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Effects of mifepristone and quinestrol on the fertility of female Brandt's voles (*Lasiopodomys brandtii*) in different reproductive phases

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Abstract

Mifepristone and quinestrol are effective drugs for controlling rodent fertility, but their inhibitory effectiveness during premating, early pregnancy, and late pregnancy is unknown. In this study, six groups of eight female Brandt's voles (*Lasiopodomys brandtii*) were administered with mifepristone, quinestrol, or a control for three days during premating, early pregnancy, or late pregnancy. In the mifepristone-treated groups, the premating females bred, whereas the early and late pregnant females did not. The reproductive rate, litter size, average body mass at birth, and survival rate of pups did not significantly differ between the mifepristone-treated premating group and the control group. By contrast, quinestrol treatment completely inhibited fertility during the three reproductive phases. In addition, fertility was not completely restored in the second pairing. The reproductive rates were higher for mifepristone, both during early and late pregnancy, than for quinestrol, but both were lower than the control. Thus, mifepristone and quinestrol both inhibited the fertility of female Brandt's voles at different reproductive periods. These results suggest that these two sterilants could be delivered during the reproductive season of the target pest animal.

Keywords

Brandt's voles; fertility control; mifepristone; reproduction; pregnancy; quinestrol

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Introduction

Being a second-generation pest management strategy (Krebs, 2014), fertility control has been the focus of many studies since Knipling (1959) proposed the sterile-male method of reducing pest populations. The three main strategies of fertility control are surgical/chemical sterilization, endocrine perturbation, and immunocontraception (Deliberto et al., 1998). Each method of pest control offers a unique set of advantages and disadvantages, which influence the practicality of its application in managing wildlife damage (Deliberto et al., 1998; Tran & Hinds, 2013). Endocrine perturbing sterilants have been widely investigated because they can interfere with the hypothalamic-pituitary-gonadal axis, improving the efficiency of fertility control against on pests (Deliberto et al., 1998; Huang et al., 2010). In China, massive explorations were conducted to select sterilants and assess their efficacy on different rodent species via physiological or behavioral tests (Zhang, 2015). In the field, delivery time can remarkably affect the efficacy of sterilants. Given that the reproductive phase of individuals in a population is not synchronized, a good sterilant should be effective regardless of the reproductive phase of the individuals. Most rodents with the *r*-strategy exhibit high reproductive rates. Therefore, a high proportion of individuals must be sterilized (Jacob et al., 2008).

Mifepristone is a potent antiprogesterone agent used as abortifacient in medical abortion and as a contraceptive in mammals (Van der Schoot & Baumgarten, 1990; Carlos & Ricardo, 1996; Croxatto et al., 1998; Sarkar, 2002; Ware & Spitz, 2003; Gemzell-Danielsson & Marions, 2004). This antifertility ability was reported in female mice and rats. In female mice, mifepristone induces infertility and its effects may last for two breeding cycles or longer (Gao & Short, 1994; Huang et al., 2013; Su et al., 2015). Mifepristone may also reduce sperm quality and reproductive rate in adult male mice (Qin et al., 2011). In rats, a subcutaneous injection of 1 mg/kg mifepristone terminates early pregnancy (Carlos & Ricardo, 1996). In addition, administration of 1 mg mifepristpone via subcutaneous injection to neonatal male and female rats caused permanent impairment of reproductive functions (Van der Schoot & Baumgarten, 1990). Moreover, quinestrol is a synthetic estrogen that has been used as a potential contraceptive agent. This drug exerts inhibitory effects on both female and male rodents. For instance, quinestrol induces atrophy of the testes or epididymis, reduces sperm count, depresses fertility, or causes complete infertility (Zhao et al., 2007; Shen et al., 2011; Wang et al., 2011; Liu et al., 2013). Quinestrol also influences the reproductive organs and sex hormones of adult females (Lv et al., 2011), and the offspring of lactating Mongolian gerbils are infertile (Lv & Shi, 2012). However, previous studies have neglected the antifertility activity of mifepristone and quinestrol at different reproductive periods, such as premating, early pregnancy, and late pregnancy. Confirming the inhibitory effects of mifepristone during different reproductive periods is vital in determining the bait delivery time in the field for fertility control.

