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Delivery Systems for Applying Quinacrine as a Tubal Closing Agent

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The use of quinacrine hydrochloride as an effective chemical agent for transcervical female sterilization has been established primarily through the pioneering work of Jaime Zipper.^{8,10,11,12} Current research is concerned with making the method commercially available through the development of dosage forms that will enhance the acceptance of the method and through toxicology or related studies that will document the safety of quinacrine chemical sterilization (QCS). The general subject of chemical sterilization has been reviewed by Richart.⁶

The ultimate measure of the success of a specific quinacrine dosage form is the number of failures, measured by pregnancy rates, provider acceptance, user acceptance, and incidence of side-effects. More than 12 years of clinical studies of QCS have been spent in developing a clinically effective method and documenting the results. If the regimen consists of depositing 250 mg quinacrine in tablet form in the uterus three times at monthly intervals, about 2 women per 100 will ever become pregnant again. Available data indicate that quinacrine sterilization is permanent, although efforts to reverse the early stages of occlusion with high doses of estrogen have been successful.⁴ Other dosage forms under consideration are slurries of quinacrine powder, pastes, sustained-release tablets, gels, fibers, and plugs intended for direct insertion into the uterotubal junction. IUDs have been tested as vectors to deliver the quinacrine proximal to the uterotubal junction and to provide supplementary contraception.

Quick ways to screen these alternative dosage forms are needed to achieve the benefits of an improved delivery system. A theoretical model of quinacrine sterilization supports the belief that the controlled release of quinacrine could prolong the exposure of the uterotubal junction to high concentrations and reduce the risk of serious side-effects as a result of systemic absorption or accidental delivery of the drug into the peritoneal cavity. Modeling, as presented in a preliminary stage in this chapter, can help focus research on activities that will ensure safe and effective use of QCS systems.

REPEATED EXPOSURE TO QUINACRINE CHEMICAL STERILIZATION

As a first approximation, the probability of successful QCS appears to be constant when quinacrine instillations are repeated at intervals. That is, if one instillation has a 50% probability of occluding a tube, the second instil-

TABLE 1 I-I. Probability of Producing One and Two Tubal Occlusions, Assuming Both Tubes are Initially Open

TUBES CLOSED	NUMBER OF INSTILLATIONS			
	1ST	2ND	3RD	4TH
50% Effective				
0	0.25	0.063	0.016	0.004
1	0.50	0.375	0.219	0.117
2	0.25	0.562	0.765	0.879
80% Effective				
0	0.04	0.002	0.001	0.000
1	0.32	0.077	0.016	0.003
2	0.64	0.922	0.984	0.997

lation will have a 50% chance of occluding any tubes not previously occluded. The work of Westrom on infertility resulting from repeated episodes of pelvic inflammatory disease shows the same trend: repeated cases of pelvic inflammatory disease each have a constant probability of occluding the fallopian tube(s) not previously occluded.⁹ Gains to be made if a 50% effective dosage form is improved to 80% effectiveness, assuming constant probability of tubal closure, are shown in Table 1 I-1.

It is apparent that it takes twice the number of instillations of a 50% effective dosage form as are required for an 80% effective dosage form to get the same tubal occlusion rate. In real situations when multiple instillations are used, pregnancies occur between instillations. The number of pregnancies that occur before the regimen is completed depends on the fecundability of the couple, the effectiveness of the QCS dosage form to occlude tubes, and the use or nonuse of supplementary contraceptives. There are probably a few women whose tubes would not be occluded by any number of QCS instillations. None of the advantages of one dosage form or another comes without a price. In this chapter, the characteristics of several dosage forms are described along with the advantages of each.

