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CLINICAL EVALUATION OF QUINACRINE HYDROCHLORIDE
FOR STERILIZATION OF THE HUMAN FEMALE*

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Abstract

Sixty women seeking sterilization were treated with 1 gm of quinacrine in 7 ml of sterile water applied via a Kahn cannula with an olive tip held against the cervix. The tubal closure rate by hysterosalpingogram and/or pregnancy was 44%. In view of the need for multiple applications of this drug and some of the potential problems of the method as yet not clarified, widespread clinical trials are not warranted. **However**, further testing may resolve the current limitations and risks of the method to yield a useful clinical technique.

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Introduction

The successful transcervical application to the Fallopian tubes of a chemical agent which will consistently produce tubal closure without **producing** serious side-effects has long been a goal of investigators interested in human fertility and its regulation. Although a number of chemical agents have been identified which will close tubes in experimental **animals** and in humans, an acceptable system for their safe delivery has been elusive.

The, ideal system would be simple, inexpensive and could be used by non-specialist physicians or paramedical personnel on an office or out-patient basis. The original description by **Zipper et al.**(1) and subsequent **description(2)** of the use of quinacrine hydrochloride as a uterine lavage to produce tubal closure were encouraging in that the delivery system was extremely simple and inexpensive, but were discouraging because even after two instillations, the failure rate was high. Due to the design of the delivery system, it was not clear whether the failures were related to a lack of the quinacrine tube-closing ability, the delivery of an inadequate drug dosage, or to a failure to deliver the drug to the tube.

As part of an effort to determine why the failures occurred, we undertook a study of tubal closure in patients in whom high concentrations of quinacrine were delivered to the uterine cavity, using an olive-tipped Kahn cannula to increase the likelihood of tubal application.

Materials and Methods

Sixty women of reproductive age who wished to be sterilized were recruited from the Family Planning Clinic of Chulalongkorn University Hospital in Bangkok and were offered the opportunity to participate in this study. Most had been using a variety of contraceptive methods for varying periods of time prior to their being treated in this study. Patients were included only if they were in good health, and each was screened through a medical history and physical examination prior to treatment. They were in all phases of the menstrual cycle, except menstruation. None was thought to be pregnant on the basis of the screening.

The patients were placed on an examining table, a pelvic examination performed, a speculum inserted and the cervix exposed. The uterus was sounded and a Kahn cannula introduced into the uterine cavity, generally without the need for cervical dilatation. A rubber olive was adjusted against the cervix and a pre-filled 10 ml syringe locked on. The contents of the syringe were injected at a uniform rate over a clocked

20-second period and the syringe and cannula held in place for an additional clocked 40 seconds. Following the **quinacrine** application, the cannula was removed and the cervix and vagina inspected for evidence of reflux, the volume of **which** was estimated by the operator. The study was conducted with an observer-recorder present at all times in addition to the operator to ensure conformity with the protocol.

The material which was instilled into the uterine cavity was made up **immediately** prior to each procedure and consisted of 1 gm. of quinacrine HCl suspended in 7 ml of sterile water. Due to the dead space in the Kahn cannula, the actual amount delivered varied between 645 mg and 860 mg. In one patient only 3 ml was delivered due to leakage, and one had 7 ml delivered because 8 ml of water was erroneously used to make up the suspension. Postprocedure contraception was one injection of 150 mg depomedroxyprogesterone acetate intramuscularly.

The patients were recalled one month following the procedure, interviewed, examined and blood withdrawn for a determination of-hemoglobin, white blood count, total bilirubin and blood urea nitrogen. Four months following the procedure, **hysterosalpingograms** were performed to determine tubal patency.

Patients who became pregnant during the study were offered a therapeutic abortion and all failures were offered alternate sterilization procedures.

Results

The rates of tubal closure are summarized in the **Table**.

TABLE

TUBAL CLOSURE BY HYSTEROSALPINGOGRAM

Four months following one instillation of Quinacrine

Hydrochloride:

Patients undergoing instillation	60
Lost to follow-up	8
Pregnant at/or before hysteroogram	6 (2 underwent x-ray)
Patients undergoing hysteroogram	48
Bilateral tubal patency on x-ray	22 (46%)
Unilateral tubal patency on x-ray	3 (6%)
Bilateral tubal closure on x-ray	23 (48%)
Failure rate by x-ray and/or pregnancy	56%

Of the forty-eight patients who had **hysteroograms**, 48% had bilaterally blocked tubes, 6% had unilateral blockage, and,

in 46% both tubes were patent. In six patients or 12% of the fifty-two with follow-up, pregnancy occurred prior to the hysterosalpingogram. Some of these pregnancies may have occurred prior to treatment as previous contraception was of variable reliability, and the procedures were performed in all phases of the cycle but menstruation. There were no adverse patient reactions, either during the procedure, immediately thereafter, or up to the time of hysterosalpingography. All blood counts and chemistries were within normal limits.