The Brandt's vole (*Lasiopodomys brandtii*) is a major rodent pest that causes great environmental and economic losses in the grasslands of Inner Mongolia,

China (Shi et al., 2002). To date, *L. brandtii* is controlled mostly through poisoning, which demonstrates limited efficacy and negative environmental effects (Zhao et al., 2007). Shi et al. (2002) conducted the model investigation and reported that fertility control is more effective than lethal control in reducing the *L. brandtii* population. Subsequently, EP-1 – a combination of levonorgestrel and quinestrol at 6:3 ratio – (Zhang et al., 2004; Zhao et al., 2007), quinestrol, and levonorgestrel (Zhao et al., 2007) have been used in the fertility control of *L. brandtii*.

However, to the best of our knowledge, no studies have compared the antifertility effects of these drugs during premating, early pregnancy, and late pregnancy of *L. brandtii*. In this study, we used 4 mg/kg mifepristone or quinestrol to determine the inhibitory effects and mechanisms of mifepristone and quinestrol in female *L. brandtii* during the three reproductive periods. We predicted that 1) quinestrol would produce better effects than mifepristone during premating, given that quinestrol more intensely interfers with ovulation than mifepristone; 2) during pregnancy, mifepristone and quinestrol would show similar inhibitory effects during early and late pregnancies, although they display different mechanisms to impair reproduction; and 3) quinestrol would exert a longer inhibitory effect, because mifepristone exhibits a faster metabolic rate than quinestrol (Shanghai First Medical Pharmacology, 1978; Ware & Spitz, 2003).

Materials and methods

Animal and drugs

The individuals of the species *L. brandtii* used in this study came from a breeding colony in the Institute of Zoology, Chinese Academy of Sciences, that started with voles live-trapped in Xilin Gol League of Inner Mongolia (41°35′∼42°10′N, 114°51′∼115°49′E) in May, 1999. Virgin adult females were maintained at 23 ± 1°C with a 16L:8D photoperiod under the air conditioned environment. Animals were kept individually in polypropylene box (30 cm × 15 cm × 20 cm), food (commercial rabbit pellets, Beijing HFK Bioscience Co., Ltd) and water were provided ad libitum. The experiment was carried out from March to May in 2013. All experimental procedures complied with the guidelines of the Animal Care and Use Committee of the Institute of Zoology, Chinese Academy of Sciences.

Mifepristone (Hangzhou Jiuheng Biochemical Technology Co., Ltd, Hangzhou, China, purity 99.9%) or quinestrol (Beijing Zizhu Medicine Co., Ltd, Beijing, China, purity 99.9%) was dissolved in peanut oil at a dose of 4 mg/kg (body mass), based on the former tests in mice (Huang et al., 2013) and Mongolian gerbils (Shen et al., 2011). The average body mass before treatment was 37.96 ± 0.70 g, and no significant difference existed among groups; thus, we adopted 40 g as the drug preparation standard. In addition, treatment for 3 d was similar to the fast feeding time in the field.

Experiments

A total of 56 animals were randomly divided into seven groups in this experiment, the voles were 5∼6 month-old without any pairing experience. The control group (C) was administered with 0.8 ml of peanut oil by gavage for three consecutive days, whereas the other groups were treated with 4 mg/kg mifepristone or quinestrol for three consecutive days.

The mifepristone- and quinestrol-treated groups during premating, early pregnancy, and late pregnancy were denoted as PM, EM, LM, PQ, EQ, and LQ, respectively. The females in group PM or PQ were treated with mifepristone or quinestrol for 3 d and then paired with normal males for 5 d to ensure that each female has experienced at least one estrus cycle, after which the males were separated from the females. An estrous cycle of female voles is approximately 5 d (Zhang et al., 2004), thus, pairing for 5 d can eliminate the nonconformity of the estrous cycle. The females in group EM or EQ were paired with males for 5 d and then treated with mifepristone or quinestrol for 3 d after mating. The females in groups LM and LQ were paired with males for 5 d, after which the males were separated from the females. Ten days after pairing, the females were treated with mifepristone or quinestrol for 3 d pairing. The body mass of all the females were recorded every 2 d during gestation. The body mass change was the indicator of pregnancy given that the body weight increases as the embryos grow.

All of the females in groups EM, EQ, LM, and LQ did not breed, and no significant body mass changes were detected. The females were then paired with males 15 d after the first mating ended to test the long-term inhibitory effects. All of the females in group PQ did not breed, although a few females in group PM were impregnated and gave birth. The females in group PQ were not paired with males for the second time to compare the inhibitory effects of the two drugs during the same reproductive period.

