

CHEMICAL OCCLUSION OF MONKEY OVIDUCTS WITH QUINACRINE:
ANTAGONISM AND REVERSAL WITH ESTROGEN*

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ABSTRACT

The effect of estrogen on quinacrine induced tubal occlusion was studied in rhesus monkeys (*Macaca mulatta*). The results suggest that estmdiol dipropionate, when given at a dose of 1 mg per animal intramuscularly daily for 5 days commencing from day 2 of instillation (Day 1 = day of quinacrine instillation), antagonises the action of quinacrine in producing tubal occlusion. It was further observed that estrogen treatment from days 16 to 20 reversed the already established tubal occlusion in monkeys.

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INTRODUCTION

The development of a simple and effective method of sterilization that can be used as an out-patient procedure, has been the subject of research by several investigators. Clinical (1) and experimental (2) work indicate that quinacrine is a potent chemical agent for occluding the Fallopian tubes and thereby causing sterility. Dose dependent functional and morphological changes have been reported in rat endometrium; thus, quinacrine at a dose of 200 mg/ml produced apparently irreversible changes in the rat endometrium (2). Previous studies revealed that quinacrine induces occlusion in the monkey Fallopian tube particularly in an area proximal to the uterus (3). It has also been reported that subcutaneous injection of estmiodol benzoate or progesterone negated the action of quinacrine in addition to the reversal of the established obstruction in rats (4). Accordingly, it was deemed worthwhile to study the effect of estrogen on quinacrine induced tubal occlusion in rhesus monkeys.

MATERIALS AND METHODS

Healthy adult female monkeys (body weight 6-8 kg) of the Institute primate colony were employed in this study. The monkeys were anaesthetised with a Nembutal solution and a ventral midline lower abdominal incision was made. The Fallopian tubes were delivered into the wound and a polyethylene (intramedic) cannula was inserted into the Fallopian tube through the fimbrial end. A suspension of 800 mg of quinacrine hydrochloride in 1.0 ml of 2% aqueous agar solution was made. This suspension is liquid at 50°C and gels at about 37 to 40°C. The gelation is temperature dependant. The syringe containing the quinacrine suspension was attached to the cannula and the solution was instilled slowly into each Fallopian tube and its passage was visualised to the uterotubal junction. The amount instilled ranged between 0.05 to 0.15 ml depending upon the size of the Fallopian tubes. The cannula was removed and the osteal opening was held lightly between two fingers to avoid any immediate reflux of the material into the peritoneal cavity and to allow the solution to gel. Each Fallopian tube was placed back in situ and the incision was closed. A batch of monkeys was instilled with carrier vehicle alone, i.e. 2% aqueous agar solution, in a similar manner to serve as controls. A 'proper antibiotic coverage was provided to each monkey. The monkeys were sacrificed at 7, 30 and 60 days post-instillation. Eight quinacrine instilled monkeys were employed for estrogen treatment. One group of 4 monkeys received 1 mg/animal estradiol dipropionate intramuscularly,

daily for 5 days commencing from day 2 of instillation (Day 1 = day of quinacrine instillation). Another group of 4 monkeys was injected with estradiol dipropionate from days 16 to 20. The animals of both groups were sacrificed 30 days after the last estmiodol injection, i.e. 36th (Group A) and 50th (Group B) days after quinacrine instillation. At autopsy the entire genital complex was dissected out and the Fallopian tubes were cleared of adhering mesometrial fat and surrounding tissue. The tubal patency was assessed by instilling India-ink into the uterine cavity under slight pressure. Tubes with positive patency allowed the dye to pass through the osteal opening. The Fallopian tubes and the uterus containing the intramural portion were fixed in Bouin's fluid and examined histologically.

RESULTS

The results of the present study (Table I) indicate that an 80 per cent suspension of quinacrine hydrochloride induces tubal occlusion within seven days after instillation. The animals sacrificed at 30 and 60 days also revealed occluded Fallopian tubes. Histology showed a granulomatous proliferation of the stromal elements in the occluded area. Monkeys instilled with 2 per cent aqueous agar solution used as carrier vehicle did not show any evidence of tubal closure.

