

Efficacy of two insertions of 100-minute releasing quinacrine hydrochloride pellets for non-surgical female sterilization

J. ZIPPER¹, L.P. COLE², M. RIVERA¹, E. BROWN² and R.G. WHEELER³

¹Hospital Sotero del Rio, University of Chile, Santiago, Chile

²Family Health International, Research Triangle Park, North Carolina, USA

³Wheeler Consulting, Product Design and Development,
Greenbank, Washington, USA

Abstract

Extensive research has been undertaken to develop a simple method of non-surgical female sterilization. Zipper and associates identified quinacrine hydrochloride as a drug likely to produce tubal occlusion when placed into the uterus. Zipper's early work with a solution of quinacrine led to the development of quinacrine pellets, a delivery system that was designed to bring the quinacrine into prolonged contact with the tubal ostia through extended uterine retention. Three transcervical uterine insertions of 10-minute releasing quinacrine hydrochloride pellets performed at monthly intervals have produced a 12-month pregnancy rate of 3.3 per 100 women. The ultimate goal is to develop an effective, single insertion procedure, but the performance of the quinacrine pellets in occluding tubes has necessitated more than one insertion. FHI developed a 100-minute extended release pellet system with the expectation that more prolonged drug exposure would produce a higher rate of tubal closure. A study of the 100-minute releasing pellet system has been conducted in Santiago, Chile. Two monthly insertions in 112 women has resulted in a 12-month pregnancy rate of 2.0 per 100 women. Postprocedure problems occurring within the first year were reported by 13% of the women; most were minor and transitory.

Introduction

Extensive research has been undertaken to develop a simple method of non-surgical female sterilization including small scale clinical investigation, in the United States. Zipper and associates have worked in this area for many years and have identified quinacrine hydrochloride as a chemical likely to produce tubal occlusion when placed in the uterus [1-3]. Zipper's work led to the development of quinacrine hydrochloride pellets which were designed to bring the chemical into prolonged contact with the tubal ostia through extended uterine retention. Early studies with pellets which dissolved over a 10-minute period showed that three insertions were required to obtain an acceptable 12-month pregnancy rate of less than 5 per 100 women [4,5]. The ultimate goal is to develop an effective, single insertion procedure; therefore, pellets were developed to dissolve over a 100-minute period. The longer release rate is expected to produce a higher rate of tubal closure and thus reduce the number of insertions required.

The efficacy of transcervical insertions of 10- and 100-minute releasing quinacrine pellets to produce tubal occlusion has been evaluated in two studies conducted in Santiago, Chile. Results from the 10-minute releasing pellet study have been presented previously [4].

Materials and methods

Each quinacrine hydrochloride pellet is cylindrical and has a diameter of less than 4 mm. The pellets are compressed to contain 10 mg quinacrine per millimeter of length. Insertion is accomplished by placing the pellets in a plastic tube with a push rod positioned behind them. The insertion procedure is essentially the same as that for inserting an IUD.

The two studies evaluating the safety and effectiveness of quinacrine hydrochloride pellets for female sterilization were conducted at an outpatient clinic at the Hospital Sotero del Rio in Santiago, Chile. The first study involved 143 patients and evaluated the efficacy of three transcervical insertions of 250 mg of 10-minute releasing quinacrine pellets. Women entered the study from December, 1978, through October, 1982. Seven pellets containing a total of 250 mg quinacrine hydrochloride were to be inserted at admission and again at one month and two months after admission. Insertions were performed during the proliferative phase of the menstrual cycle in women who had not recently been pregnant (>42 days since last pregnancy terminated). No additional contraceptives were used. Clinical follow up was scheduled at 6, 12 and 24 months after the third insertion and at any time when complications or complaints occurred.

The second study involved 112 patients enrolled from July, 1982 through October, 1984, and used 250 mg of 100-minute releasing quinacrine pellets at each insertion. Two insertions were given; the procedure was repeated one month after the first insertion. Otherwise, the same protocol used in the first study was followed.

For both 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. The end point of the studies was pregnancy and not tubal patency as demonstrated by hysterosalpingogram.