QUINACRINE SOLUTIONS AND PASTES

In the initial clinical evaluation of quinacrine as a chemical sterilizing agent, the dosage form was a solution or slurry delivered into the uterine cavity through a cannula attached to a syringe.¹¹ Solutions and pastes provide a continuum of quinacrine concentrations up to a maximum in the paste form of approximately 800 mg/ml. Since an aqueous solution will hold only 29 mg/ml, Zipper and associates resorted to slurries to achieve the 100 to 1000 mg needed to produce tubal occlusion.¹¹ This mode of delivery is mostly of historical interest now, since it has been superseded with the solid form because of the low efficacy of the slurries and occasional cortical excitation (toxic psychosis) they produced.* High intrauterine pressure can be developed inadvertently when slurries are delivered by a syringe with the possibility of accidental intravenous or intraperitoneal delivery. Use of lidocaine with quin-

acrine slurries was once thought to be beneficial, but the practice is now out of favor because the lidocaine appears to be unnecessary and possibly hazardous.

Various dispersing agents have been used to make quinacrine pastes and to increase the quinacrine-holding capacity of slurries. If any agent normally safe for food and drugs is used as an additive, care should be taken to ensure that it does not react with the quinacrine and decrease its effectiveness. Polyethylene oxide has been an effective binder for tablets and a dispersing agent for slurry dosage forms over a wide range of polyethylene oxide concentrations. Malaviya and coworkers took advantage of the gel transition temperature of 2% aqueous agar solution containing 800 mg quinacrine per milliliter. They instilled the dose at 50°C in the fallopian tubes of monkeys as a liquid that quickly reverted to a gel *in situ* at body temperature. Forming the gel *in situ* slows down quinacrine absorption and dissolution, thus providing a sustained release. Gel-forming additives in the tablet dosage form also cause gel formation *in situ*. Quinacrine powder in a gelatin capsule is a possible alternative to pellets for delivering solid quinacrine.

QUINACRINE TABLETS

Quinacrine tablets first used by Zipper were made with a simple die and plunger set (Fig. 11-1).¹⁰ The quinacrine powder was moistened to cause binding of the powder into a solid tablet, and the tooling was dusted with magnesium stearate as a lubricant. Two tablets 1.25 cm long and weighing 125 mg each were deposited in the uterus through a 4 mm-diameter polyethylene inserter. Quinacrine has been produced in 1/8-inch diameter 35-mg tablets using commercial tableting equipment. Test lots of tablets were made by the University of North Carolina Division of Pharmacy Services from quinacrine hydrochloride obtained from Sigma Chemical Company, St. Louis, Missouri. To produce free-flowing powder, the quinacrine was granulated through a 35-mesh screen. Tablets were produced with flat-faced 3/8-inch diameter punches on a Stokes Model E single-cavity tablet machine. Tablets with nominal dissolution times of 10, 100, and 800 minutes were produced as described by Onay and associates.⁵ Cholesterol was the principal additive used to delay dissolution. The proportions of quinacrine in the tablets varied inversely with the dissolution time and were 89%, 79%, and 46%, respectively. An assembly for insertion of the pellets is illustrated in Figure 1 1-2.

DELIVERY SYSTEMS FOR TABLETS

A simple polyethylene or polypropylene straw and push rod system (Fig. 1 1-2) has been an entirely satisfactory method for intrauterine insertion of tablets. There should be some frictional resistance between the inserter straw and the push rod to prevent the rod from falling out and spilling the tablets. A rolled tip on the inserted end of the straw has two functions. It guides the straw through the cervix without scraping and holds the tablets within the straw until they are discharged by pulling the straw over the push rod. Four

