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What RU-486 means for animals

WASHINGTON D.C.--The pharmacological race to be first to market a safe, affordable, easily administered contraceptive drug for dogs, cats, and nuisance wildlife may have heated up with the September 28, 2000 decision of the U.S. Food and Drug Administration to allow Danco Laboratories, of New York City, to market the RU-486 abortion pill.

The Danco formulation, called Mifeprex, includes five separate tablets, to be taken in a two-step sequence. The first three tablets, taken at once, contain mifepristone. Better known by the chemical index number RU-486, mifepristone is an androgen steroid which blocks the production of progesterone, a hormone required to sustain pregnancy. Two days after taking the mifepristone tablets, the user takes two more tablets containing misoprostol, another hormonal drug which causes her body to expell the aborted fetal tissue.

Mifepristone is a close chemical relative of mibolerone, an androgen steroid developed and manufactured by the Upjohn Company. Mibolerone has been used by prescription for more than 20 years to suppress estrus in racing greyhounds, sled dogs, some show dogs, and many species of animals kept in zoos, but has not been marketed to the general public.

Mibolerone has never been available for use in controlling populations of street dogs, partly because of the difficulty involved in providing the necessary regular doses, but mostly because of political opposition.

In theory, mibolerone could be mixed with food and fed as

necessary to street dogs recognized by a neighborhood caretaker. Proper precautions, such as feeding only one dog at a time, could minimize the risk of overdose or underdose.

In present formulations, mibolerone is not cost-competitive with surgical spaying. It also doesn't offer the advantages of surgical spaying in modifying animal behavior to increase compatibility in human households. In addition, unlike immunocontraception drugs, which have been developed more recently, mibolerone cannot be given in stronger dosage to induce permanent sterility. Indeed, one advantage of mibolerone for temporary use by zookeepers and owners of racing dog or show dog kennels is that the animals can readily breed if regular doses are discontinued.

If manufactured in sufficient volume and in appropriate formulations, however, mibolerone could become much less expensive-- and could become an efficient humane means of controlling street dog or feral cat reproduction temporarily while rescuers catch and spay the females. Stabilizing numbers of street dogs or cats and beginning to achieve a reduction typically requires sterilizing approximately 70%. Getting to 70% by catch-and-spay process often seems painfully slow to communities eager to rid themselves of animals perceived as public health threats, even when the dogs or cats are also part of those communities' first line of defense against vermin.

Meanwhile, until the rescuers reach 70%, sterilizing part of the population can actually increase the numbers of dogs or cats because there is less competition for food among pregnant females, who then bear more live young, and nurse longer, and because more puppies or kittens from each litter survive.

The use of mibolerone could accordingly save millions of animals per year from being poisoned, shot, drowned, electrocuted, or gassed with car exhaust, which are the typical fates of street dogs, especially,

and sometimes feral cats too in parts of Asia, Africa, and Latin America. In those places, rabies continues to kill thousands of humans each year, the majority of them young children who play with street dogs, while the barbituates used to dispatch animals by needle are either not affordable, not legally sold, or are simply not available.

Anti-rabies inoculation and surgical neutering have been introduced throughout the world in recent years, but have just begun to become affordable in many underdeveloped nations, where the amount of sterilization surgery needed to reduce the numbers of street animals continues to far exceed the amount that veterinarians can quickly accomplish.

By preventing births in advance of surgery, mibolerone could markedly reduce the numbers of dogs to be vaccinated and sterilized eventually. Seventy percent of the females could be taken out of the breeding population almost overnight, pending sterilization surgery.

A similar product for cats could prevent the growth of an immense feral cat population to take over the food sources and shelter vacated by falling numbers of dogs--a phenomenon retrospectively evident but not recognized in U.S. animal control pickup data from the 1970s and 1980s.

Scarcely even considered a serious animal control problem by most public health authorities circa 1960, U.S. animal shelter feral cat intake soared throughout the next three decades in almost inverse proportion to dog intake, which has fallen steadily since the mid-1960s.

Feral cat intake has, however, fallen rapidly since the advent of neuter/return in the early 1990s, especially in cities like San Francisco and San Diego, which have long had very large and aggressive donor-funded feral cat sterilization programs.

Culture clash

Despite the potential benefits to be had from introducing mibolerone into the animal care-and-control chemical arsenal, the cultural obstacles to making it more widely available have proved immense.