Results

Mean age and number of live births of women entering the two studies are provided in Table 1. Mean age was 33.5 in the study evaluating the 10-minute releasing pellets and 31.4 in the 100-minute releasing pellet study. Mean number of live births was 3.7 and 3.6 for the two studies.

Table 1 Age and live births for women entering studies of quinacrine hydrochloride

	Three insertions of 250 mg of 10-minute releasing quinacrine pellets (n = 143)	Two insertions of 250 mg of 100-minute releasing quinacrine pellets (n = 112)
Mean age (years)	33.5	31.4
Mean number of live births	3.7	3.6

Of the women entering the 10-minute releasing pellet study, 14.0% did not complete the scheduled three quinacrine insertions, compared with 5.4% who did not complete the two scheduled quinacrine insertions in the 100-minute releasing pellet study. Reasons for failing to complete the insertion schedule are given in Table 2.

Two of the women who had 10-minute releasing quinacrine pellets 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. One pregnancy terminated in an induced abortion and the other ended in a spontaneous abortion.

Two women, one in each study, who did not return for their second insertion as scheduled became pregnant, one at three months and the second at two months after the first insertion.

In the 10-minute releasing pellet study, one woman, after the second insertion, developed an acute pelvic inflammatory reaction which lasted 48 hours. The pellets may have perforated into the peritoneal cavity. The clinical course of the complication precluded the necessity for surgical diagnosis or treatment. The woman was treated with penicillin; no more treatment was required and no additional problems were encountered.

The gross cumulative life table pregnancy rate per 100 women at 12 months after completed treatment was 3.3 for the 10-minute releasing pellets and 2.0 for the 100-minute releasing pellets (Table 3). One-year life table rates reflect a total of four pregnancies with the 10-minute releasing pellets and two pregnancies with the 100-minute releasing pellets.

Events reported within one year of completed insertions of quinacrine (Table 4) include the usual problems seen in any gynecologic clinic, and

Table 2 Reasons women did not complete scheduled insertions of quinacrine pellets

	Three insertions of 250 mg of lo-minute releasing quinacrine pellets (n = 143)		Two insertions of 250 mg of 100-minute releasing quinacrine pellets (n = 112)	
	No.	%	No.	%
Reasons for not performing second insertion				
Pregnancy	5*	3.5	1**	0.9
Cervical synechiae	1	0.7	0	0.0
Pelvic inflammatory disease	0	0.0	2	1.8
Patient failed to return		2.1		2.7
Total	9	6.3		5.4
Reasons for not performing third insertion				
Pregnancy	2	1.4		
Possible perforation	1	0.7		
Cystic mass	1	0.7		
Metrorrhagia	1	0.7		
Intense vaginitis	1	0.7		
Patient failed to return		3.5		
Total	1	7.7		

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

** Patient failed to return for second insertion as scheduled

Table 3 Gross life table pregnancy rate per 100 women completing scheduled insertions of quinacrine pellets

	Three insertions of 250 mg of lo-minute releasing quinacrine pellets (n = 123)		Two insertions of 250 mg of 100-minute releasing quinacrine pellets (n = 106)	
	No.	%	No.	%
6-month rate	1.7	(97.5)	2.0	(93.3)
12-month rate	3.3	(96.7)	2.0	(83.7)
24-month rate	6.7	(96.5)		

Table 4 Events occurring within 12 months of completed insertions of quinacrine pellets

Events	Three insertions of 250 mg of lo-minute releasing quinacrine pellets (n = 121)*		Two insertions of 250 mg of 100-minute releasing quinacrine pellets (n = 103)**	
	No.	%	No.	%
Pregnancy	4	3.3	2	1.9
Pelvic				
Vaginitis	0	0.0	1	1.0
Trichomoniasis	0	0.0	1	1.0
Vaginal bleeding	0	0.0	1	1.0
Cervicitis	0	0.0	1	1.0
Uterine/cervical synechiae	3	2.5	0	0.0
Hematometra		0.8	3	2.9
Uterine myoma		0.8	0	0.0
Endometritis	1	0.8	0	0.0
Pelvic mass	0	0.0	1	1.0
Tender/enlarged adnexa	1	0.8	1	1.0
Urinary tract infection	3	2.5	0	0.0
Pyelitis		0.8	0	0.0
Other				
Headaches	0	0.0	2	1.9
Total women with one or more events	13	10.7	13	12.6

