



Phase I Prehysterectomy Studies of the Transcervical Administration of Quinacrine Pellets

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To determine the safety of transcervical administration of quinacrine pellets as a method of voluntary female sterilization, three noncomparative Phase I clinical trials of the administration of 250 mg quinacrine were carried out in 21 women who were scheduled to undergo hysterectomy 24 h or one month later.

Detailed results are presented for one of the trials using 10-min pellets. Six of 10 women had minor transitory complaints during the postinsertion 24-h follow-up period. Five women reported pelvic/abdominal cramping, one experienced headache, and one experienced dizziness. Blood chemistry values were not adversely influenced by the quinacrine. The average plasma level of quinacrine peaked at 3 h, 36.1 ng/ml, slightly lower than the value observed 4 h after oral administration of 200 mg in a previous study. An average of 27% of the administered dose was recovered in tampons. Quinacrine was detected in the plasma of two women at the four/six-week visit. Selected results are presented from two other trials that were halted because of slow recruitment.

The transcervical administration of 250 mg of 10-min quinacrine pellets was well tolerated. However, based on recent mutagenicity testing and meetings with regulatory officials, it appears unlikely that the use of quinacrine for nonsurgical sterilization could be approved in the United States or Europe. © 1996 Elsevier Science Inc. All rights reserved. CONTRACEPTION 1996;54: 18 1-1 86

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Introduction

Since the mid-1960s, researchers have been working toward the development of inexpensive non-surgical methods of female sterilization that involve simple delivery methods and are associated with minimum morbidity. The transcervical insertion of pellets of quinacrine hydrochloride with the use of a modified IUD inserter has been proposed as one such method. The quinacrine pellet method was developed by Dr. Jaime Zipper of Santiago, Chile, in collaboration with Family Health International (FHI).¹

In the mid 1980s, FHI conducted three Phase I studies of quinacrine pellets in the United States under an Investigational Exemption for a New Drug (IND) that had been granted to FHI by the U.S. Food and Drug Administration (FDA) in 1981. One of the studies was a 24-h prehysterectomy study using "lo-minute" quinacrine pellets formulated to have a dissolution half-life of about 10 min. The other two were one-month prehysterectomy studies, one with 10-min quinacrine pellets and the other with specially prepared, slow-dissolving, or "100-minute", pellets. The 100-min pellets were composed of a mixture of quinacrine and cholesterol. It was hypothesized that slow release of the quinacrine might increase exposure of the tubes to quinacrine. Due to slow recruitment, both of the one-month prehysterectomy studies were closed before completion.

FHI canceled its IND in 1990 due to various factors, including lack of funding and concerns about long-term safety and service delivery issues. However, a number of other researchers in various countries have continued to explore the use of quinacrine pellets.²⁻⁵ Due to recently increased interest and controversy regarding the use of quinacrine pellets,⁶⁻⁸ we are presenting the data from our Phase I studies.

We will present the methodology and results from the 24-h prehysterectomy study in detail. For the two, one-month prehysterectomy studies we will only present certain results: the data on adverse events, some

limited pathology data, and the data on the blood levels attained with the 100-min pellets.

Methods: 24-h Prehysterectomy Trial

Design

This study was designed to evaluate the safety and pharmacokinetic profile of quinacrine over a 24-h interval between the transcervical intrauterine administration of quinacrine hydrochloride pellets, 250 mg, and hysterectomy.

This noncomparative Phase I clinical trial was performed at a single clinical site in San Antonio, Texas, in 1983-84. Plasma, saliva, urine, and tissue collections were made as described below. The study protocol was reviewed and approved by the Institutional Review Boards of the University of Texas Health Science Center at San Antonio and Family Health International. All subjects gave written informed consent before entering the study. Women were observed for abdominal pain, headache, dizziness, or other adverse effects over the 24-h postinsertion interval.

Drug, Dosage, and Administration

Quinacrine hydrochloride pellets, with a dissolution half-life of about 10 min, were prepared by the University of North Carolina School of Pharmacy, packaged in modified IUD inserters, and sterilized. A total dose of 250 mg of quinacrine in pellets was transcervically administered into the uterus of each participant approximately 24 h before a scheduled hysterectomy. The insertion technique was similar to the insertion of a copper-T IUD. After measuring the depth of the fundus, the investigator introduced the IUD inserter into the fundus up to the indicated depth. The investigator then retracted the outer inserter tube while holding the plunger completely still, thus releasing the quinacrine pellets.

