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Overview of Clinical Trials With Quinacrine

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Surgical female sterilization is the most effective method of contraception for women who desire no additional children. In developing countries, the demand for female sterilization usually exceeds the ability of the countries to provide services; therefore, the development of a rapid, effective, and safe nonsurgical method that can be performed by paramedical personnel remains a high priority. In developed countries, such as the United States, a nonsurgical method of sterilization could considerably reduce the high cost of sterilization services, thereby making the method accessible to more women.

For over a decade, Zipper and associates have evaluated the use of the transcervical instillation of quinacrine hydrochloride for effecting permanent sterilization. The results from initial animal studies indicated that quinacrine selectively produced significant morphological changes in the reproductive tract and caused permanent tubal fibrosis and tubal occlusion in the rat.⁵ In subsequent clinical trials, various doses, concentrations, and solvents for the quinacrine instillation schedules were evaluated.^{6,7} These trials demonstrated that the use of quinacrine was potentially an effective method of permanent sterilization. Other investigators have also found the use of quinacrine to be effective for permanent female sterilization.¹⁻⁴

This chapter presents an overview of the results of three clinical studies conducted to evaluate the safety and efficacy of quinacrine as a method of nonsurgical female sterilization.

MATERIALS AND METHODS

The studies on the safety and effectiveness of quinacrine were conducted at an outpatient clinic in Santiago, Chile. The first study involved 200 patients and evaluated the efficacy of the repeated transcervical instillation of 1500

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mg quinacrine hydrochloride dissolved in 5 ml 2% lidocaine (Xylocaine). All instillation procedures were performed during the proliferative phase of the menstrual cycle. The second instillation was made in the first menstrual cycle following the initial instillation, and the third and last instillation at 6 months after the first. None of the patients used any adjunctive contraceptives. Follow-up visits were scheduled at 6-month intervals after the last instillation.

The second study, in 165 women, evaluated the efficacy of transcervical insertions of 250 mg quinacrine pellets preceded by a single pellet of 20 mg sodium thiopental, a hydrosopic agent used to increase the viscosity of the uterine fluid in an attempt to improve the uterine retention of the quinacrine. The procedure for inserting the quinacrine was essentially the same as is used for inserting an IUD. Insertions were performed only during the proliferative phase of the menstrual cycle. The procedure was repeated 1 month and again 2 months after the first insertion. None of these patients used any adjunctive contraceptives. Clinical follow-up was scheduled at 6-month intervals after the last insertion.

The third study, involving 138 women and also using quinacrine pellets, followed the same protocol as the second but without the sodium thiopental pellets.

For all studies, only those women who requested sterilization for family planning reasons and who did not have a history of psychiatric disorders were selected as subjects. Any woman excluded from the study was either scheduled for a surgical sterilization procedure or provided with another method of contraception. In these studies on the efficacy of quinacrine, the study end point was pregnancy and not tubal patency as demonstrated by hysterosalpingogram.

RESULTS

Mean age and number of live births of women entering the three studies are provided in Table 9-1. Mean age ranged from 3 1.3 to 33.5 years, and the mean number of live births ranged from 3.7 to 4.7.

Of the women entering the quinacrine solution study, 30% did not complete the three quinacrine instillation schedule, compared with 10.3% in the study of pellets with sodium thiopental and 12.3% in the study of pellets without sodium thiopental (Table 9-2). In part, this was a reflection of a difference in protocol, since in the quinacrine solution study there was a 6-

TABLE 9-1. Age and Live Births for Women Entering Studies of Quinacrine Hydrochloride

	QUINACRINE SOLUTION (N = 200)	QUINACRINE PELLETS WITH SODIUM THIOPENTAL (N = 165)	QUINACRINE PELLETS WITHOUT SODIUM THIOPENTAL (N = 138)
Mean age (years)	31.3	33.4	33.5
Mean number of live births	4.1	4.7	3.7

TABLE 9-2. Reasons Women Did Not Complete Three Administrations of Quinacrine Solution and Quinacrine Pellets

