

LACK OF TUBAL OCCLUSION BY INTRAUTERINE QUINACRINE  
AND TETRACYCLINE IN THE PRIMATE

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## ABSTRACT

The effects of slow- and fast-releasing quinacrine pellets and tetracycline tablets on the genital tracts of 20 cynomolgus monkeys was evaluated. After surgical implantation of the pellets, the primates were observed for three months. No signs of toxic effects to the drugs were observed during the three-month period and on autopsy. Histopathological evaluation of the fallopian tubes, cervix, ovaries and uterus (except the endometrium) indicated they were all within normal limits. In no case were the uterotubal junctions obstructed. Endometrial changes were more frequent for quinacrine-treated monkeys. The results of the study point to the need for additional research regarding the optimal dose and duration of quinacrine administration.

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## INTRODUCTION

Since the late 1960s, studies have been conducted to evaluate the intrauterine use of quinacrine hydrochloride to produce permanent occlusion of the fallopian tubes in women. Following several encouraging reports, one study of the intrauterine administration of a solution containing 1.5gm quinacrine was found to be rather ineffective (1). Among women who completed the three required instillations, the pregnancy rate was 7.1%. Also, 27% of the women experienced toxic psychosis. The safety and effectiveness of the intrauterine administration of quinacrine appears to be improved by using 250mg of the drug in pelletized form, so that the drug is released over a period of about 10 minutes. In one study of 151 women who were scheduled for three insertions of 250mg quinacrine pellets, there were no serious complications. The cumulative 36-month pregnancy rate (life-table) was 4.3 per 100 women (2). In the human, quinacrine produces local necrosis and fibrosis in the interstitial portions of the fallopian tubes and tubal closure through scarring.

Concerns over the safety of intrauterine quinacrine have been expressed by some investigators. The drug is known to intercalate with DNA and may also have mutagenic activity on the basis of bacterial test systems (Ames test) (3). Furthermore, recent studies have shown that high doses of quinacrine pellets or suspensions placed in the peritoneal cavities of monkeys result in pathology and death (4,5). To reduce the potential risks resulting from the rapid intrauterine administration of high amounts of quinacrine, slow-releasing pellets were constructed that released quinacrine over a seven-day period. Also, other drugs have been evaluated that might have a "sclerosing" effect on the tubal epithelium. Recent studies (6,7) indicate that tetracycline hydrochloride may be as effective as quinacrine in producing tubal closure when administered directly to the uterotubal junction.

The present study was undertaken to evaluate the effects of slow-releasing and fast-releasing quinacrine pellets as well as tetracycline tablets on the genital tract morphology of cynomolgus macaque monkeys.

## METHODS AND MATERIALS

The following types of pellets were implanted in the uterine cavities of healthy, mature cynomolgus monkeys:

1. Fast-releasing quinacrine pellets, 3.3mm in diameter and 7mm long were prepared by R.G. Wheeler, Family Health International, Research Triangle Park, NC. Each pellet contained  $25 \pm 1$  mg quinacrine and about 25% cholesterol and magnesium stearate by weight to control the dissolution time

to a nominal *in vitro* value of 800 minutes (13.3) hours. A silicone band was placed around the outside of each pellet that provided a means for attaching the pellet to a prolene suture strand, used to secure the pellet in the uterus after surgical implantation.

2. Slow-releasing (7 days) quinacrine pellets, 3.7mm in diameter and 5.7mm long were prepared by R.L. Dunn, Southern Research Institute, Birmingham, AL. Each pellet contained  $40 \pm 2$  mg quinacrine. The pellets consisted of a bundle of polymer fibers loaded with quinacrine and enclosed in a polycaprolactone sheath. Each pellet had a hollow core so that a prolene suture could be threaded through the pellet to secure it in the uterus after implantation.
3. Fast-dissolving (<1 hour) tetracycline tablets, 5.6mm in diameter and 4.4mm long, were prepared under the direction of Dr. N.H. Dubin, The Johns Hopkins University, Baltimore, MD. Each pellet contained 100mg tetracycline.

