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The Development of Contraceptive Methods for Captive Wildlife

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Abstract: Contraception has become critical in managing zoo populations, both to limit production of surplus animals and to promote genetic health. One role of the Contraception Advisory Group, formed in 1989, is to coordinate research to develop new contraceptive methods. Because melengestrol acetate (MGA) implants, which have been used by zoos for almost 20 years, recently have been associated with uterine pathology in felids, several new contraceptive techniques are being evaluated. These include other steroid hormone formulations, such as the birth control pill Depo-Provera,® the Norplant® implant, and MGA added to feed; bisdiamine, an oral male contraceptive; zona pellucida (ZP) vaccine; and vas plugs. Bisdiamine reversibly blocked spermatogenesis while sparing testosterone in its first test in gray wolves. ZP vaccine has been effective in preventing births in a variety of species of hoofstock, primates, and carnivores; however, long-term deleterious effects on the ovaries have been found in some controlled trials. Injectable vas plugs that conform to the shape of the vas make it possible to successfully treat a wide variety of species; reversal trials are currently underway. As research efforts continue, we hope to expand our collaborations with scientists working on contraceptive development for humans, companion animals and wildlife, to better make use of the limited resources available for these investigations.

Keywords: contraception, captive animals, zoo, vas plugs, bisdiamine, indenopyridine, zona pellucida vaccine, GnRH agonist, LHRH vaccine

Introduction

The modern zoo now faces the consequences of becoming too successful at breeding and maintaining the animals in its care. Advances in husbandry, nutrition, and medicine have resulted in more births and longer lives for most captive species. The major benefit of this success is that these captive populations can be self-perpetuating and not dependent on importation of animals from the wild. However, due to limited space and resources, zoos cannot allow uncontrolled reproduction.

In addition, zoos give high priority to proper genetic management, that is, reduction of inbreeding and balanced genetic representation of the founders of captive populations. Both genetic management and limiting production of surplus animals are being accomplished through contraception.

Although physical separation of males and females can prevent unwanted conceptions, most zoos consider this an undesirable measure. Not only can such an arrangement be stressful for species in which males and females typically associate, lone animals present an unnatural view of that species to the visiting public. A primary mission of zoos is education, a mission that is better served by maintaining animals in social groupings which are as representative as possible of the organization that would occur in the wild.

In recognition of the importance of contraception in responsible animal management, the American Association of Zoos and Aquariums approved formation of the Contraception Advisory Group in 1989. Composed of zoo curators, veterinarians, and reproductive physiologists, the group surveys the use of contraception in zoos for inclusion in a computerized data base, advises zoo personnel, and initiates and coordinates research into alternative methods.

The International Wildlife Contraception Database, housed at the St. Louis Zoo, was developed and is maintained by Ingrid Porton and Betsy Hornbeck of the Contraception Advisory Group. Begun in 1990 and updated from yearly surveys, it currently contains more than 2,000 complete records on 184 species and serves as a resource for zoo animal managers and for researchers.

Contraception of captive wildlife in zoos began in the mid-1970's. After preliminary tests with lions and tigers (Seal et al. 1976, Seal and Plotka 1978) comparing medroxyprogesterone acetate (Provera,® The Upjohn Co., Kalamazoo, MI, USA) and melengestrol acetate (MGA, also Upjohn), MGA in silicone implant form was selected as the more suitable. Of the more than 80 percent of North American zoos that reported using contraception (Porton et al. 1990), most use the MGA implant.

However, concern has arisen about possible pathology in progestin-treated carnivores (Kollias 1988, Kollias et al. 1984) because deleterious effects have been associated with progestin use in domestic dogs and cats (reviewed in Asa and Porton 1991, Asa et al. 1996). Indeed, histological examination of uteri from MGA-treated felids has revealed significantly more pathology than those from untreated felids (Munson and Mason 1991).

No comparable effects are expected in primates, based on the extensive studies that have been conducted in laboratory primates, as well as decades of progestin administration to human females. In general, birth control methods that have been approved for human use should be safe and effective for nonhuman primates. Birth control pills (combination progestin and estrogen, various formulations commercially available), Depo-Provera, Norplant (levonorgestrel implant system, Wyeth–Ayerst, Philadelphia, PA, USA), and intrauterine devices have been used in primates, especially in the great apes (Porton et al. 1990). However, few data exist on progestin effects in ungulates and other mammals.

A number of research trials are under way to evaluate new approaches with the hope of providing a broader selection of contraceptives, especially alternatives to the progestin-based formulations for carnivores. These include vas plugs, the antispermatogenic compounds bisdiamine and indenopyridine, and short-term Depo-Provera for seasonal breeders. Additional work is focusing on specific aspects of MGA treatment. For a discussion of the progress of zona pellucida trials in zoos, see Kirkpatrick et al., this volume.