	QUINACRINE SOLUTION (N = 200)		QUINACRINE PELLETS WITH SODIUM THIOPIENTAL (N = 165)		QUINACRINE PELLETS WITHOUT SODIUM THIOPIENTAL (N = 138)	
	NO.	%	NO.	%	NO.	%
Reasons for not performing second administration						
Pregnancy	18	9.0	4*	2.4	5†	3.6
Transient psychosis	4	2.0	0	0.0	0	0.0
Ovarian cyst		0.5	1	0.6	0	0.0
Cervical synechia	0	0.0	0	0.0	1	0.7
Adnexitis	1	0.5	0	0.0	0	0.0
Amenorrhea	3	1.5	0	0.0	0	0.0
Severe headaches	1	0.5	0	0.0	0	0.0
Nerves	0	0.0		0.6	0	0.0
Patient choice	0	0.0	2	1.2	0	0.0
Patient failed to return	4	2.0	2	1.2	3	2.2
Total	32	16.0	10	6.1	9	6.5
Reasons for not performing third administration						
Pregnancy	23	11.5	0	0.0	2	1.4
Cervical synechia	0	0.0		0.6	0	0.0
Possible perforation	0	0.0	0	0.0		0.7
Cystic mass	0	0.0	0	0.0		0.7
Amenorrhea	1	0.5	0	0.0	0	0.0
Metrorrhagia	1	0.5	0	0.0		0.7
Intense vaginitis	0	0.0	0	0.0		0.7
Allergic skin reaction	0	0.0		0.6	0	0.0
Pelvic pain	0	0.0		0.6	0	0.0
Headaches	0	0.0	2	1.2	0	0.0
Patient choice	2	1.0	0	0.0	0	0.0
Patient failed to return		0.5	2	1.2	2	1.4
Total	28	14.0	7	4.2	8	5.8

*Two women were pregnant at first insertion and one failed to return for second insertion as scheduled.

†Two women were probably pregnant at first insertion and one failed to return for second insertion as scheduled.

month time period between instillation two and instillation three, compared with a 1-month period for both pellet studies. The data show that the unacceptably high pregnancy rate associated with the solution procedure in the time between the first and second instillations appears to have been reduced in the pellet studies. Four of the women who had quinacrine inserted and who were diagnosed as pregnant after the first insertion were thought to have been pregnant at the time of enrollment in the study. Two of these pregnancies were terminated by induced abortion, and two ended in spontaneous abortions.

TABLE 9-3. Gross Life-Table Pregnancy Rates Per 100 Women Completing Three Administrations of Quinacrine Solution and Quinacrine Pellets

	QUINACRINE SOLUTION (N = 131)	QUINACRINE PELLETS WITH SODIUM THIOPENTAL (N = 147)	QUINACRINE PELLETS WITHOUT SODIUM THIOPENTAL (N = 122)
6 month rate	6.5 ± 2.2 (95.2)*	1.4 ± 1.0 (96.6)	3.1 ± 2.2 (42.0)
12 month rate†	9.9 ± 2.7 (88.9)	4.3 ± 1.7 (93.0)	3.1 ± 2.2 (33.9)
24 month rate	13.1 ± 3.3 (49.6)	6.5 ± 2.1 (79.0)	

*Follow-up rate.

†Difference in the cumulative rates over 12 months (Mantel-Cox): quinacrine solution, quinacrine pellets with sodium thiopental, $p < 0.11$; quinacrine solution, quinacrine pellets without sodium thiopental, $p < 0.22$; quinacrine pellets with sodium thiopental, quinacrine pellets without sodium thiopental, $p < 0.70$.

The use of quinacrine pellets appears to have reduced the incidence of transient psychosis, a side-effect that has been observed in studies using intra-uterine quinacrine solutions. No women in the pellet studies developed transient psychosis, compared with 2.0% in the solution study. In the pellet study without sodium thiopental, one woman, after the second insertion, developed an acute pelvic inflammatory reaction that lasted 48 hours. We suspected that the pellets had perforated into the peritoneal cavity. The woman was treated with penicillin. No additional problems were encountered, and no more treatment was required.

The pellet method of quinacrine insertion appears to be more effective than the solution method (Table 9-3), although the differences in the cumulative rates are not statistically significant ($p > 0.05$). The gross life-table rate per 100 women at 12 months after the third quinacrine administration was 9.9 for the solution method, 4.3 for the pellets with sodium thiopental, and 3.1 for the pellets without sodium thiopental. To date, 16 women who completed the three instillations of quinacrine solution, 10 who completed the pellets with sodium thiopental regimen, and 7 who completed the pellets without sodium thiopental insertions have become pregnant (Table 9-4). Pregnancies have occurred from 2 to 27 months after the third administration; in some women, the tubes were probably never occluded, and in others, recanalization may have occurred. None of the pregnancies was ectopic. Most pregnancies were terminated by induced abortion. Four women carried their pregnancies to term without any apparent ill effects to the mother or fetus.