Each type of pellet or tablet was inserted into the uterine cavities of five monkeys. In a fourth group of five monkeys a fast-releasing and a slow-releasing quinacrine pellet were inserted. Since the pellets and tablets were too large to pass through the cervical canal, they were implanted surgically. The tablets were secured in the uterine cavity by means of the prolene suture that prevented them from being expelled through the cervix.

The pellets and tablets were implanted at any time of the menstrual cycle. The uterus was exposed and a 0.5cm incision was made by cautery just distal to the internal cervical os. A 4-0 prolene suture was placed through the incision and passed via the uterine lumen through the middle of the fundus. A slow- or fast-releasing quinacrine pellet, or both, were attached to the suture and pushed into the uterine lumen. The two ends of the suture were tied together in the abdominal cavity and the knot was pulled into the uterine lumen. The uterine incision was closed with 4-0 dexon. The tetracycline tablets were placed in the uterine fundus, but were not secured with a prolene suture. This was not necessary since they had a rapid dissolution time. The operative procedures were well tolerated by the animals and no problems were encountered. All animals remained in good health throughout the three-month observation period. At the end of this period, the entire genital tract (uterus, cervix, fallopian tubes) was excised. Small liver and kidney specimens were obtained from each animal at the end of the three-month period. All tissues were preserved in Hartman's solution. The histological and pathological observations of the excised tissues of each animal were made without knowledge of the treatment group to which the animal had been assigned.

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RESULTS

None of the monkeys showed any toxic reactions to the implanted pellets. All animals remained healthy throughout the three-month observation period.

Multiple adhesions between the uterine incision, urinary bladder and peritoneum were noted for a number of the primates in the groups treated with quinacrine but not tetracycline (Table I). The uterine incisions had healed in all 1 monkeys, and no visible lesions were noted in any of the abdominal organs. For two monkeys who had both fast- and slow-releasing quinacrine pellets inserted, the "devices" were found to be outside of the uterus.

Table I

FREQUENCY OF ADHESIONS IN THE TREATED MONKEYS

Type Pellet	Number Treated	Number With Multiple Adhesions
Quinacrine		
Slow release	5	2
Fast release	5	2
Slow + fast release	5	5
Tetracycline	5	0

Examination of the excised uteri showed that none of the tetracycline pellets or their residues were visible. For fast-releasing quinacrine pellets, only the prolene sutures and silicone bands remained. As was expected, only the shell and matrix of the slow-releasing quinacrine pellets remained. All of the quinacrine had been released as determined by extraction studies.

No histological changes were found in the fallopian tubes, uterus (except for the endometrium) or cervix of any animal. Neither the slow- nor the fast-releasing quinacrine pellets nor the tetracycline tablets caused obstruction of the fallopian tubes. Changes were noted in the endometrial cavities of most monkeys (Table II), and were more frequent (0.05 < p < 0.10) for the quinacrine-treated monkeys. However, the endometrial alterations may have been due to the physical presence of the pellets and not to the quinacrine.

Some pathologic changes were noted in the liver and kidney specimens. These included: mild chronic pericholangitis, diffuse swelling of hepatocytes, nonsuppurative hepatitis, chronic hepatitis and perivascularitis (12 monkeys), and mild chronic interstitial nephritis, periglomerular fibrosis and intratubular casts (10 monkeys). None of these changes were more frequent in any of the four groups of

monkeys. From the study, it cannot be ascertained whether any of these changes are due to drug exposure, colony or surgical factors.

Table II

ENDOMETRIAL CHANGES

Endometrial Change	Type Pellet Inserted	
	Quinacrine	Tetracycline
	Fast Release	Slow Release
Superficial damage and repair	2	2
Highly atypical epithelial proliferation	4	
Consistent with repair		1
Recent repair consistent with spontaneous menstruation		1
Spontaneous menstruation	3	2
None		4

