KINETICS OF MEDROXYPROGESTERONE ACETATE AND EFFECTS OF A SINGLE ORAL DOSE ON FERTILITY IN FEMALE RABBITS

N.O. OGUGE and G.K. BARRELL

Animal and Veterinary Sciences Group, Lincoln University

SUMMARY

Separate trials were conducted to investigate the kinetics and effects of a synthetic progestagen, medroxyprogesterone acetate (MPA), on female rabbits following single oral dosing (2, 10, 100 or 1000 mg MPA/rabbit). Plasma levels of MPA reached maximum concentration 1-12 hrs post treatment and declined to undetectable levels after 1 or 18 days depending on dosage. An oral dose of 10 mg MPA/rabbit caused complete infertility in females mated 1 day and did not reduce fertility in those mated 8 days after treatment. Animals orally dosed with 100 or 1000 mg MPA were infertile when mated 1 day but not 29 days post treatment. The study suggests that development of this approach to population control may have some application on feral rabbits.

INTRODUCTION

Feral rabbit populations over most of New Zealand are generally restrained by natural factors at below damage thresholds although severe problems persist in some drier districts. This has led to the conclusion that rabbit proneness is an inherent property of particular types of land and climate (Bell *et al* 1989). Although the annual productivity of adult female rabbits in semi-arid regions is low at 25 young/female (Bell *et al* 1989) compared with other areas of New Zealand (e.g. 53 young/female in Wairarapa, Gilbert *et al* 1987), survival of juveniles is higher. Unlike other areas in New Zealand, predation or disease does not play an effective role in restraining rabbit numbers in semi-arid regions (Bell *et al* 1989) and application of poison bait therefore remains the primary method of control in these areas. According to Fraser (1988), poisoning operations in Central Otago often leave about 30% of the population alive and numbers may return to their original densities within 1 year. Thus there is clearly a need for follow up control measures in the drier districts. One such measure may be by application of chemosterilant baits. Strategic application of such baits before and during the breeding season may significantly lower rabbit productivity and thus allow for longer intervals between control operations.

Progestagens in general can suppress gonadal function by inhibiting release of gonadotrophin releasing hormone (GnRH) from the hypothalamus and thus, in turn, luteinising hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland. More specifically medroxyprogesterone acetate (MPA) is an orally active progestagen which can block ovulation in females of various species (Chang 1966, 1985; Zhang and Miller 1989) and suppress testicular function in males (Rivarola *et al* 1968; Gordon *et al* 1970; Barbieri and Ryan 1980; Muir *et al* 1982) following intramuscular (i.m.) or subcutaneous (s.c.) injections or oral administration. In this study varying doses of MPA were administered to rabbits orally and the effects on plasma MPA concentration and fertility were monitored.

MATERIALS AND METHODS

Mature female New Zealand white rabbits, purchased from a local breeder were housed indoors in individual cages at Lincoln University. Room temperature was not regulated and the animals experienced natural daily photoperiods (August 1988-May 1989). They were fed a commercial pelleted diet (17% protein, 16% fibre and 3% fat) and had water *ad libitum*.

Proc. 43rd N.Z. Weed and Pest Control Conf. 1990: 274-278

MPA (2 or 10 mg) was either dissolved in 5 ml of ethanol and administered at a single feed after injection into a piece of raw diced carrot (15 x 15 x 10 mm³) or adsorbed on feed pellets using vegetable oil (10, 100 or 1000 mg MPA). MPA was fed to experimental animals at time 0. On days 1 and 8 rabbits orally dosed with 10 mg MPA were mated to two reproductively competent males. Those orally dosed with 100 or 1000 mg MPA were similarly mated on day 1. Animals which failed to conceive were then remated on day 29. Blood samples (2 ml) were collected from all experimental animals at 0, 3, 6, 12, 24, 48, 72, 96, 192 and 432 h. The samples were obtained from a small incision in the marginal ear vein, collected in heparinized test tubes (62 i.u. heparin/tube) and centrifuged (1160 g) at 10°C for 20 min. Plasma was then removed and stored at -20°C until assayed. Plasma MPA and progesterone levels were determined by enzyme-linked (ELISA) immunoassays (L.K. Lewis and G.K. Barrell, unpublished; Elder *et al* 1987).

Mean plasma MPA concentrations were log transformed and the significance of differences determined for times 1, 3, 6, 12 and 24 h by analysis of variance (ANOVA). The least significant difference (LSD) test was then used to separate the means.

Fisher's exact test (Bailey 1959) was used to determine the effects of a single oral dose of MPA on fertility.