Blood and Saliva Specimens

Samples of venous blood and saliva were obtained at nine points over a 48-h interval, ranging from 24 h before to 24 h after hysterectomy (preinsertion and at ½, 1, 2, 3, 4, 10, 24, and 48 h postinsertion; total blood volume did not exceed 150 ml). Additional samples of blood, saliva and urine were to be obtained just before hospital discharge and at the four/six-week follow-up visit.

Urine and Tampon Collection

Total urine was collected from 0-48 h after quinacrine administration. Tampons were inserted in the vagina during the 24-h period from quinacrine inser-

tion to hysterectomy in order to recover any unabsorbed drug.

Tissue Samples

Following each hysterectomy, five uterine tissue specimens of about 500 mg each were taken, one from each cornua, one each from the posterior and anterior myometrium, including the endometrium, and one from the cervix, including the mucosa.

Assays

Clinical Chemistry Clinical chemistries of blood samples were determined by sequential multiple analyzer (SMA) for the following tests: cholesterol, triglycerides, glucose, blood urea nitrogen (BUN), creatinine, uric acid, sodium, potassium, chloride, CO₂, calcium, inorganic phosphorus, total protein, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Quinacrine Assays Frozen urine, saliva, plasma, and tissue specimens were shipped to Johns Hopkins University, Baltimore, Maryland, where quinacrine was measured spectrophotometrically.^{9,10}

Subject selection

The following inclusion and exclusion criteria were used for subject selection. For inclusion, the criteria were: (1) menstruating women, 2 1-50 years of age with a normal pelvic examination aside from the condition leading to hysterectomy; (2) >42 days since last pregnancy ended; (3) written informed consent; and (4) the procedure was able to be scheduled 6-12 days post-onset of menses.

Women were excluded if they had any of the following: (1) D&C within the previous six months; (2) use of an IUD in the past 30 days; (3) invasive cancer; (4) positive pregnancy test; (5) previous surgical sterilization; (6) history or evidence of pelvic inflammatory disease; or (7) history of significant disease of the cardiovascular, renal, hepatic, or central nervous system.

Results: 24-h Prehysterectomy Trial

Participants

The average age of the women was 26.6, with a range of 20-40. The average number of total live births that each woman had prior to the study was 2.6, with a range of 0-4. One subject's age constituted a protocol violation because she was only 20 years of age rather than 21. The reasons for hysterectomy included uter-

ine prolapse, dysfunctional uterine bleeding, and cervical carcinoma in-situ.

Adverse events

All 10 women completed the study. Six women reported minor transitory complaints during the 24 h following quinacrine administration. These complaints included pelvic/abdominal cramping or low back pain reported by five women, similar to the pain usually associated with menses. The duration of the pain ranged from 10 min to 3 h. The timing of the pain in relation to the quinacrine insertion procedure was variable, beginning as early as 2 h to as late as 18 h after the procedure. No medication was required by any of the women.

Two women had minor side effects relative to the central nervous system. One of the women who experienced cramping also had a brief episode of dizziness that occurred about 4 h after the procedure. While she attributed the dizziness to hunger, mild dizziness is commonly associated with orally administered quinacrine. She required no medication. A sixth woman complained of a headache, which started about 3 h after the procedure and lasted for about 2 h; she was given oral acetaminophen.

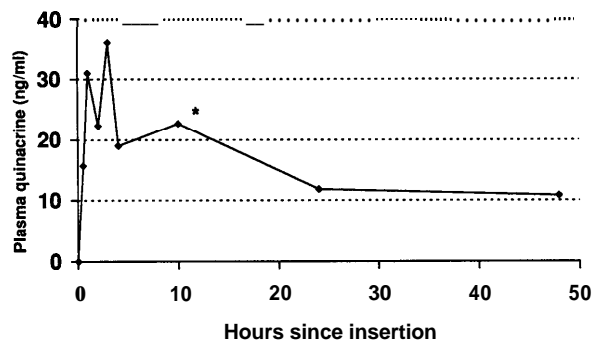
Clinical Chemistries

Although values for a few parameters fell outside the normal range, the abnormalities were generally minimal, sporadic, and transitory and were not considered clinically important or related to quinacrine administration. Of the abnormalities that were seen, most occurred in women who had had abnormal or borderline baseline results.