COMMENT

The present study shows that 25mg quinacrine released over about 13 hours or 40mg quinacrine released over about 7 days did not produce any tubal lesions in 15 cynomolgus monkeys by the end of a three-month observation period. This confirms the results from a previous study of 10 pigs in which slow-releasing (7 day) quinacrine pellets (121mg) were surgically inserted. The oviducts, uteri and ovaries of these animals were histologically within normal limits when evaluated 2-10 weeks after insertion (8). In the human, Laufe and Wheeler (9) evaluated the effects of the intrauterine insertion of 100-300mg of quinacrine contained on the upper arms of T- or Y-shaped IUDs in women before a scheduled hysterectomy. In these studies the dissolution time of the quinacrine was about four hours. These authors noted that in some cases the quinacrine produced lesions that could lead to tubal closure. However, in other cases no lesions were found. Similarly, by one week after the intrauterine insertion of quinacrine or tetracycline in the primate, lesions were observed only in 25% of the animals that could have led to the obstruction of the fallopian tubes (7). In the present study, it is possible that the quinacrine or tetracycline produced lesions initially, but that epithelial regeneration occurred before fibrosis and tubal scarring took place.

In human studies, in which a three-instillation

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procedure of either quinacrine solutions (1) or rapidly dissolving pellets (<1 hour in vitro) were **used(2)**, **there is evidence to suggest, on the basis of the observed decrease in pregnancy rates, that quinacrine produces permanent lesions that result in tubal occlusion.** The tubal occlusion rate appears to be proportional to the number of quinacrine instillations. Studies of the effects of intrauterine quinacrine in the primate and pig may indicate that a single application of a relatively low dose of quinacrine over a prolonged period of time is insufficient to cause tubal occlusion. Alternatively, it is possible that the primate and the pig are inappropriate animal models for these studies. Before additional clinical trials of quinacrine are conducted in humans, it would be worthwhile to perform appropriate dose-response studies in a suitable animal model. On the basis of the results of the present work and others (6,8), it is not evident what laboratory animal should be used for this purpose.

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## REFERENCES

1. Zipper, J., Medel, M., Goldsmith, A., Edelman, D.A., Pastene, L., and Rivera, M. The clinical efficacy of the repeated transcervical instillation of quinacrine for female sterilization. *Int J Gynaecol Obstet* **14:499-502** (1976)
2. Guzman-Serani, R., Bernales, A., and Cole, L.P. Quinacrine hydrochloride pellets: three-year follow-up on a nonsurgical method of female sterilization. Paper presented at the first annual meeting of the Society for the Advancement of Contraception (SAC), Cairo, November, 1983.
3. Blake D.A., Dubin, N.H., Dfbiasi, M.C., Parmley, T.H., Stetten, G., and King, T.M., in *Female Transcervical Sterilization* (G.I. Zatzuchni, J.D. Shelton, A. Goldsmith, J.J. Sciarra, Editors). Harper & Row Publishers, Hagerstown, 1983, p. 71-88.
4. Chandra, H., and Malaviya, B. Toxic effects of quinacrine hydrochloride in rhesus monkeys. *Contraception* **24:269** (1981)
5. Dubin, N.H., Strandberg, J.D., Craft, C.F., Parmley, T.H., Blake, D.A., and King, T.M. Effect of intrauterine and intravascular qufnacrine administration on histopathology, blood chemistry, and hematology in cynomolgus monkeys. *Fertil Steril* **38:741-747** (1983)
6. Dubfn, N.H., Parmley, T.H., Ghodgaonkar, R.B., and King, T.M. Comparative effects of intrauterine instillation of analogs of quinacrine and tetracycline on uterine morphology in the rat. *Contraception* **29:553-559** (1984)
7. Dubin, N.H., Parmley, T.H., Ghodgaonkar, R.B., Rosenschein, N.B., and King, T.M. Effect of intrauterine **administration of tetracycline** on cynomolgus monkeys. *Contraception* **29:561-571** (1984)
8. Zaneveld, L.D.J., and Goldsmith, A., in *Female Transcervical Sterilization* (G.I. Zatzuchni, J.D. Shelton, A. Goldsmith, J.J. Sciarra, Editors). Harper & Row Publishers, Hagerstown, 1983, p. 122-127.
9. Laufe, L.E., and Wheeler, R.G., in *Female Transcervical Sterilization* (G.I. Zatzuchni, J.D. Shelton, A. Goldsmith, J.J. Sciarra, Editors). Harper & Row Publishers, Hagerstown, 1983, p. 115-121.

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