RESULTS

MPA was detectable in rabbit plasma 1 h after oral dosing and reached maximum concentration between 1 and 12 h depending on dosage (Fig. 1). Levels then declined and reached undetectable values after 24, 48 and 72 h in animals orally dosed with 2, 10 or 100 mg MPA, respectively. In rabbits orally dosed with 1000 mg MPA, the compound was still detectable in blood at 192 h but not at 432 h. Differences in mean plasma MPA concentration between the treatment groups were highly significant ($P < 0.001$). The differences between specific pairs of means were significant at 5% level except between means for 2 and 10 mg MPA/rabbit administered in carrots (Table 1).

Fig. 1: Mean plasma medroxyprogesterone acetate concentration in female rabbits following single oral dosing with 2 (n = 2), 10 (n = 2 on carrots; n = 4 on pellets), 100 (n = 4) or 1000 (n = 4) mg MPA/rabbit at time 0.

Female rabbits mated 1 day following an oral dose of 10, 100 or 1000 mg MPA failed to conceive (Table 2). This was statistically significant only for the 10 mg MPA group although if all data for treated animals are pooled there is a highly significant ($P < 0.001$) effect of treatment. Two of the three females mated 8 days and all females mated 29 days following oral MPA treatment were pregnant.

TABLE 1: Differences in mean plasma MPA concentrations in female rabbits orally dosed with 2, 10, 100 or 1000 mg MPA/rabbit. The solid line connects sets of means judged not significantly different.

MPA dose (mg/rabbit)	carrots		pellets			LSD
	2	10	10	100	1000	
LogE of mean plasma MPA concentration ng/ml	0.60	1.03	1.96	3.4	4.57	0.47

TABLE 2: Effects of a single oral dose of medroxyprogesterone acetate (MPA) on fertility in female rabbits.

MPA dose (mg/rabbit)	Time (days) of mating post treatment	No. of rabbits preg/total
0	1	4/9
10	1	0/10*
10	8	2/3
100	1	0/7
1000	1	0/7

*indicates significant ($P < 0.05$) difference from untreated.

DISCUSSION

The present study demonstrates that MPA can be successfully administered to rabbits in baits. MPA could be measured in rabbit blood one hour following oral dosage and it persisted for up to 200 h depending on dose level. The pattern of plasma MPA concentration in orally treated rabbits was similar to that reported for orally treated women (Cornette *et al* 1971; Salimtschic *et al* 1980) and female monkeys (Cornette *et al* 1971).

In this study a single oral dose of 10, 100 or 1000 mg MPA/rabbit caused complete infertility in females mated one day after treatment. However, animals mated 28 days later were fertile. A dose of 10 mg MPA/rabbit did not reduce fertility in females mated 8 days after treatment. The results of the present study are similar to those reported by Chang (1966) who orally administered 6 mg MPA/rabbit to does and demonstrated a complete degeneration of oocytes 6 days later. Chang (1985) also showed that a subcutaneous injection of 20 or 50 mg MPA/rabbit induced infertility in the females for 83 days. The results following oral dosing suggest that a much shorter duration of infertility is achieved by this route irrespective of dose. This difference indicates that intestinal absorption of MPA may be limited and the unabsorbed residue may pass along the gastrointestinal tract without forming a reservoir as would be the case following injection.

The highly significant increase in mean plasma MPA levels following increase in dose (Table 1) suggests linear kinetics in the dose range tested. However, the correlation between plasma MPA and contraceptive efficacy cannot be determined from this study. Significant differences in plasma MPA levels which occurred solely due to the different modes of preparation of baits (Table 1, 10 mg dose) suggests that the effectiveness of oral dosing may depend on the way such preparations are formulated. The effects of physico-chemical states of MPA on its absorption in the intestinal tract has been documented (Helmreich and Huseby 1965).

Clearly, because mating in this study was carried out only on days 1, 8 and 29 post treatment, it is not possible to determine the exact duration of the effects of single oral dosing of MPA on female rabbits. It is clear, however, that the infertility observed was complete on day 1 but not present on day 8 or day 29 (10 or 1000 mg/rabbit).

Although further studies are required to define the period of complete infertility in female rabbits following a single oral dose of MPA, the present results indicate that

development of this approach for population control may have some application on feral rabbits.

The use of contraceptives in rabbit control may have certain desirable attributes relative to poisoning because the approach is more humane, socially acceptable, eliminates death of non-target species, has no prebaiting requirement and may not provoke selection for neophobic behaviour. It is suggested, however, that antifertility agents be used to complement, rather than be a strict alternative to, conventional methods of rabbit control. It is possible that such a strategic approach to rabbit control may significantly alleviate the chronic pest problem in the semi-arid regions of New Zealand.

ACKNOWLEDGEMENTS

The authors would like to thank Bob Harrow for providing funds for the study. The first author is on a Commonwealth Scholarship.

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