Upjohn and the Carnation Company began developing a contraceptive dog food with mibolerone as the active ingredient in 1975. In August 1980, the same year that RU-486 was first synthesized by French chemical researcher Emile Baulieu, Carnation pet food division director L.G. Miller, Ph.D., wrote to Long Island animal rescuer Severa Agüero that the contraceptive dog food was almost ready to sell.

"We are currently involved with the FDA to get clearance on our birth control dog food," Miller confirmed. "We may receive a marketing permit on our product this year," Miller continued. "We would then be able to market the product through veterinarians. Hopefully in a couple of years we could market the product through retail stores."

Approval for distribution of mibolerone as an Upjohn product called Cheque Drops was obtained, after testing at racing greyhound kennels. Cheque Drops caught on with greyhound racers, and use soon spread to sled dogs. The Iditarod and other major dog sled races prohibit giving the dogs steroids or other drugs with similar effects, but mibolerone is exempted.

But all did not go well for Carnation --not because of any problems associated with giving mibolerone to dogs, but because of fallout from mifepristone testing in France by the original manufacturer, Rousel Ucalf, a subsidiary of the German firm Hoescht A.G.

As well as having contraceptive properties, mifepristone was in 1982 discovered to be an abortifacient. That projected the entire mibolerone chemical family into the middle of the international controversy over human abortion.

Opposition to human abortion was just reaching peak momentum,

worldwide. Then-U.S. President Ronald Reagan had been swept into office in 1980 partly for his opposition to the 1973 Roe-vs.-Wade U.S. Supreme Court decision legalizing abortion. Reagan received his strongest voting support from religious Catholics and Christian fundamentalists.

Also in 1980, Islamic fundamentalists overthrew the Shah of Iran, bringing the late Ayahtolah Khomeini to power. Khomeini's anti-abortion views reinforced the position of most of Islam.

In India, Hindu fundamentalism rose with opposition to abortion-as-birth-control promoted by then-prime minister Indira Gandhi as a rallying focus. Ironically, the Blue Cross of India and Beauty Without Cruelty-India were actively investigating chemosterilants for street dogs, and might have eagerly promoted mibolerone had it become available to them.

Politically, it was a bad time to try to market anything with potential for causing human abortion--even if a pregnant woman would have to eat enough hard-to-stomach dog food in one meal to feed a Great Dane for a week in order to achieve abortion.

Coincidentally, advocates for the poor were just then opposing federal budget cuts proposed by the Reagan administration by amplifying stories of homeless people, senior citizens, and large low-income families who were purportedly forced to eat dog food to make ends meet.

The RU-486 issue heated up in 1983, with fallout for mibolerone, when the FDA authorized a nonprofit organization called the Population Council to begin sponsoring clinical trials of mifepristone on human volunteers at the University of Southern California.

Abortion opponents swiftly linked RU-486 and mibolerone, using the images of humans eating dog food to squelch the Upjohn/Carnation contraceptive product.

Life term for selling

Upjohn and Carnation did not give up easily. In early February 1985, Carnation pet food division new products manager Hugh Chamberlin released to media the then-current national animal shelter killing statistics and announced that Carnation would soon seek FDA approval to sell a contraceptive dog food called Extra Care in grocery stores.

"We have requested FDA clearance for over-the-counter sales of this birth control dog food. If we obtain this clearance, the product would be available in late 1985," L.G. Miller confirmed to Severa Aguero on February 25, 1985.

By 1988, RU-486 was already in general use in France and China. China, in fact, reportedly made compulsory abortion by means of forced ingestion of RU-486 a central part of a one-child-per-family policy. The violations of human rights inherent in the policy and that it was advanced by a Communist nation which was actively repressing religion made RU-486 an even larger target for the U.S. religious right.

Roussel Uclaf withdrew plans to sell RU-486 in the U.S.

The FDA then banned importation of RU-486 into the U.S.

Carnation quietly withdrew from the fight. The Extra Care brand name was trademarked but forgotten. Upjohn equally quietly continued to sell Cheque Drops, in low-key competition with a canine formulation of the human birth control drug Ovaban.

Ovaban, available for dogs since circa 1983, also has some following among sled dog racers and show dog fanciers, but apparently has unpopular side effects in some dogs, and never been successfully incorporated into dog food.