The birth rate of females, litter size, mortality and survival of pups, and body mass of one litter at birth (±0.1 g) were recorded. Few females from all of the seven groups died in this experiment; thus, the reproductive indexes were based only on the survivors. The females in groups EM, EQ, LM, and LQ were euthanized by CO_2 inhalation at d 15 after the second mating ended. Moreover, the reproductive rate (number of pregnant voles/number of paired voles), and the number of embryos and uterine spots were recorded. The uterine implantation site and placental scar were considered as the uterine spots (Aplin et al., 2003).

Statistical analysis

Statistical analysis was performed using SPSS13.0. Normality and homogeneity were tested before further analysis. Crosstabs was used to analyze the reproductive or birth rate of females and the survival rate of pups, and Pearson Chi-Square test was applied because the theoretical value was greater than 5. Independent-sample *t*-test was used to analyze the litter size and body mass changes in groups C and PM.

The body mass changes were analyzed by one-way analysis of variance (ANOVA) and repeated measures analysis of variance (RM-ANOVA) in groups C, PM and PQ. RM-ANOVA and Independent-sample t-test were employed to analyze the body mass changes in groups EM and EQ, LM and LQ. Data were presented by mean ± SE except for reproductive, birth rate and survival rate. The values were considered statistically significant at $P < 0.05$.

Results

Fertility of females

The females in groups PQ, EQ, and LQ did not breed after treatment, indicating that quinestrol treatment at 4 mg/kg strongly inhibited reproduction in *L. brandtii* during premating, early pregnancy, and late pregnancy. At 4 mg/kg Mifepristone also completely inhibited reproduction during early and late pregnancies. In addition, the reproductive rate was 50% (4/8) in the PM group, although the reproductive rate (87.5%, 7/8; $\chi^2 = 2.455$, $N = 16$, $P = 0.117$), litter size ($t_{1,9} = 0.080$, $P = 0.938$), body mass of litters ($t_{1,9} = -0.471$, $P = 0.649$) and the pup survival ($\chi^2 = 1.666$, $N = 89$, $P = 0.197$) in the PM group were not significantly different from those of control (table 1). Moreover, the changes in body mass resulting from embryo development were consistent with the breeding condition (fig. 1).

Reproductive indexes after second pairing

On the basis of the litter calculation after autopsy, a number of females were pregnant in groups EM, EQ, LM, and LQ (during the second reproduction), although the reproductive rate during early ($\chi^2 = 0.124$, $N = 13$, $P = 0.725$) and late pregnancies ($\chi^2 = 0.625$, $N = 10$, $P = 0.429$) was not significantly different between the two drugs (table 2).

Table 1.
The fertility of female Brandt's voles treated by mifepristone or quinestrol after the first pairing.

Group	Reproductive rate[a] (%)	Litter size[b]	Number of offspring surviving	Body weight at birth[b] (g)	Number of offspring dying	Survival rate[a] (%)
Control	87.5	7.9 ± 0.6	55	2.54 ± 0.06	3	94.8
PM	50	7.8 ± 1.5	27	2.60 ± 0.13	4	87.1
PQ	0	0	0	0	0	0
EM	0	0	0	0	0	0
EQ	0	0	0	0	0	0
LM	0	0	0	0	0	0
LQ	0	0	0	0	0	0

Abbreviations: a, crosstabs; b, independent-samples t-test.