Melengestrol Acetate

As mentioned, MGA is the most frequently used contraceptive for captive mammals. MGA is incorporated into silicone rods by E. D. Plotka (Marshfield Medical Research Foundation, Marshfield, WI) and distributed to zoos throughout the world. When inserted subcutaneously, the implants provide effective contraception for at least 2 years (Porton et al. 1990). The only side effect noted in primates has been weight gain (Portugal and Asa 1995), which is also common in human females treated with progestins.

Because of concern about possible effects on social behavior, a study was conducted with a troop of hamadryas baboons *(Papio hamadryas)* at the St. Louis Zoo (Portugal and Asa 1995). Administration of MGA was not associated with social disruption. Treated females were involved in fewer affiliative interactions, but there was no increase in aggression compared to control animals.

Although MGA implants have been effective in a wide range of monkeys and apes, some New World primate species have proven resistant. Because they have naturally high levels of endogenous steroids, these species may require larger exogenous doses to achieve contraception. Research is being conducted to test this hypothesis (E. Plotka, pers. comm.).

Recognizing that individual capture and immobilization for implant insertion may be inadvisable in some situations, Bronx Zoo veterinarians (B. Raphael, pers. comm.) have tested adding MGA to feed for herds of antelope and deer. Although this procedure is generally successful, drawbacks include contraceptive failure in some subordinate animals that apparently did not ingest a sufficient dose and alteration of the antler cycle in male barasinga *(Cervus duvauceli)*.

Pathological effects of MGA and related progestins are being investigated by Linda Munson (University of Tennessee, Knoxville). Early work concentrated on reproductive tracts of felids (Munson and Mason 1991), and research is now extending to other carnivores and primates. In general, progestins have been found to stimulate growth of the uterine lining of felids and canids, resulting in hyperplasia, pyometra, and neoplasia (reviewed in Asa and Porton 1991). Effects of dosage, length of treatment, and age during treatment are currently being studied.

Depo-Provera

The belief that side effects can be minimized by a shorter treatment period has created interest in the progestin medroxyprogesterone acetate in its injectable, slow-release formulation. In particular, seasonal breeders that are fertile for only part of the year might benefit from progestin exposure for only that period, as opposed to the continual, long-term exposure imposed by an implant. An injection every 2–3 months is thought to be preferable to the repeated surgical procedures required for implant insertion and removal.

Dose/response trials and evaluation of weight gain have been conducted with ruffed lemurs *(Varecia variegata)* and black lemurs *(L. macaco)* at the St. Louis Zoo, in collaboration with the Henson–Robinson and Metro Toronto zoos. Using vaginal cytology to monitor suppression of cycles, researchers found the minimum effective dose to be 5 mg per kilogram of body weight. Pelage darkening in treated black lemur females was an unexpected side effect, probably related to the ability of this progestin to bind androgen receptors (Labrie et al. 1987). (Black lemurs are sexually dimorphic in color, with males having a black and females a brown coat).

Depo-Provera also is being used in hippopotamuses *(Choeropsis liberiensis),* giraffes *(Giraffa camelopardus),* sea lions *(Zalophus californianus),* and gray seals *(Halichoerus grypus),* although not part of controlled research projects. There is concern about sea lions and seals, in particular, because they are closely related to the carnivores and because they have extensive fat stores that may absorb and hold steroids, which are lipophilic. Fat stores may also present a problem with hippos.

Norplant

Although no controlled studies have been published, several zoos are using these implants, which contain levonorgestrel, a synthetic progestin related to both MGA and Provera. Its advantage over MGA is the much thinner capsules, which can be inserted with a trocar. Compared to the incision and sutures needed for the MGA implants, the small puncture site attracts less grooming and reduces the chance of loss.

Birth Control Pills

As with Norplant, some zoos opt to use oral birth control pills, another product developed for the human market. The willingness of many apes to take pills placed in food treats dispenses with the need for immobilization and insertion of an implant. The vast majority of pills contain estrogen in combination with a much lower dose of progestin than is present in the progestin-only forms discussed above. Although this combination does not significantly alter the associated side effects for primates, it is not appropriate for carnivores. Adding estrogen to progestin in formulations given to dogs exacerbates uterine pathology (Teunissen 1952).