Pharmacokinetic Results

Of 110 planned blood samples, there were two missing, one each at the 1-h and 48-h sampling points. Plasma, saliva, urine, and tissue concentrations of quinacrine and tampon quinacrine content are presented below.

The mean plasma quinacrine concentration at each sampling time is shown in Figure 1. Blood plasma quinacrine concentrations peaked within the first 4 h after insertion. Six women had their highest levels 1 h after insertion (11.8-99.1 ng/ml), and four women at 2/4 h postinsertion (8.7-137.5 ng/ml). By 48 h postinsertion, the levels had decreased to about one-third of the peak values. Two of 10 women had detectable plasma quinacrine concentrations at the four/six-week follow-up visit; levels were low, 8.9 and 4.0 ng/ml. The highest average plasma level was 36.1 ng/ml at 3 h after intrauterine administration, while the av-



* The 10-hour value may be falsely elevated due to hemolysis.

Figure 1. Mean plasma quinacrine concentration by time since insertion (n= 10).

erage of the individual peak values, independent of time, was 46.3 ng/ml.

Saliva concentrations of quinacrine usually peaked later than blood plasma concentrations. However, the values were highly variable and were not correlated with plasma levels. Four women had their highest levels at 0.25 h after insertion (43.1-220.5 ng/ml); five women had their highest levels at 24 h or later after insertion (30.4-860.0 ng/ml); and quinacrine was not detectable at any time in the saliva samples of one woman.

Over the first 48 h, a mean of 2.3 mg of quinacrine was excreted in the urine (0.6-8.7 mg). This represents about 1% of total dose and is consistent with the well-known slow elimination of quinacrine and other related compounds following oral administration.

Table 1 shows quinacrine concentrations in the uterine tissues. No solid remnants of the quinacrine pellets were found, i.e., the pellets had completely dissolved. Mean tissue quinacrine concentrations

Table 1. Tissue quinacrine concentrations ng/mg net weight)

Patient	Anterior	Posterior	Left Tube	Right Tube	Cervix
1	51.3	9.7	51.3	70.5	19.0
2	28.6	9.5	28.5	14.8	52.1
3	11.4	54.9	17.1	32.2	39.4
4	72.7	130.8	41.3	5.2	24.1
5*	62.6	50.5	48.3	170.9	61.9
6*	39.9	5.1	23.2	12.8	6.7
7	5.0	4.0	28.7	23.2	20.9
8	12.0	5.2	61.5	26.1	5.1
9	59.9	9.9	7.8	76.2	-t
10	10.9	8.8	12.5	20.9	-t
Averages	36.2	28.8	32.0	45.3	28.7

* Specimen arrived thawed.

t - = Missing values.

ranged from 28.7 ng/mg in the cervical tissue sections to 45.3 ng/mg in the right cornual sections. Tissue quinacrine concentrations varied greatly within and among subjects. The mean concentrations in the five tissue segments studied did not differ significantly.

Tampons, which had been worn for 24 h after quinacrine insertion, were analyzed for nine of the 10 women. The mean quinacrine content of tampons was 68.0 mg (27% of dose), with a range of **13.5-111.8** mg (5% to **45%**).

Results: One-Month Prehysterectomy Trials

Adverse Events

Subsequent one-month prehysterectomy Phase I clinical trials were begun in 1985 and 1986 with 10-min pellets and 100-min pellets, respectively. Recruitment was difficult and only five and six patients were recruited in the two trials before they were discontinued. In the trial of the 10-min pellets, two of the five women reported adverse events.

Patient number 4 reported heavy vaginal bleeding that started approximately 24 h after insertion and lasted for two days, at which time a heavy brown discharge was noted, which had stopped by day 14. On day 21, the same woman complained of a thick, yellow discharge.

Patient number 5 complained of severe cramping pains and a spotty discharge which began about 2 h after the insertion. The pain decreased with oral acetaminophen, but occasional cramping pains similar to menses lasted for about two weeks. The same woman complained of headaches about a week later. None of these complaints were judged to be serious by the investigator and none required treatment other than oral analgesics.

In the trial of the 100-min pellets, five of the six women reported adverse events as follows: Patient number 2 reported copious clear, yellow vaginal discharge on day seven which was resolved by day 14.

Patient number 3 had low-abdominal pain and watery, blood-tinged vaginal discharge starting at 12 h postinsertion; the abdominal pain resolved by 24 h postinsertion and the discharge resolved by day seven.