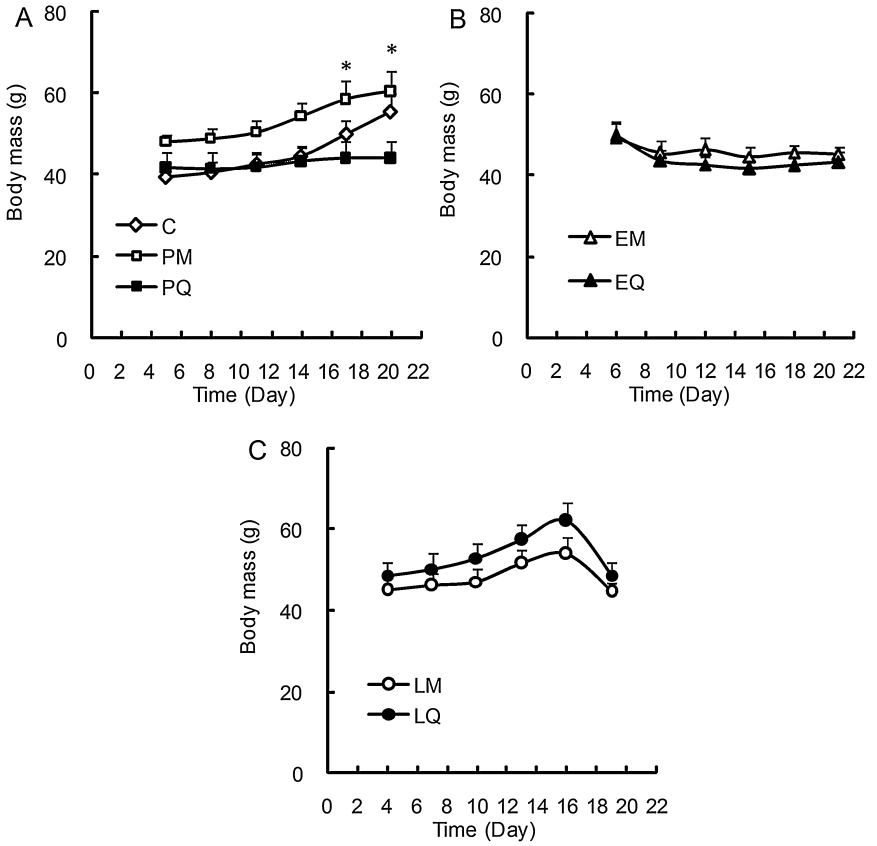

Figure 1. Body mass changes after treatment in all groups. Panel (A) shows C, PM and PQ; panel (B) shows EM and EQ; panel (C) shows LM and LQ after the first pairing. Body mass changes were tested using an ANOVA and RM-ANOVA in the groups C, PM and PQ; body mass changes were analyzed by independent-samples t-test and RM-ANOVA in the groups PM and PQ or EM and EQ. The values on the x-axis (days 1∼22) represent the days after the first pairing. Abbreviations and symbol: PM, EM, LM, mifepristone-treated groups during premating, early and late pregnancy, respectively; PQ, EQ, and LQ, quinestrol-treated groups during premating, early and late pregnancy, respectively; *, $P < 0.05$.

Table 2.
The fertility of female Brandt's voles treated by mifepristone or quinestrol after the second pairing.

Group	Reproductive rate (%)	Number of dead voles	Litter size of pregnant voles	Uterine spots of non-pregnant voles
EM	66.7 (4/6)	2	5, 5, 9, 10	0, 10
EQ	57.1 (4/7)	1	3, 3, 10, 11	7, 9, 13
LM	50 (3/6)	2	11, 11, 12	4, 6, 7
LQ	25 (1/4)	4	6	5, 7, 8

Note: reproductive rate was analyzed using crosstabs.

Discussion

The present results largely accorded with our predictions. Mifepristone (at 4 mg/kg) partially impaired the fertility of female Brandt's vole during premating, and completely induced breeding failure during early and late pregnancy. By contrast, quinestrol (at 4 mg/kg) effectively inhibited *L. brandtii* reproduction during premating, early pregnancy, and late pregnancy. The inhibitory effects were not fully reversible 12 d after treatment during early or late pregnancy in both treated groups.

In addition, mifepristone partially inhibited reproduction during premating in female voles. This result may be attributed to the varying follicular developmental stages and to the fast mifepristone metabolism. For instance, administration of mifepristone in the mid- or late follicular phase delays ovulation (Gemzell-Danielson et al., 1996), whereas administration of mifepristone immediately after ovulation inhibits endometrial development (Swahn et al., 1990). In rats, the terminal $t_{1/2}$ of mifepristone is 4 h, and its clearance is 2.7 l/h/kg bodyweight (Ware & Spitz, 2003). Fast metabolism of mifepristone may also weaken its inhibitory effect during premating in *L. brandtii*.

Mifepristone also inhibits the activity of progesterone, which is essential in implantation and maintenance during early pregnancy, and induces failure of early pregnancy (Gao & Short, 1994; Gemzell-Danielson & Marions, 2004). For example, mifepristone treatment after ovulation can block implantation in rhesus monkeys (Ghosh & Sengupta, 1993) and in human females (Gemzell-Danielson et al., 1996). Mifepristone at 10 mg/kg also exerts antinidatory and abortifacient effects in rats regardless of treatment time (Ware & Spitz, 2003). Mifepristone effectively terminated late pregnancy in female *L. brandtii*, mainly by inducing decidual degeneration, and the embryos may be delivered and eaten because of lack of progesterone. In addition, mifepristone treatment during late pregnancy induces labor in rats (Cabrol et al., 1991). Frydman et al. (1992) found that mifepristone is a safe, efficient, and suitable labor-inducing agent in women at term.

