90%)</td>
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*Indicates a significant difference from the control ($P < 0.01$).

**Indicates a significant difference from the control ($P < 0.05$).

duced. Because proportions were comparable between years, ($\chi^2 = 0.04$, d.f. = 1, $P > 0.50$), data were pooled for comparison with control does (Table 1). Nineteen of the 23 control deer reproduced. The percentage of does reproducing in the treated group (12%), relative to control (83%) does, was significant ($\chi^2 = 24.1$, d.f. = 1, $P < 0.001$). Six of the 12 does treated with 14 mg norgestomet implants in fall 1994 reproduced. Four of the six treated does that reproduced gave birth in August. Eleven of the 12 control does also reproduced. The reduction in fertility, although less pronounced (50% vs. 92%) than for the 42 mg dose, was significant ($\chi^2 = 5.04$, d.f. = 1, $P < 0.05$).

In Indiana, none of the 13 does administered 28 or 42 mg norgestomet implants in 1993 reproduced. The reproductive status of two does treated with 28 mg norgestomet implants could not be determined with certainty, and they were omitted from data analysis. Twenty-five of 26 (96%) control does reproduced in spring 1994. Levels of fertility were significantly reduced for the 42 mg dose (0%, $\chi^2 = 34.99$, d.f. = 1, $P < 0.0001$) and the 28 mg dose (0%, $\chi^2 = 32.23$, $P < 0.0001$).

None of the nine does administered 21 mg norgestomet in 1995 reproduced. One of the treated does was not pregnant but did have an active corpus luteum on one ovary, indicating that ovulation had occurred in early March. Two additional does had antral follicles (3–4 mm). Thirteen of 14 (93%) control does were pregnant in March 1996. Levels of fertility were significantly reduced for the 21 mg dose (0%, $\chi^2 = 6.78$, d.f. = 1, $P < 0.005$).

Consistent with results from Connecticut, the reduction in fertility was significant but less pronounced for Indiana does treated with 14 mg norgestomet implants ($\chi^2 = 4.52$, d.f. = 1, $P < 0.05$). Upon necropsy of the 11 deer euthanized in Indiana in March 1995, six were pregnant (55%). Three of the six treated does that were
pregnant contained 1–2-month-old fetuses, whereas the other three does had fetuses of size comparable to the control does (~4 months old). One of the treated does was not pregnant but did have an active corpus luteum on one ovary, indicating that ovulation had occurred in late February. Seventeen of 19 control does (89%) were lactating when euthanized in August 1995.

A test of homogeneity of proportions across treatments showed significant differences ($\chi^2 = 20.44$, d.f. = 3, $P < 0.001$).

However, the majority (70%) of this difference was attributable to a reduced efficacy of the 14 mg treatment.

**DISCUSSION**

Jacobsen et al. [1995] found that norgestomet implants (42 mg) were 100% effective in preventing reproduction in black-tailed deer, and the efficacy of our 42 mg dose was comparable when used on white-tailed deer. We were successful in preventing conception in 88% of does treated remotely with 42 mg of norgestomet in Connecticut and 100% of the does treated in Indiana. Our inability to verify whether each biobullet was delivered appropriately under field conditions may have been the cause for the failure to reach 100% efficacy at the Connecticut site. In some instances implants were delivered at night from a vehicle with the aid of a spotlight. Therefore, we were not always able to observe and verify the point of biobullet impact. There also was the potential for problems when treating deer in areas of dense understory vegetation. We were unable to determine if the implant had been deflected slightly and not hit the animal squarely. In most instances the sound of the implant hitting the deer could be heard, but the implant may not have entered the skin. The dense vegetation also would prevent the shooter from observing whether there was any sign that the implant had penetrated the skin (e.g., a droplet of blood at the point of impact).

Our second objective was to determine the lowest dose that would provide efficacy similar to the 42 mg dose. Our trials indicated that a substantial decline in effectiveness resulted when using a 14 mg implant at both sites, with some does conceiving in late February. Such a late conception date presumably would lead to elevated levels of mortality in does and their fawns. Thus, we evaluated a slightly higher dose (21 mg) to prevent conception in the latter part of the breeding season.

