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An FDA Phase I clinical trial of quinacrine sterilization (QS)

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Abstract

Objective: To review the significance of a United States Food and Drug Administration (FDA) approved Phase I clinical trial of a new use for an old drug, quinacrine. To discover whether ultrasound may have utility in quinacrine sterilization (QS). *Method*: This clinical trial began on 16 September 2000 at the Women's and Children's Hospital of Buffalo (WCHOB) in Buffalo, New York. Ten patients volunteered to have QS. These subjects were carefully followed with regularly scheduled examinations, including extensive laboratory blood tests. In addition, each patient had a trans-abdominal ultrasound examination six weeks or later past the date of the second insertion of quinacrine. The trial was completed on 30 April 2003. *Results*: Laboratory results fell within normal limits, thus providing additional evidence to affirm the lack of toxic effects of QS. With ultrasound, we were able to see scars in both oviducts on all of our patients. One patient with a small scar as seen on ultrasound became pregnant. *Conclusion:* QS was found to be safe and effective. Ultrasound holds the promise of reducing the failure rate.

Keywords: quinacrine sterilization (QS), FDA, oviducts, ultrasound

1. Introduction

Quinacrine has been safely used for over 70 years to treat malaria. More than a 100 million people have taken this drug and no toxicity of any major importance has been reported. The drug is still being used for treating other diseases including giardiasis, rheumatoid arthritis, lupus and tapeworm. In 1942, the Winthrop company published a 71-page bibliography with 171 toxicology articles attesting to the safety of quinacrine [1].

QS now has a history spanning more than 30 years of continuously improving results attesting to its safety and effectiveness [3–7]. Kessel reported on 100,000 documented cases of QS without a death and without a major adverse event (AE) requiring surgery [7].

This paper describes an FDA-approved Phase I clinical trial of QS. It was directed and managed at the Women's and Children's Hospital of Buffalo (WCHOB), in Buffalo, New York. The protocol for this study was approved by the Investigational Review Board (IRB) of WCHOB. The investigators took the on-line course and exam for the protection of human subjects offered by the United States National Institutes of Health (http://ohsr.od.nih.gov/cbt). This hospital is one of the main teaching institutions of the School of Medicine of the State University of New York at Buffalo.

2. Materials and methods

An important concern of any clinical investigation

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is protection of human subjects. For this trial, the investigators read and became familiar with the Belmont Report, The Helsinki and International Harmonic Conventions, a requirement of the IRB of the WCHOB for any research involving human subjects.

Recruitment of patients was accomplished by posting notices in various hospital clinics and advertising in local newspapers, with the prior approval of the IRB of WCHOB. Each patient was informed about quinacrine sterilization when she made an inquiry. She was provided with written materials and watched a video describing the technology. Patients, who were all Caucasian, were then given an informed consent document to take home for one month or longer if needed. This enabled them to read it at their leisure and consult with relatives, spouses, friends and advisors, as they deemed necessary. At the second clinic visit, they signed the informed consent, keeping a copy for themselves. At this visit, a medical history was obtained and a complete physical examination, including a pelvic exam, was performed. All except one of these women had regular menses. Extensive laboratory work was done at this visit as well as on subsequent visits. Laboratory tests included a urinary pregnancy test (UPT), a urine analysis (UA) and a complete blood count (CBC) with a differential count. Other tests administered were electrolytes, a blood urea nitrogen (BUN), creatinine, blood glucose and glucose-6-phosphate dehydrogenase (G6PD). Quinacrine is contraindicated in patients with a G6PD deficiency.

A Pap smear of the cervix and vagina was done, and cultures were obtained for gonorrhea and chlamydia. These were repeated every six months. Patients who demonstrated pathology either on physical exam, laboratory tests or with the cultures were either treated or referred to an appropriate clinic for further therapy. They were readmitted into the program when these conditions were cleared and the appropriate laboratory tests came within normal limits. Timing of the third visit was determined by the patient to have QS performed within three days of the end of the next menses.

At the time of this first quinacrine insertion, a UPT was done and patients were given a choice of a backup contraceptive to be used for three months to prevent pregnancy during the scar-forming period. Depot medroxyprogesterone acetate (DMPA) was one convenient way to provide the desired three months of protection. Other contraceptives were offered with the choice being left to the patient. A second insertion of quinacrine was set to follow four weeks after the first one. At each visit, a UPT was done before the procedure to avoid inserting quinacrine into a pregnant uterus. Follow-up visits were scheduled at 3, 6, 12 and 15 months after the second visit. To manage pain and cramps we used Tylenol® and/or Tylenol® with codeine, and avoided relying on non-steroidal anti-inflammatory drugs (NSAID). AEs were carefully recorded at all patient contacts, including telephone calls. Fifteen months of follow-up of each subject were summarized to allow at least one year of exposure to QS for analysis.