Patient number 4 reported vaginal bleeding starting at 2 h postinsertion which was resolved by day 14. This patient also experienced an achy feeling and a low-grade fever and chills beginning 2-4 h after quinacrine insertion. In addition, soreness of the left shoulder and right leg, palpitations, and a shaky feeling were reported at 12 h postinsertion; chills, fever, neck pain, shortness of breath, and buzzing in the ears were reported at 24 h postinsertion. The patient reported

that taking alcohol baths and eating garlic relieved the shortness of breath. The patient was followed closely on an outpatient basis, and did not require hospitalization or specific therapy.

The investigator summarized this episode as having lasted five days, with the worst symptoms lasting for about the first 24 h. The event was judged to be of moderate severity.

Patient number 5 experienced vaginal bleeding starting at 2 h postinsertion which resolved by day seven. She reported low-abdominal cramping at 12 h postinsertion, which was followed by intermittent pain in the right lower quadrant lasting about two weeks. At one-day postinsertion she reported labial irritation with burning, and also said that she had chills and fever the previous evening. Her temperature had returned to normal at the time of the one-day follow-up visit.

Patient number 6 experienced cramping and vaginal bleeding from 2 h postinsertion until day seven; on day seven the patient complained about leg numbness from the knees down and ankle edema, neither of which were present at the physical examination.

Pathology and Blood Levels from the One-Month Trials

Gross examinations of the removed uteri from the one-month trials did not show any evidence of intra-uterine adhesions, synechia, or extra-uterine adhesions. However, in one woman who had received the 100-min pellets, the surgeon reported the presence of filmy adhesions from the cornu and top of the uterus to the omentum. It was not possible to determine whether those adhesions were due to quinacrine or whether they were pre-existing.

Histologic examination of removed segments of the Fallopian tube, mostly the interstitial segments, showed mixed results. Data were missing for five tubes. Of available data on 17 tubes, there was absence of the epithelium or obliteration of the lumen in nine tubes, while eight tubes showed normal epithelium, or only mild inflammatory changes.

Histological examination of endometrial sections showed either normal secretory or proliferative pictures, depending on the woman, and four minor abnormalities. Two women had findings of adenomyosis; these probably predated their quinacrine insertions. One woman had evidence of chronic endometritis and one woman had a report of "focal cystic change," which is sometimes seen in cases of atrophic endometrium. These two findings may have been related to quinacrine.

The blood levels measured in the trial of the 100-min pellets were, as expected, significantly lower than the levels seen after the 10-min pellets. No con-

centration of quinacrine could be found in any of the baseline samples or in any sample collected at day 14 or later; the mean standard deviation (SD) quinacrine serum concentration was 7.23 (2.9) ng/mL at 2 h, 7.01 (2.8) ng/mL at 12 h, 3.51 (0.7) ng/mL at day one, and 0.29 (0.3) ng/mL at day seven.

Discussion and Conclusions

Adverse Events

No serious adverse events were reported among the 15 women who received the lo-min pellets. This number of women is too small to make any generalizations about adverse events; however, reports of larger, more recent clinical studies also suggest that the procedure is well tolerated.²⁻⁵

More adverse events were reported from the study of the 100-min pellets, including one which was judged to be of moderate severity by the investigator. A larger trial of 100-min pellets conducted by Dr. Zipper in Chile² reported two cases of pelvic inflammatory disease among 112 women following the first insertion of the 100-min pellets. It is possible that those cases of pelvic inflammatory disease were actually cases of chemical peritonitis resulting from spillage of some quinacrine through the tubes into the peritoneal cavity. Three cases of hematometra were also reported among the 103 women in that study who received two insertions.

Cases with signs of peritoneal irritation, or hematometra, have been much less commonly reported following the use of lo-min pellets.²⁻⁵ In a recent study of quinacrine pellet insertions, 10% of 100 women complained of fever after the first insertion. However, none of these women were judged to have had a serious reaction.²

It is possible that the 100-min pellets caused local toxicity due to their prolonged presence in the uterus. One could speculate that as the uterus tried to expel the slow-dissolving pellets, occasionally a still-solid pellet might physically obstruct the cervical canal. If that occurred, continuing uterine contractions might result in the expulsion of some dissolved quinacrine out into the peritoneal cavity through the Fallopian tubes.