The 21 mg dose prevented reproduction in 100% of the treated does. This appears to be the approximate optimal dose for white-tailed deer, in that it exposes the treated does and potential secondary consumers to the lowest amount of steroids and yet is highly effective. Because three does showed signs of ovarian activity in March, the end of the breeding season, the 28 mg dose may be appropriate if treatments are administered before September.

As previously mentioned, numerous contraceptive agents have been evaluated. However, the potential negative effects of each agent deserve consideration to determine their suitability under varying circumstances. For example, steroidal contraceptive agents have been demonstrated to be highly effective in several species [Jacobsen et al., 1995; Matschke, 1980; Plotka and Seal, 1989]. One delivery approach has been through the surgical implantation of controlled release silicone rods [Matschke, 1980; Plotka and Seal, 1989]. However, this technique is labor-intensive and costly and subjects the target animal to substantial stress [Eagle et al., 1992;
Garrot et al., 1992). In addition, conception by treated females can lead to complications and death of the female and fetuses [Plotka and Seal, 1989].

Immunocontraceptives, particularly porcine zona pellucida (pZP), show promise as a versatile means to prevent reproduction [Turner and Kirkpatrick, 1991; Turner et al., 1992]. However, there are potential problems associated with the postponement of conception in free-ranging wildlife. In particular, because white-tailed deer vary in their immune system responses when treated with the pZP immunocontraceptive [Turner et al., 1996], differences in the duration of effectiveness may result. This could result in blood titers falling below effective levels in some does during late winter. Because white-tailed deer exhibit polyestrous behavior and can breed into early March [Turner et al., 1992], does that come into estrus at this time and are impregnated will give birth from late August to early October. This rarely occurs in wild populations, and therefore the implications for fawns and does are unknown. It is likely that late-season fawns probably would incur greater mortality, due to entering winter with low body mass and with insufficient energy reserves.

Another consideration is that the effects of long-term exposure of deer to vaccines are unknown. For example, repeated treatment of other species with the pZP vaccine can result in permanent sterilization [see Kirkpatrick et al., 1992]. Finally, because there is considerable variation in efficacy between and within species, situations requiring 100% reduction in fertility may necessitate the use of another agent.

In contrast to the aforementioned contraceptive agents, the synthetic progestin norgestomet, when remotely delivered before the mating season, avoids problems with practicality of delivery, compromised efficacy, complications during parturition, or postponement of conception [Jacobsen et al., 1995; Kesler, in press; Plotka and Seal, 1989]. In addition, norgestomet has been demonstrated to be safe to both treated animals and secondary consumers [reviewed by Kesler, in press]. Furthermore, it has been approved by the Food and Drug Administration for use in cattle entering the human food chain. Whether steroids pose a real or perceived threat to consumers of treated does has yet to be resolved [Garrott, 1995]. Regardless, it appears that misconceptions about the potential negative effects of human exposure to steroids will limit the applications of norgestomet on free-ranging wildlife species. Pending resolution of this debate, the use of norgestomet and other synthetic steroids on free-ranging deer will most likely be restricted. Nonetheless, there is still great potential for its use in captive herds and zoo populations where there is no concern over the human consumption of treated animals.

CONCLUSIONS

1. Pregnancy was prevented in 92% of does treated with 42 mg norgestomet implants over 3 years.
2. None of the does treated with 28 mg norgestomet implants reproduced for 1 year at one of two sites (Indiana).
3. Norgestomet implants (21 mg) prevented pregnancy in 100% of treated does for 1 year at the Indiana site.
4. Fifty-two percent of does treated with 14 mg norgestomet implants reproduced between the two research sites.
5. A dose of 21 mg appears to be the lowest dose that prevented pregnancy consistently in white-tailed deer of various sizes and ages.
6. Norgestomet is a highly effective contraceptive agent that is safe to secondary consumers and treated animals and simple to deliver.

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REFERENCES