3. The use of ultrasound

After initiating our clinical trial, we learned about the value of pelvic ultrasound (US) as applied to QS from Dr. Claudia Ramos Ferreira of Belo Horizonte, Brazil [8]. We were impressed by Dr. Ferreira's pictures demonstrating, for the first time, scars in the oviducts. US was then used to evaluate oviductal scar formation on all our ten patients. An ATL-5000 ultrasound machine with three-dimensional software enabled us to obtain an in-depth view of the pelvis. Utility was found with a 5 to 4 MHz transducer and on those occasions where endovaginal examination was done, a 7 to 10 MHz endovaginal transducer was used. All US pictures were taken with the transducer viewing the pelvis transabdominally. Results of this are presented in Figs. 1 through 4.

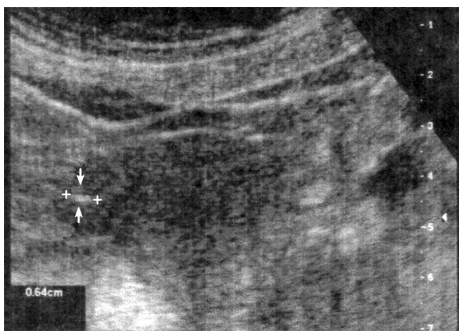

Fig. 1. Scar in right oviduct measuring 0.64 cm. Women's and Children's Hospital of Buffalo. Buffalo, New York, 2002.

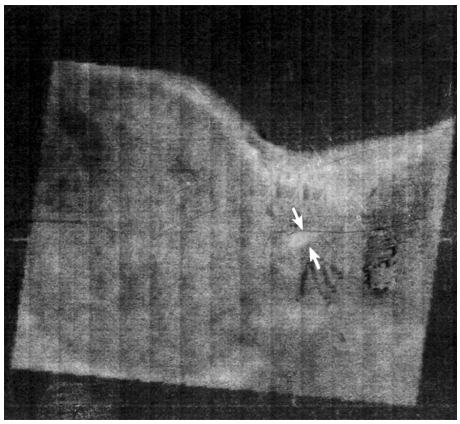

Fig. 2. Scar in left oviduct. Women's and Children's Hospital of Buffalo. Buffalo, New York, 2002.

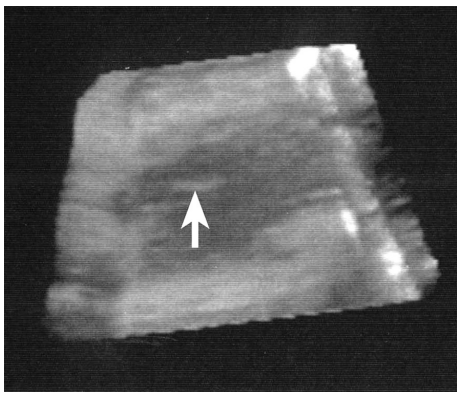

Fig. 3. Scar in oviduct. Women's and Children's Hospital of Buffalo. Buffalo, New York, 2002.

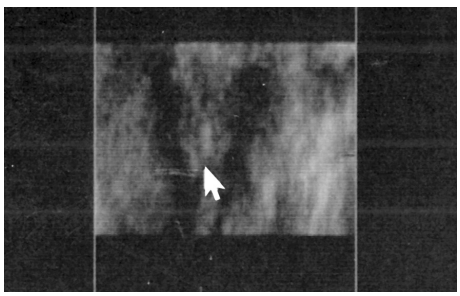

Fig. 4. Scar in oviduct. Note: Canalization through this 3 mm scar. Women's and Children's Hospital of Buffalo. Buffalo, New York, 2002.

4. Results

Ten patients had volunteered for QS in this FDA approved study. Admission and follow-up of these women provided data summarized in Table 1, which also shows the demographic characteristics of the study population. The primary goal of a Phase I FDA study is safety, and this was demonstrated when none of the patients suffered any serious AEs, Pap smears showed no adverse cytologic changes and all laboratory tests fell within normal limits. One exception was a patient who had a hematocrit slightly lower than normal. She was placed on iron with vitamin C and her family doctor was notified about the mild anemia.

Since the FDA had requested that the majority of our subjects should be at high risk, eight of the ten were so recruited. In this high-risk definition is obesity and heavy smoking. Four patients were diagnosed as obese and four were known to be heavy smokers. One also had hypertension. Another had suffered degenerative lumbar discs and vertebrae which necessitated surgical placement of a spinal prosthesis. As she was unable to lie on her back for more than ten minutes, she was considered a high risk for general anesthesia and/or surgery. Two patients were normal.

Some of the women suffered minor AEs, e.g., abdominal cramps, mild pain, nausea, yellow vaginal discharge and pruritis. One had nausea and emesis the evening after a quinacrine insertion. After the first patient complained of yellow discharge and pruritis, we recommended that they all douche once a day as soon as they see the discharge. This eliminated the annoying side effect of pruritis for the remainder of our group. Minor complaints were easily managed.

The second part of this trial involved the use of transabdominal ultrasound of all patients. Oviductal scars could be seen in all ten cases. Typical US pictures are shown in Figs. 1–4. Scars varied in size from 3 mm to 15 mm. There was one pregnancy failure which occurred 18 months after the patient had received her second insertion of quinacrine. Interestingly, the smallest measured scar of 3 mm was observed in this patient, and US examination was repeated for her at 12 weeks' gestation. A canal could be seen coursing through this small 3 mm scar (Fig. 4). Scanning, which is a motion picture of the pelvis, is frequently necessary to ascertain that a scar is definitely present and a snapshot can be taken but may not be persuasive, as exemplified in Figs. 3 and 4.