Quinestrol completely inhibited reproduction during premating in female *L. brandtii*. Quinestrol may block the release of gonadotropin-releasing hormone from the hypothalamus during premating, thereby inhibiting follicle growth, and ultimately inducing pregnancy failure. For example, quinestrol markedly inhibits the development and maturation of ovarian follicles in rats (Arronet et al., 1969; Gioia et al., 1975). Quinestrol also inhibits follicle maturation and ovulation by lowering gonadotropin levels, and as well as prolongs fertility inhibition in Mongolian gerbils (Lv & Shi, 2011).

The results we obtained during premating in *L. brandtii* reflected higher efficacy than those obtained by Zhao et al. (2007). This discrepancy may be ascribed to the differences in dose and treatment interval. Our theoretical dose was 5.88 times higher than that of Zhao et al. (2007). In addition, they facilitated mating 30 or 75 d after treatment. This long waiting time may have weakened the inhibitory effects of quinestrol.

Normal endometrial development is important in implantation of fertilized egg and in maintenance of early pregnancy. Quinestrol may transform endometrium and induce mesenchyme edema, thereby terminating early pregnancy. For example, quinestrol causes uterus edema, and abnormal estradiol and progesterone levels in *M. unguiculatus* (Lv & Shi, 2011). In rabbits, oral administration of 10 mg/kg quinestrol terminates early pregnancy (Shanghai First Medical Pharmacology, 1978). During middle or late pregnancy, quinestrol induces degenerative shedding of endometrium and may cause embryonic resorption (Shanghai First Medical Pharmacology, 1978). In rabbits, treatment with 10 mg/kg quinestrol 10 d after pairing terminates pregnancies, and the embryos are necrotic or absorbed, traces of which were only visually reflected (Shanghai First Medical Pharmacology, 1978). However, the actual mechanism requires further investigations.

Under the same dose and treatment time, mifepristone and quinestrol exerted similar inhibitory effects during early and late pregnancies in *L. brandtii*. However, quinestrol exerted a stronger inhibitory effect than mifepristone during premating. Quinestrol can be stored in adipose tissue to be slowly released into the circulation, supporting its strong inhibitory effect (Zhang, 2015). By contrast, mifepristone exhibits fast elimination and metabolism rate (Ware & Spitz, 2003). When compared with the mifepristone-treated voles, more quinestrol-treated female voles died in their late pregnancy during the second reproductive cycle. Mifepristone is an antiprogestin that causes endometrial shedding and softens the cervix (Sarkar, 2002; Ware & Spitz, 2003). The mechanism of quinestrol may be not favorable for shedding embryo out of the uterus, leading to death of the females. Further studies must explore the inhibitory differences between mifepristone and quinestrol in female *L. brandtii*.

L. brandtii typically begins to breed in April and breeding usually ceases around the time they reach their density peaks in August (Shi et al., 2002). A family of voles consists of several adult females or males, with juveniles being added during the breeding season. Once the fertility of adult female voles during premating, early pregnancy or late pregnancy is inhibited, the population may not increase in the current or even in the next breeding season. Computer simulations indicated that 50% to 80% and >50% of females must be sterilized to achieve effects at the population level in eruptive house mouse populations (Davis et al., 2003) and in noneruptive ricefield rats, respectively (Jacob et al., 2004). The fertility of juveniles may also be inhibited. Mifepristone and quinestrol both effectively inhibited the fertility of female *L. brandtii* during premating, early pregnancy and late pregnancy. Furthermore, quinestrol (Shen et al., 2011a, b) and mifepristone (Qin et al., 2011) exerts inhibitory effects on the reproductive organs and hormones, as well as in sperm production in male rodents. These properties may contribute to the fertility control in field. In addition, baits with mifepristone or quinestrol may be delivered in the field during the initial stages or during reproduction, but not during population outbreaks. McLeod et al. (2007) concluded that house mice could be effectively managed if the fertility control agent persists or can be introduced at early stages of

population outbreaks. Casting the bait for more than 5 d is also required to coincide with the estrous cycle of *L. brandtii*. A previous study showed that quinestrol can reduce the population abundance of Plateau pikas in field (Liu et al., 2012). A single baiting with EP-1 significantly suppresses the birth rates, reduces the densities, and changes the age structures of gerbil populations (Fu et al., 2013).

In summary, the fertility of female *L. brandtii* was profoundly inhibited by mifepristone and quinestrol during premating, early pregnancy and late pregnancy, and fertility was not fully restored during the second reproductive cycle. This study confirms that both drugs are promising contraceptive agents to control *L. brandtii* population in the field. However, the precise mechanism of mifepristone and quinestrol in female *L. brandtii* during the aforementioned reproductive phases requires further investigation.

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