* Of the 123 patients completing three insertions of quinacrine pellets, 121 returned for one or more follow-ups

** Of the 106 patients completing two insertions of quinacrine pellets, 103 returned for one or more follow-ups

most were minor and transitory. However, in the first year, 20 women (16.5%) in the lo-minute releasing pellet group and 15 women (14.6%) in the 100-minute releasing pellet group reported amenorrhea. The duration of amenorrhea was variable. In most cases it occurred in the first six months after the last insertion and lasted from one to three months. Menses restarted spontaneously in the majority of patients. For those women requiring treatment, menses was induced with combined oral contraceptives, three pills per day for two days.

Four women had hematometra. One woman was hospitalized and cervical dilatation performed under anesthesia; approximately 15 ml of blood were removed. Simple hysterometry resolved the problem for the other women. None of the women had a repeat occurrence of hematometra.

The studies began at different times and to date about 90% of the women in the lo-minute releasing pellet study have returned for 36-month follow-up visits, compared with 27% who returned for 24-month follow-up visits in the 100-minute releasing pellet study. In the first two years, eight women who completed three insertions of the lo-minute releasing pellets and three who have completed two insertions of the 100-minute releasing pellets have become pregnant. Pregnancies have occurred from two to 17 months after the completed insertions. None of the pregnancies were ectopic. Most pregnancies terminated in abortion, but two women carried

their pregnancies to term without any apparent ill effects to the mother or fetus.

Most complications and complaints reported in the second and third years were minor and transitory, although two were serious. One woman had a hysterectomy for carcinoma of the cervix 18 months after receiving the IO-minute releasing quinacrine pellets. A Pap smear was not completed at admission so that the finding of dysplasia at the six-month follow-up visit does not necessarily represent the beginning of new disease. A second woman underwent a hysterectomy for an intra-epithelial metaplasia 28 months after lo-minute releasing pellet insertion; she had had two negative Pap smears at the study site. The hysterectomy was performed at another institution and the diagnostic slides are unavailable.

Discussion

In an effort to meet a demand for female sterilization services that far exceeds the current medical care system worldwide, attention has been given to the development of a safe, effective non-surgical method that can be performed by paramedical personnel. Studies have shown the use of quinacrine hydrochloride to be effective for permanent female sterilization [3-6]. The procedure requires multiple administrations to be effective.

The present study suggests that two insertions of 100-minute releasing pellets may be as effective as three insertions of lo-minute releasing pellets. It is reassuring that no ectopic pregnancies have occurred to date.

Some women experienced temporary amenorrhea after the final quinacrine insertion; in most cases return to menses occurred spontaneously for women within three months after onset of amenorrhea.

Hematometra has not been reported with non-surgical sterilization previously, but since quinacrine is designed to occlude the tubal ostia by scarring, there is a possibility that the same type of scarring can occur in the endocervical canal. The hematometra were resolved by hysterometry or cervical dilation and the problem did not recur for these women.

Intra-epithelial cervical abnormalities are common in Latin America. It is not possible to assess the significance of two cases occurring in 129 women followed for three years, but it is important to note that approximately 650 women who have received quinacrine as a sterilization procedure in Chile will continue to be followed annually.

Acknowledgements

Partial support for this work was provided by Family Health International with funds from the US Agency for International Development and the Mellon Foundation.