Table 1
Summary of 10 patients receiving intrauterine quinacrine sterilization (QS). Women's and Children's Hospital of Buffalo, Buffalo, New York. September 16, 2000 – May 1, 2003

Patient #	Age	Parity	Gravida	Medical complications	Menses	1st Visit EDU	2nd Visit H&P	3rd Visit 1st Insert	Phone Call	Lab Work	Contra-ception	4th Visit 2nd Insert	2nd Phone Call	Adverse Events	WM
1	33	5	5	Smoker	Reg	9/16/00	10/17/00	10/26/00	11/3/00	WNL	DMPA	11/29/00	12/6/00	None	18.0
2	29	1	1	Obesity, 181 lbs.	Irreg	12/4/00	1/8/01	3/5/01	3/12/01	WNL	DMPA	4/2/01	4/9/01	Severe cramps and emesis after 1st insert	36.5
3	40	2	2	None	Reg	1/8/01	2/7/01	2/21/01	2/28/01	WNL	OC	3/21/01	3/28/01	Slight bleeding; Slight Cramps, 1st Insert	37.5
4	45	7	9 2 AB	Smoker, 1 small fibroid	Reg	2/1/01	2/21/01	4/20/01	4/27/01	WNL	Condoms	5/17/01	5/24/01	Slight cramps, 1st insert and pruritis	32.5
5	38	3	6 2 spont AB 1 ectopic	3 degenerative discs Walks with cane. On methodone	Reg	2/16/01	4/4/01	6/6/01	6/13/01	Low hct 1st visit	Condoms	8/27/01	9/3/01	Mild cramps 1st insert Moderately severe cramps 2nd insert	27.0
6	30	2	2	None	Reg	3/5/01	4/20/01	5/8/01	5/15/01	WNL	OC	7/6/01	7/13/01	Slight cramps	30.5
7	32	2	3	Obesity, 176 lbs.	Reg	3/12/01	5/3/01	5/29/01	6/5/01	WNL	OC	6/27/01	7/4/01	None	31.0
8	36	4	4	Smoker, Obesity 169 lbs.	Reg	4/19/01	5/30/01	6/5/01	6/12/01	WNL	Condoms	7/6/01	7/13/01	Night sweats after each insertion	30.5
9	41	3	4	Smoker	Reg	8/17/01	9/11/01	11/19/01	11/26/01	WNL	DMPA	12/19/01	12/26/01	Mild cramps Slight vaginal discharge 1st insert	19.0
10	41	1	1	Obesity	Reg	9/27/01	11/12/01	12/4/01	12/11/01	WNL	DMPA	1/16/02	1/23/02	Slight vaginal discharge each insert	17.0
Mean	36.8	3.0	3.5												28.0
															Total[a] 279.5
															Range 17–45 months

Abbreviations:
EDU, Educational visit
WNL, Within normal limits
DMPA, Depot medroxyprogesterone acetate
AE, Adverse event
WM, Woman-months
H&P, History & physical examination
OC, Oral contraceptive

[a] 1.5 months subtracted from each case after date of 2nd insertion. During this time, alternate contraception was used to allow for scar formation.
Race: all patients were Caucasian.

5. Discussion

This paper adds to the volume of literature on the safety and effectiveness of QS. It is important to note that this study was carried out with the approval of the United States Food and Drug Administration (FDA) as well as the IRB of the WCHOB. The concern that intrauterine quinacrine might cause cancer is now seen to be remote. Long clinical experience in many countries has revealed no evidence of an increase in the incidence of uterine or any other cancer associated with QS [9]. Furthermore, the National Cancer Institute, in its annual report of 1994, lists quinacrine as an anti-carcinogenic compound [10]. Previously, the FDA had approved a pre-hysterectomy study of QS [2].

For pain or cramps patients received or were prescribed Tylenol® or Tylenol® with codeine. We avoided using nonsteroidal anti-inflammatory drugs (NSAID). Our rationale for this is that pre-hysterectomy studies of QS have shown it to produce inflammation followed by sclerosis and scarring [2]. As inflammation preceded scarring, it seemed reasonable to expect that an anti-inflammatory drug might inhibit the effect of quinacrine. QS produced no changes in extensive laboratory tests performed repeatedly on all ten patients. In this small series, QS has proved to be both safe and effective as is already well documented in the world's medical literature [2–6].

The ability to see the oviductal scars with ultrasound was reassuring to both patients and staff. The observation that the one failure coincided with the smallest fallopian tube scar presents a potential practical application of ultrasound for QS. A thesis is suggested that the size of the scar may correlate with failures of QS, i.e., the smaller the scar the greater the chance for a failure or pregnancy. Will we arrive at the day when the gynecologist will be able to recommend a third insertion of quinacrine because the scar in the oviduct is too small? This knowledge can only be acquired when QS is in the hands of many clinicians and we can collect and analyze data from a large number of collaborative studies.

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