The controversy over RU-486, and by extension mibolerone, raged on. Leading scientists told Congress in 1990 that RU-486 should be

legalized for use in cancer treatment. Austria, Belgium, Britain, Denmark, Finland, Germany, Greece, Israel, the Netherlands, Russia, Spain, Sweden, and Switzerland joined France and China in approving it. The U.S. Supreme Court in 1992 upheld the FDA ban on RU-486, but President Bill Clinton lifted the ban upon taking office in January 1993, and directed the Department of Health and Human Services to investigate ways to test, license, and manufacture it.

In May 1994 Roussel Uclaf donated its patent on RU-486 to the nonprofit Population Council. Clinical trials on 2,100 women began in October 1994 at the University of California-San Francisco.

Private investors formed Danco Laboratories in 1995, specifically to market RU-486. The FDA conditionally approved RU-486 in September 1996, but required another three years of research before issuing the recent notice of final approval.

Mibolerone meanwhile came into use for treating uterine cancer in dogs--and became the canine birth control method of choice throughout northern Europe, where many nations restrict use of surgical spaying.

Mibolerone became relatively familiar to athletic officials and law enforcement during the 1990s for wholly unrelated reasons, as result of largely illegal use by body-builders--almost all of them male. Arizona eventually included mibolerone by name on a list of drugs which if given or sold to juveniles can cost the source a life term in prison.

Questions

To date, formulations using mibolerone seem to have been commercially manufactured only for use in canids. However, there seem to be no technical obstacles to making doses suitable for cats, deer, beavers, and other mammal species whose numbers may be considered

problematic. The major questions about whether Upjohn and Carnation or perhaps another pet food maker will try again to introduce a contraceptive pet food containing mibolerone center on three other issues:

* Will the U.S. religious right reimpose a ban on RU-486 and related chemicals through an Act of Congress? Republicans including Presidential candidate George W. Bush, U.S. Senator Sam Brownback of Kansas, and U.S. Representative Tom Coburn of Oklahoma indicated almost immediately that they would favor banning RU-486 et al by law. Upjohn is unlikely to do anything that might again catch mibolerone in the crossfire.

* Will the U.S. FDA action significantly influence acceptance of RU-486 and related drugs in Africa, Asia, and Latin America? In general, once a drug is widely distributed in the U.S., it becomes available worldwide, including in unauthorized "knock-offs"--as with the penile stimulant Viagra- -whether or not other nations' regulatory bodies approve. However, animal care-and-control is a sufficiently public function, even when done mostly by private nonprofit organizations, that animal rescuers are unlikely to be able to use mibolerone or locally made knock-offs without at least tacit official approval.

* Will a market still exist for mibolerone after the advent of immunocontraceptives, which might be as easily deployed and less expensive? Even more to the point for animal rescuers, will mibolerone still be of value after immunosterilants reach the market?

Vaccines

Immunocontraceptives and immunosterilants work by activating the natural bodily defenses against foreign cell tissue--from which sperm cells of the same species as the female receptor are normally exempt. The immunocontraceptives and immunosterilants closest to becoming generally

available, at least by prescription, must be given by injection.

However, the dose may be combined with anti-rabies vaccination and vaccinations against other common dog and cat diseases.

The effect of immunosterilization is not quite the same as that of sterilization surgery because the animal's behavior does not change, except in not becoming pregnant. Therefore immunosterilization may never replace spaying as the contraceptive treatment most popular with petkeepers

At the 2000 Spay-USA conference held in July at Bentley College in Waltham, Massachusetts, six leading immunocontraceptive and immunosterilant researchers agreed that final FDA approval of several promising methods may be only two to five years away. [See "Introducing a different needle," ANIMAL PEOPLE editorial, September 2000.]

Although some controversy may attend immunocontraceptives and immunosterilants because they are genetically engineered, even the most adamant opponents of genetic engineering tend to exempt vaccines from their criticism because of the potential vaccines have to reduce human and animal suffering.

As the uproar over RU-486 is unlikely to simmer down at any time soon, Upjohn may decide that trying again to sell a mibolerone-based contraceptive dog food isn't worth the bother. But, during the next two to five years and perhaps for longer, animal rescuers around the world will continue to wish they had it--by the truckload. --M.C.