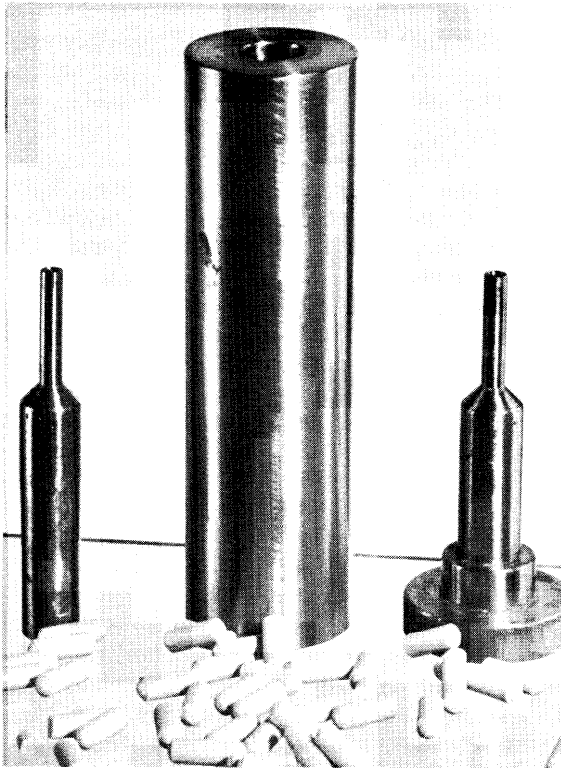


FIG. 11-1. Die and plunger set for fabrication of quinacrine tablets.

diametrically opposed slits in the nosed portion of the straw allow the aperture to expand and pass the tablets. Although curved inserters intended to deliver quinacrine closer to the uterotubal junction have been proposed, there are no published data indicating a curved inserter increases the probability of tubal closure.

The International Fertility Research Program (IFRP) has used a two-step method to ensure the sterility of the quinacrine tablets. The tablets are gamma sterilized in bulk at 2.5 M rad, a dosage that does not denature the quinacrine. The assembled kits are ethylene oxide sterilized. The gamma sterilization step might be avoided if the bioburden of the quinacrine is monitored throughout the production process according to USP guidelines.

UTEROTUBAL PLUGS

The IFRP has cooperated with Dr. R. Quinones in developing a system for placement of small rods of quinacrine directly in the uterotubal isthmus by way of a hysteroscope. A system such as the one illustrated in Figure 1 1-3 has been tested on specimens from women who have undergone hysterectomy, but no clinical trials have been attempted.

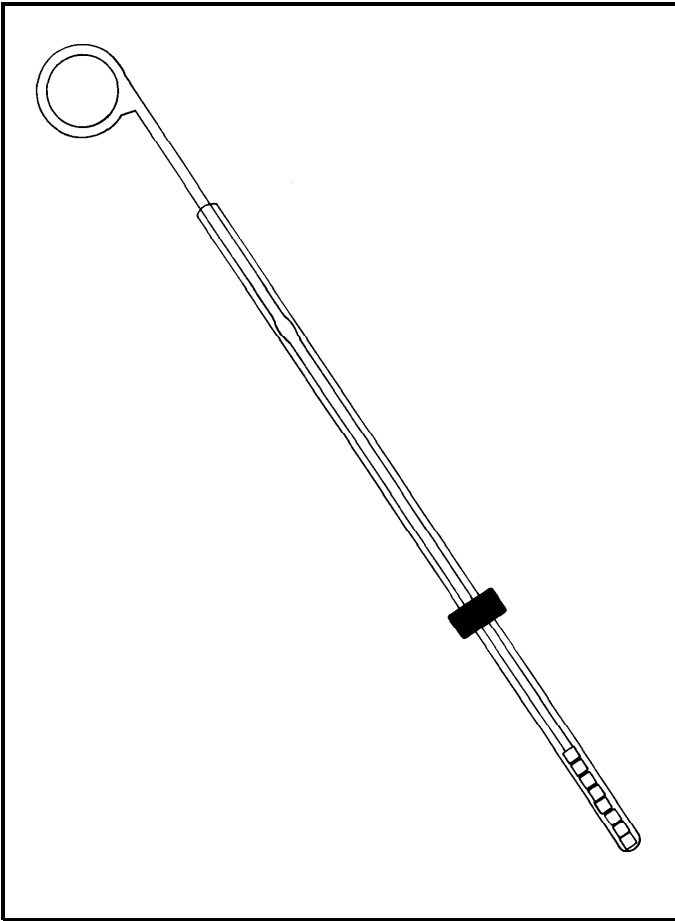


FIG. 11-2. Quinacrine tablet inserter assembly.