Little additional data are available concerning the 100-min pellets. Difficulties in formulating pellets with uniform dissolution time led to the abandonment of their development. Given the small sample sizes involved in the studies of the 100-min pellets and the absence of any randomized trials comparing the 10-min with the 100-min pellets, it is not possible to conclude whether the adverse events observed in the trial of the 100-min pellets were related to their slow dissolution time or to the presence of chole-

sterol, or were just a reflection of better reporting. A randomized, blinded study comparing lo-min versus 100-min pellets was never done.

Pathology

An unpublished manuscript by Alegria et al. reports the presence of necrotic endometrial tissue after 48 h, and regeneration of normal endometrium after one month. While we do not have pathology data on the uteri removed after 24 h, the uteri removed after one month showed grossly normal endometrial tissues. Two women had endometrial abnormalities on histological examination that may have been due to quinacrine, but their clinical significance is unclear.

A paper by El Sahwi³ reported hysteroscopic observations after one, two, and three insertions. He reported no endometrial abnormalities after a single insertion, but increased abnormalities after two and three insertions. He noted mainly atrophic and polypoid reactions; in addition, three of 20 women had fine adhesions after three insertions. In the absence of symptomatic hematometra, most authors have not attributed any clinical importance to intrauterine lesions caused by quinacrine, but this issue may merit additional study.

On histologic examination, only about 50% of the Fallopian tubes had appeared to be obstructed. This does not seem consistent with the clinical observations of pregnancy rates following one or two quinacrine insertions. There are at least two hypotheses which could be considered as explanations for this apparent discrepancy. First, based on Merchant's suggestion that Fallopian tube closure takes up to six weeks, one might hypothesize that some of the apparently normal tubes would have closed if given more time.¹²

The second hypothesis takes into account El Sahwi's observations, described above, regarding endometrial changes. While it has been generally considered that quinacrine acts only by occluding the Fallopian tube, it is possible that some of quinacrine's effectiveness is due to its ablative effect on the endometrium. Endometrial ablation procedures generally result in subsequent infertility, and quinacrine may act partially through a similar mechanism.

Pharmacokinetics

The lo-min pellets of quinacrine used in the 24-h hysterectomy study produced plasma levels of quinacrine that were similar to levels found after oral administration of 200 mg. Using the same spectrophotometric assay method,¹⁰ Shannon reported an average level of 59.9 ng/ml 4 h after an oral dose of 200 mg, compared with an average level of 36.1 ng/ml

3 h after intrauterine administration in the current study.¹³ The average of the peak values from the present study is 46.3, still below the level reported from oral administration. Shannon's study also showed a wide range of values, from **19** to **124 ng/ml**. While both investigators used the same method,¹ it should be noted that these two studies were done in different laboratories, and about 40 years apart, so there may be some unknown limitations in the comparability of the results.

Plasma levels of quinacrine after administration of the 100-min pellets were considerably lower, with values of only around 7 ng/ml at 2 and 12 h, compared to about 30 and 20 ng/ml, respectively, for the 10-min pellets.

There was only a weak correlation ($r = 0.47$) between peak plasma levels and the absorbed dose, which was calculated as 250 mg minus the amount of quinacrine found on tampons. The wide variation in tampon content could be an artifact due to leakage of some quinacrine around the tampons.

As is the case with other anti-malarials such as chloroquin, quinacrine has a long elimination half-life in humans. Two women still had low, but detectable, plasma levels of quinacrine at four/six weeks after the insertion.

In conclusion, the transcervical administration of 250 mg of 10-min quinacrine pellets was well tolerated. The peak plasma levels were similar to those observed following oral administration. The use of 100-min pellets was associated with more side effects, but because of the small sample sizes, the reasons and significance of this difference cannot be determined.

Future Prospects

WHO has recommended that appropriate toxicology testing be completed on quinacrine prior to further human studies of quinacrine pellets. In response to this recommendation, FHI sponsored a Toxicology Experts Meeting held April 24, 1994, in Arlington, VA. FHI then sponsored the conduct of four genetic toxicology tests by Microbiologic Associates in late 1994. These tests confirmed quinacrine's mutagenicity. Based on the results of these tests and consultation with representatives of regulatory agencies, it is unlikely that the transcervical use of quinacrine pellets could be approved in the U.S. or Europe.

While FHI is involved in long-term safety studies of women who have received quinacrine, FHI is not conducting or planning any clinical studies with quinacrine. Pre-clinical studies could be planned to

evaluate potential non-mutagenic substitutes for quinacrine, if funding were available.

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