References

1. Zipper, J., Stachetti, E. and Medel, M. (1970). Human fertility control by transvaginal application of quinacrine on the fallopian tube. *Fertil. Steril.*, 21, 581
2. Zipper, J., Stachetti, E and Medel, M. (1975). Transvaginal chemical sterilization. *Contraception*, 12, 11
3. Zipper, J., Medel, M., Goldsmith, A. et al. (1976). The clinical efficacy of the repeated transcervical instillation of quinacrine for female sterilization. *Int. J. Gynaecol. Obstet.*, 14, 499

4. Zipper, J., Edelman, D., Cole, L.P. and Rivera, M. (1983). Overview of clinical trials with quinacrine. In: Female Transcervical Sterilization. G.I. Zatzuchni, J.D. Shelton, A. Goldsmith and J.J. Sciarra, eds., Harper & Row, Hagerstown, MD, pp. 94-99
5. Guzman-Serani, R., Bernales, A. and Cole, L.P. (1983). Clinical report: quinacrine-fused pellets. In: Female Transcervical Sterilization. G.I. Zatzuchni, J.D. Shelton, A. Goldsmith and J.J. Sciarra, eds., Harper & Row, Hagerstown, MD, pp. 100-104
6. Guzman-Serani, R., Bernales, A.S. and Cole, L.P. (1984). Quinacrine hydrochloride pellets: three-year follow-up on a nonsurgical method of female sterilization. *Contracept. Deliv. Syst.*, 5, 131

MS received 3 Dec. 86

Accepted for publication 22 June 87

Résumé

De nombreux travaux de recherche ont été entrepris en vue de développer une méthode simple non chirurgicale de stérilisation féminine. Zipper et ses collaborateurs ont constaté que le chlorhydrate de quinacrine était une substance susceptible d'amener l'occlusion des trompes lorsqu'elle était placée à l'intérieur de l'utérus. Les premiers travaux de Zipper sur une solution de quinacrine ont été suivis par la mise au point de pellets de quinacrine et d'une technique destinée à mettre plus longtemps en contact la quinacrine et l'orifice des trompes grâce à une rétention utérine prolongée. Trois insertions utérines transcervicales de pellets libérant du chlorhydrate de quinacrine pendant 10 minutes, pratiquées à intervalles d'un mois, ont produit, sur 12 mois, un taux de grossesses de 3,3 pour 100 femmes. L'objectif final est de mettre au point une technique efficace d'insertion unique, mais l'action occlusive des pellets de quinacrine sur les trompes a nécessité plusieurs insertions. FHI a développé une méthode par laquelle les pellets libèrent la substance pendant une période prolongée de 100 minutes, dans l'espoir qu'une exposition médicamenteuse plus longue entraînera un taux plus élevé de fermeture des trompes. Une étude sur cette méthode de pellets libérant la substance pendant 100 minutes a été menée à Santiago (Chili). Deux insertions mensuelles pratiquées sur 112 femmes ont produit un taux de grossesses de 2,0 pour 100 sur une période de 12 mois. Des problèmes consécutifs à l'insertion, survenus au cours de la première année, ont été signalés par 13% des femmes; la plupart de ces problèmes étaient d'importance mineure et passagers.

Resumen

Se han hecho extensas investigaciones para desarrollar un método simple, no quirúrgico, para la esterilización femenina. Zipper y asociados identificaron el hidrocloreto de quinacrina como una droga capaz de producir la oclusión tubaria total cuando colocada dentro del útero. Los primeros trabajos de Zipper con solución de quinacrina, condujeron al desarrollo de los comprimidos de quinacrina, un sistema de liberación que fue designado para poner la quinacrina en contacto prolongado con los orificios tubarios por medio de retención uterina prolongada. Tres inserciones uterinas con un mes de intervalo, produjeron una tasa de embarazo de 3.3 por 100 mujeres en 12 meses. La meta es desarrollar un procedimiento efectivo con una inserción única, pero la acción de los comprimidos de quinacrina para ocluir las trompas ha necesitado más de una inserción. El FHI desarrolló un sistema de liberación extendido de 100 minutos en la esperanza que una exposición más prolongada a la droga produjera una tasa más alevada de oclusión tubaria. En Santiago, Chile, se ha hecho en estudio de este sistema. Dos meses de inserciones en 112 mujeres resultó en una tasa de embarazo de 2,0 por 100 mujeres en 12 meses. Se encontraron problemas posteriores al procedimiento en 13% de las mujeres durante el primero año; la mayoría fueron menores y transitorios.