The monkeys treated with estradiol dipropionate at 1 mg/animal per day for 5 days either commencing from day 2 (Group A) or day 16 (Group B) after quinacrine instillation did not reveal tubal occlusion as evidenced by patency tests (Table II). The histological entity of the entire Fallopian tube was normal. There was no evidence of stromal proliferation and the epithelial integrity was intact.

DISCUSSION

The results thus obtained indicate that quinacrine at an 80 per cent concentration (w/v) induced tubal occlusion within 7 days in all the monkeys which was found present up to 60 days post-instillation of the observation period. Previous studies from our laboratory have revealed that 80% (and 100%) quinacrine in aqueous agar solution induced tubal occlusion which was seen during the entire observation period of 120 days. The observations from Groups A and B reveal that the Fallopian tubes are patent after estrogen therapy. Since these monkeys were sacrificed well within the period of quinacrine induced tubal occlusion, it clearly shows that estrogen treatment not only antagonised the tuboocclusive action of quinacrine (Group A) but also reversed the already established occlusion of the Fallopian tubes (Group B). It is pertinent to note that similar

TABLE I
CHEMICAL OCCLUSION OF MONKEY OVIDUCT WITH QUINACRINE

Instillation Treatment	No. of days post-instillation	7 days (3)*		30 days (4)		60 days (4)	
		Patency	Histological	Patency	Histological	Patency	Histological
Agar alone		Positive	Normal No occlusion	Positive	Tube normal No occlusion	Not done	Not done
80% Q in agar		Negative	Tube occluded by granulomatous tissue	Negative	Tube occluded by granulomatous tissue	Negative	Tube occluded by granulomatous tissue

* Number of monkeys
(Partly adopted from Chandra *et al.* (3))

TABLE II
EFFECT OF ESTROGEN TREATMENT* ON QUINACRINE INDUCED TUBAL OCCLUSION
IN RHESUS MONKEYS

Groups	NO. of monkeys	Interval between quinacrine instillation and estrogen treatment	Interval between quinacrine instillation and sacrifice	Results	
				Patency	Histological
A	4	24 hrs	36 days	Positive	Tube normal No occlusion
B	4	15 days	50 days	Positive	Tube normal No occlusion

*Estradiol dipropionate 1 mg/day/monkey for 5 days.

observations have been made by Zipper et al. (4) in rat uterus. In point of fact, if such results can be extrapolated clinically, this method will open an unexpected perspective in fertility control.

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PLASMA PROFILE OF PITUITARY GONADOTROPINS AND OVARIAN STEROIDS IN WOMEN DURING 17 α -ACETOXY-11 β -METHYL-19-NOR-PROGESTERONE ADMINISTRATION *

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ABSTRACT

The effects of 17 α -acetoxy-11 β -methyl-19-nor-progesterone (SC-21009), a synthetic, active progestin on pituitary and ovarian function, were studied in eleven healthy normally ovulating women. SC-21009 was administered orally at three different doses during a complete menstrual cycle. Four subjects received 40 μ g daily; 3 subjects received 200 μ g daily and 4 others received 1000 μ g daily. Pituitary gonadotropic function was assessed by the daily measurement of radioimmunoassayable levels of plasma LH and FSH. Ovarian steroidogenic function was evaluated by determining the daily plasma levels of estradiol and estrone, and the levels of progesterone on appropriate days. In addition, the urinary excretion of pregnanediol was also determined. Since we have established the normal hormone profile of these women throughout the menstrual cycle prior to the study, it was possible to compare the data with those obtained during SC-21009 administration. The results obtained demonstrate that the lower dose of SC-21009 (40 μ g) significantly increased the plasma LH levels ($p < 0.001$) through the follicular phase. A concomitant and slight, although not significant, increase in plasma FSH levels was observed. No significant changes at mid-cycle nor during luteal phase were noted. In contrast, higher doses of the synthetic progestin did not induce significant changes on the plasma gonadotropin profile. Estrogens and progesterone levels during SC-21009 at the three doses employed were similar to that observed in the control cycle. These data are interpreted as demonstrating LH-FSH positive feedback mechanisms at follicular phase during low-dose SC-21009 therapy and a lack of ovulation inhibitory activity of this progesterone derivative.

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