Other events reported after three administrations of quinacrine are shown in Table 9-4. It is not known whether all of these events are a result of the quinacrine Procedure or are merely the usual problems that would be seen in any gynecologic clinic. In addition to the two hysterectomies for chronic pelvic inflammatory disease reported in Table 9-4, two other hysterectomies were performed for genital prolapse, a condition unrelated to the quinacrine procedure.

TABLE 9-4. Events Occurring After Three Administrations of Quinacrine

Events§	QUINACRINE SOLUTION (N = 124)*		QUINACRINE PELLETS WITH SODIUM THIOPENTAL (N = 145)†		QUINACRINE PELLETS WITHOUT SODIUM THIOPENTAL (N = 83)‡	
	NO.	%	NO.	%	NO.	%
Pregnancy	16	12.9	10	6.9	7	8.4
Menstrual						
Amenorrhea	12	9.7	4	2.8	0	0.0
Menorrhagia	8	6.5	2	1.4	0	0.0
Dysmenorrhea	0	0.0		0.7	0	0.0
Pelvic						
Pelvic inflammatory disease	4	3.2	3	2.1	0	0.0
Endometritis		0.8	7	4.8		0.3
Leukorrhea	3	2.4		0.7	0	0.0
Urinary tract infection	3	2.4	3	2.2	3	3.6
Ovarian cyst	2	1.6	4	2.8	0	0.0
Adnexal mass	0	0.0		0.7	0	0.0
Uterine synechia	2	1.6	3	2.1	2	2.4
Myoma	0	0.0	4	2.8	0	0.0
Transient complaints						
Pelvic/abdominal pain	7	5.6	2	1.4	2	2.4
Headaches	3	2.4	6	4.1	0	0.0
Dispareunia		0.8		0.7	0	0.0
Total women with one or more events	50	40.3	40	27.6	16	19.3

*Of the 140 patients completing three instillations of quinacrine solution, 124 returned for one or more follow-ups.

†Of the 148 patients completing three insertions of quinacrine pellets with sodium thiopental, 145 returned for one or more follow-ups.

‡Of the 122 patients completing three insertions of quinacrine pellets without sodium thiopental, 83 returned for one or more follow-ups.

§Multiple events may be reported for each woman.

||Two women underwent hysterectomies.

CONCLUSION

Extensive research has been undertaken to develop a simple method of non-surgical female sterilization. The intrauterine use of quinacrine hydrochloride as a method of nonsurgical sterilization has evolved from instillations of a solution, to the development of pellets used with a potentiating agent, and then to the use of quinacrine pellets alone.

The major adverse effect of quinacrine solution administration was transient psychosis (2.0%); the use of pellets seems to have eliminated the risk of that complication (0.0%), probably because the pellet dissolves relatively slowly

(≤ 10 minutes) within the uterine cavity, reducing the risk of rapid intravascular absorption.

Animal studies were initiated to identify problems occurring if perforation occurs and quinacrine is accidentally placed in the peritoneum. At high doses, several animals died (see Chapter 6).

Excessive peritoneal absorption produced a high blood level of quinacrine, leading to death, and perhaps caused by a central nervous system reaction. High doses of quinacrine when administered intraperitoneally are clearly toxic. Additional animal studies are planned to determine if, by prolonging the *in utero* rate of release of quinacrine, the toxic side-effects may be avoided without affecting the ability of the drug to cause tubal fibrosis.

A comparison of results from various studies conducted by Zipper show that the pellet method of quinacrine delivery is an improvement over the solution method. Sodium thiopental does not seem to be a necessary adjunct to the procedure. However, the procedure still requires three administrations of quinacrine to be effective, thus falling short of the ultimate goal of an effective, blind, one-insertion procedure.

The erratic performance of the quinacrine pellets in occluding the tubes is probably caused by the uneven distribution of the quinacrine to the tubal ostia. Improvements in the delivery of quinacrine are being explored, including the use of an IUD to deliver the quinacrine to the tubal ostia. Another effort will explore the efficacy of a sustained-release pellet system in the hope that extended exposure of the drug will produce a higher rate of tubal closure.

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