QUINACRINE IUDS

A novel combination of family planning methods occurs when an IUD is used as a vector to deliver quinacrine into the uterine cavity and to position the quinacrine close to the uterotubal junctions. (See Chapter 12 for details on this method.) The IUD provides back-up contraception as long as it is retained. Quinacrine itself is spermicidal only at concentrations approaching saturation (20 mg to 30 mg/ml).^{*} The success of quinacrine IUDs as QCS systems depends on obtaining a high probability of tubal closure with one IUD insertion. One insertion of quinacrine pellets when the patient returns

^{*}Chvapil M: Testing the spermicidal effectiveness of quinacrine and potassium sorbate. Personal communication, October 1981.

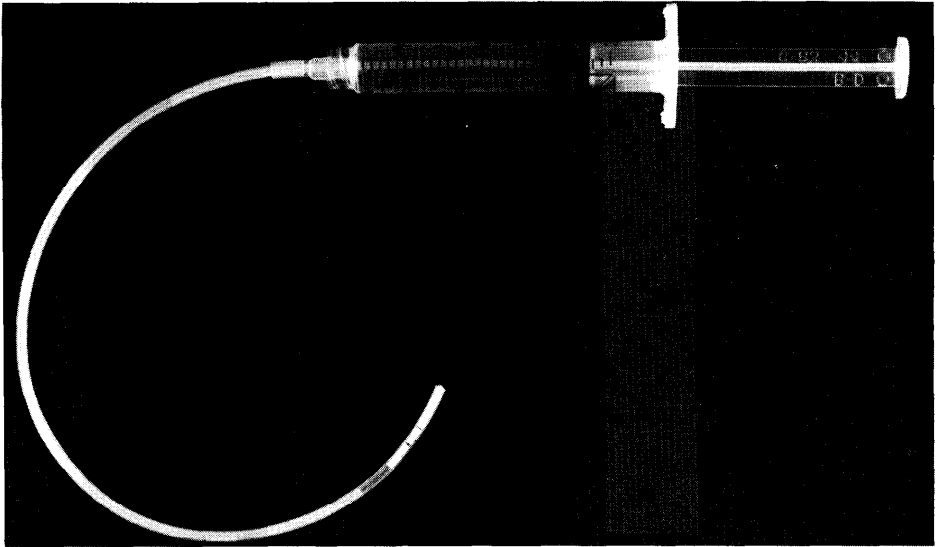


FIG. 11-3. Assembly for direct insertion of quinacrine into the uterotubal junction hysteroscopically.

to have the IUD removed could significantly increase the probability of tubal closure without increasing the amount of medical intervention. Since the IUD displaces a volume that could otherwise be occupied by quinacrine, the amount of quinacrine that can be delivered is less and the amount of cervical dilation is greater for the quinacrine IUD system than for quinacrine tablets.

A THEORETICAL MODEL OF THE QCS SYSTEM

A theoretical model of the QCS system provides a helpful frame of reference for the evaluation of various dosage forms, even though some of the physiological parameters of the model are only estimates. A simple mechanical analog of the system is shown in Figure 1 1-4. The uterus prior to insertion of the quinacrine tablets is represented in Figure 11-4, A. The uterine cavity is expandable as indicated by the spring-loaded piston. Under normal conditions, the amount of fluid flowing into the uterus is less than the water absorption capacity of the uterus, such that the uterine volume remains constant and there is no cervical discharge.

In Figure 1 1-4, B, after the insertion of quinacrine tablets, the water influx exceeds the rate of absorption and causes the uterine cavity volume to increase until there is a discharge of the excess flow out of the cervix. The particulate filter in the mechanical analog ensures that only dissolved quinacrine is absorbed systemically, but the cervical discharge contains both dissolved and particulate quinacrine. A sequence of events might be as follows:

1. Tablets containing 250 mg quinacrine are deposited into the uterus at time zero.

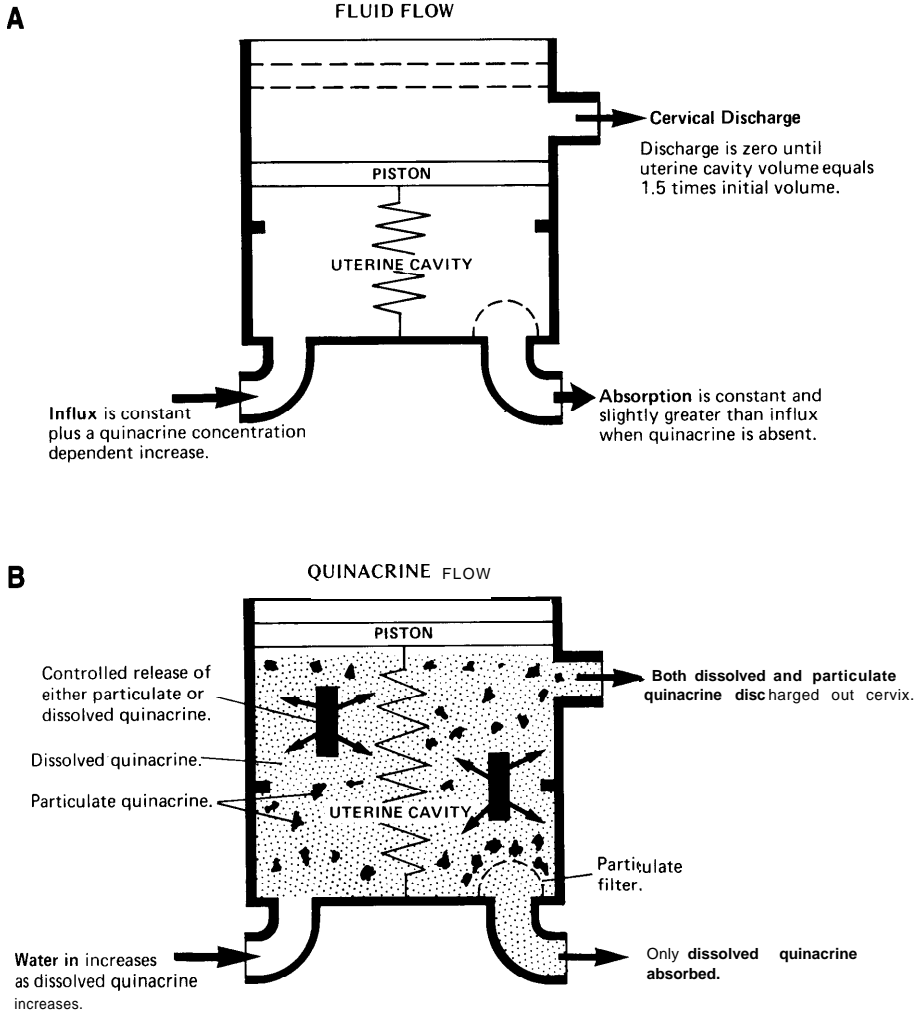


FIG. 11-4. Schematic input-output model of the flow of intrauterine quinacrine. (A) Uterus prior to insertion of the quinacrine tablets. (B) Uterus after quinacrine insertion.

2. Every minute one half of the weight of quinacrine in tablet form converts to a slurry of particulate quinacrine in the uterine fluids.
3. The particulate quinacrine goes into solution at a rate depending on the concentration of dissolved quinacrine and particle size until the solution becomes saturated at a value of 29 mg quinacrine per milliliter of solution.
4. Quinacrine in solution produces a concentration-dependent osmotic increase of water flow into the uterus until it reaches a maximum value of 1.5 times the nominal preinsertion value of 10 ml/hr.