Closure rates were tabulated for the various types of contraception reported by the patients just prior to the instillation of quinacrine. No significant correlations were found. The closure rate of women using systemic steroidal contraception was not different than those using local forms or none. The DMPA administered following the procedure may have an effect on the quinacrine action, but the study cannot evaluate this question.

Fifteen patients who were treatment failures at sixteen weeks underwent an alternative procedure for sterilization. Seven had hysteroscopic tubal cauterization performed and eight underwent laparoscopic sterilization. At laparoscopy, no abnormal findings were noted, and tubal cauterization with transection was done. In the hysteroscopy group, two patients were noted to have fine adhesions in the cornual regions of the endometrial cavity. The findings in the other five were normal.

Discussion

The data confirm the findings of **Zipper(3)** and **Davidson and Wilkins(4)** that quinacrine exerts an occlusive effect on the tube. The toxicity in this limited series was nil which also confirms their reports. Indeed, the rate of tubal closure in this trial was not significantly different from that reported by **Zipper(3)** (43.6%) after one instillation. Thus, this technique of application of quinacrine did not augment effectiveness for a single application.

Filling of the endometrial cavity with the quinacrine suspension as described by **Davidson(4)** rather than the lavage technique employed by **Zipper(3)** is more likely to deliver the quinacrine to the interstitial tube. Unfortunately, we are unable to determine from our data the specific relationships between quinacrine delivery to the Fallopian tube and the subsequent status of the tube. However, **Alvarado et al.(5)** have reported a series of cases in which a quinacrine suspension was placed in the Fallopian tube under direct hysteroscopic

control. The closure rates were low although the concentrations of quinacrine used by **Alvarado** were in the same range as those employed by **Davidson(4)** and by us. The technique they reported does not rule out the possibility that the quinacrine was washed from the tube following the intratubal injection. Nevertheless, **Alvarado's(5)** experience and the published data do suggest that quinacrine is a weak tubal sclerosing agent which will require multiple applications as **Zipper** has reported, to produce the desired effect in a significant percentage of women.

A sterilization technique requiring multiple treatments raises an obstacle to the ultimate applicability of such a method. In order to be acceptable the method cannot expose the patient who does not get the follow-up for whatever reason to an increase in life threatening risk. Such a situation was recently reported by **Israngkun(6)** following hysteroscopic tubal cauterly without follow-up hystero-graphy where the rate of ectopic pregnancy was inordinately high. The ectopic pregnancy rate following quinacrine treatment is unclear. **Zipper(3)** did not report any ectopic pregnancies in his series. More recently, he has described two ectopic pregnancies in his patients, but believes the ectopic pregnancy rate is not elevated over normal(7). On the other hand, the pathological data reported by **Davidson(4)** and **Alvarado(5)** suggest that partial tubal damage is a real possibility. Therefore, the ectopic pregnancy rate must be carefully established in a well followed group in order to clarify this important question.

Recently, **Joseph and Kincil(8)** have reported enteromegaly in rats treated with intratubal quinacrine leading to death in some animals. This effect is similar to findings initially described by **Keeler et al.(9)** following intraperitoneal injection in rats. This effect has not been seen by **Zipper(10)** in rats or humans. In our laboratory(preliminary tests in a small group of rhesus monkeys treated intraperitoneally with 1 gm of quinacrine suspension instilled into the pelvis at laparotomy demonstrated no local effect at sacrifice six weeks later. Obviously, the enteropathy question will have to be clarified, but it is of sufficient significance to merit caution for clinical application.

In view of the relatively low tubal closure rate after one treatment, even with the technique described which increases the likelihood of direct tubal application, the promise of quinacrine is limited unless some other method is found to augment the effect. The risks of accidental intravascular injection of quinacrine via the uterine veins, the new adverse animal data reported by **Joseph(8)**, and the undetermined ectopic pregnancy risk in a large treated population, limit the widespread clinical applicability of this method at this time.

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Plasma Levels of d-Norgestrel, Estradiol and Progesterone During Treatment with Silastic Implants Containing d-Norgestrel

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ABSTRACT

Six silastic capsules, each containing approximately 30 mg d-norgestrel, were inserted subcutaneously in 5 women. During treatment the plasma levels of d-norgestrel, estradiol and progesterone were determined by radioimmunoassay.

The highest levels of d-norgestrel in plasma were found initially. Decreasing levels in plasma were found during the first 60 days of treatment in most of the patients. Thereafter, the d-norgestrel concentrations were found to be fairly constant. Individual variations in the levels of d-norgestrel were observed.

The concentrations of d-norgestrel in plasma did not inhibit the baseline levels nor the surges of estradiol in plasma, but ovulation was inhibited in most of the patients. Ovulatory pattern of progesterone was restored within 50 days after removal of the capsules.

The calculated lifetime of the capsules suggest a contraceptive efficacy of at least 5 years.

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