Megestrol Acetate

Another synthetic progestin—available as Megace® (Mead Johnson Laboratories, Evansville, IN, USA) or Ovaban® (Schering–Plough, Union, NJ, USA)—is sometimes used as a contraceptive in domestic dogs and cats. However, because of the attendant risk of hyperplasia and pyometra, this synthetic it is not recommended for more than two consecutive treatments.

Lupron Depot®

An agonist of GnRH (gonadotropin-releasing hormone also called LHRH, luteinizing-hormone releasing hormone), Lupron Depot (TAP Pharmaceuticals, North Chicago, IL, USA) has been used in males of several species in attempts to block spermatogenesis. Although theoretically tenable, this approach has been unsuccessful due to incomplete suppression of sperm production. Sperm numbers must be reduced below the level required for fertilization for this to be an effective contraceptive. Because the GnRH agonists and antagonists block production of testosterone, they

also can find application in suppression of aggression in some individuals.

Lupron Depot also has been given to females to suppress cyclicity. However, because agonists first stimulate the endocrine cascade that results in ovulation, administration to induced ovulators, such as the felids, may stimulate ovulation and pseudopregnancy before suppressing cycles by negative feedback.

Although analogues show promise in providing the equivalent of reversible chemical castrations, their current cost prohibits for widespread use. Long-term delivery also is a problem. Because these compounds are not orally active and do not follow the same diffusion dynamics as steroids, traditional delivery methods such as silicone implants have not been effective. Both a silicone elastomer matrix and a reservoir system are being tested (Vickery et al. 1989).

LHRH Vaccine

Immunization against LHRH can provide contraception for both males and females (Fraser 1986). LHRH initiates the cascade of hormonal events that results in testosterone and sperm production in males and in production of estrogen and progesterone and ovulation in females. Because this vaccination would accomplish the equivalent of a reversible chemical castration, it can be especially appropriate for males to suppress testosterone and thus aggression and for female carnivores to completely suppress secretion of progesterone. Vaxstrate, an LHRH vaccine that is commercially available in Australia (Arthur Webster Pty. Ltd., New South Wales, Australia) for domestic cows (Hoskinson et al. 1990), has also been used with success in some exotic species at the Western Plains and Perth zoos (D. Blyde and S. Haigh, pers. comm.). In this country, both The Population Council in New York and Colorado State University are developing LHRH vaccines.

Bisdiamine

All the steroid hormone preparations in use in zoos target the female. However, if prevention of reproduction is desired in polygynous social groups, it is more efficient to treat the males than the females. The bisdiamine WIN 18,446 (Sterling Winthrop, Rensselaer, NY, USA) was tested in the early 1960's as a birth control pill for men. It works by selectively interfering with spermatogenesis but not testosterone production. Although initial trials demonstrated the drug to be effective, safe, and reversible, it was soon discovered to interact with an enzyme that detoxifies alcohol. Thus, men taking bisdiamine who then drank alcohol became ill, making the compound unsuitable for general marketing. Because we assume that we can prevent alcohol consumption in captive animals, bisdiamine may be a feasible contraceptive alternative for this application.

The first test of bisdiamine in a wildlife species was conducted with a captive colony of gray wolves (Asa et al. 1995). Daily administration in ground meat at a dose of 200 mg/kg suppressed spermatogenesis without affecting mating behavior. In the subsequent breeding season, semen samples of the previously treated males were comparable to those of controls, confirming reversibility.

Indenopyridine

This drug (Research Triangle Institute, Research Triangle Park, NC, USA) is similar to bisdiamine in that it is orally active and blocks sperm production without interrupting testosterone secretion. To date, it has been tested only in rodents (Fail et al. 1991, Gurtler and Donatsch 1979, Hodel and Suter 1978), so the extent of its efficacy and safety has not been adequately determined. A dose response trial with domestic cats, as a model for exotic felids, is currently being conducted (Fail et al., unpubl.)

Vas Plugs

L.J.D. Zaneveld and I investigated vas plugs. Silicone injected into the vas deferens, the tube carrying sperm from the testis, hardens to form a barrier that prevents the passage of sperm. Plugs were placed in 59 mammals, including marsupials, felids, primates, and ungulates, at 17 different zoos. Early use of the preformed plug (Zaneveld et al. 1988), which is also in clinical trials with humans, proved inadequate for the range of vas sizes encountered in zoo animals. The injectable plugs were successful in blocking passage of sperm, but fertility was not restored after removal.

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Haigh, Stephanie. Perth Zoo, South Perth, Western Australia.

Plotka, Ed. Marshfield Medical Research Foundation, Marshfield, WI 54449, U.S.A.

Raphael, Bonnie. Animal Medical Center, Bronx Zoo, New York, NY 10460, U.S.A.