TABLE 11-2. Predicted Distribution of Quinacrine After Placement of 250 mg Tableted Quinacrine in the Uterine Cavity

AMOUNT OF QUINACRINE PER 250 MG OF TABLETS	FRACTION OF REMAINING QUINACRINE RELEASED PER MINUTE	QUINACRINE ABSORBED SYSTEMICALLY	QUINACRINE DISCHARGED FROM CERVIX	QUINACRINE DISSOLVED IN UTERINE FLUIDS AFTER 30 MINUTES
250	0.5	96	154	16.3
200	0.07	118	82	16.8
125	0.01	112	13	0.94

5. Since the increased water influx is not balanced by an increased water absorption, the excess influx causes the uterus to expand to 1.5 times its nominal volume of 1.0 ml.
6. When the uterine cavity volume reaches 1.5 times its nominal volume, all the excess influx is discharged out the cervix, carrying with it both dissolved and particulate quinacrine.
7. Systemic absorption of quinacrine is linearly dependent on the concentration of quinacrine in the uterine fluids and, in the example represented in Table 1 1-2, was assumed to be 120 mg/hr at saturation.

Given the above assumptions, the results obtained with 250 mg of tablets having three different quinacrine release rates are presented in Table 1 1-2. The decrease in the amount of quinacrine available as the release rate decreases represents an estimate of the amount of diluent necessary to delay release. For example, 250 mg of tablets with an 800-minute dissolution time contain only 125 mg quinacrine hydrochloride. The dosage form that releases 0.07 of its contained quinacrine every minute appears to be better than the first example because it is just as effective in maintaining a high concentration of dissolved quinacrine in the uterus. It also has the added safety of using less quinacrine that is released slower. The estimated concentration of dissolved quinacrine in the uterine fluids as a function of time after insertion for the 100-minute dosage form is 16.8 mg at 30 min. Since it takes five to seven tablets to make up 250 mg, there is the option of mixing tablets with different release rates.

Mortality risk may set an upper boundary on systemic absorption. If the risk is to be similar to the risk of mortality from surgical sterilization in the United States, it would be 1: 1 0,000.² If the plasma level of quinacrine exceeds a threshold value, there appears to be a small risk of toxic psychosis, a side-effect that carries a mortality risk.¹ Based on early work on the use of quinacrine in the treatment and prevention of malaria, the plasma limits of quinacrine concentration may be around 200 n g/ml.¹ Since psychosis is potentially the most serious known side-effect of QCS, the following is quoted directly:

Lidz and Kahn (1946) have suggested that mepacrine (quinacrine hydrochloride), without giving rise to actual psychoses, may produce mental impairment as judged by scores on the Kohs-Block test, in which the mental age is assessed by forming standard patterns with coloured cubes, whenever the serum levels are above 18

µgm per 100 ml. Thus doses of 2.1 gm of mepacrine in seven days were without action in causing impairment of the mental faculties, but 4.5 gm in six days caused a very definite impairment. It would thus seem that mepacrine psychoses are likely to develop only if the plasma or serum levels are allowed to remain at a consistently high level.

To stay below a plasma concentration limit, an upper boundary on the rate of quinacrine release from the dosage form should assume that it has accidentally been delivered into the peritoneal cavity. A guess at this limit is a maximum of 300 mg delivered in 1 hour or less. The product of a low probability of toxic psychosis and a low probability of uterine perforation could make the limit considerably higher unless other effects of interperitoneal quinacrine are controlling.

The estimate of water volume exchange in the uterine cavity is based on the definitive studies of tritiated water volume and exchange in the uterine cavities of rhesus monkeys reported by Shaw and associates.⁷ They found the apparent volume of the monkey uterine cavity to be only 0.032 ml and the half-life of the water in the cavity to be 1.17 minutes. This half-life is equivalent to a 24-hour turnover of 19.5 ml. Dubin and co-workers found the half-life of plasma quinacrine to be 2 hours in rhesus monkeys (see Chapter 6). When 1 ml of water saturated with quinacrine (29 mg/ml) was placed in the uterus of the monkeys, a blood plasma measurement 30 minutes after quinacrine instillation fell on the 2-hour half-life decay curve. This failure to observe an initial rise in plasma quinacrine levels indicates an absorption of at least 260 mg/hr. It is probably safe to assume that quinacrine absorption will be equal to the product of water absorption and the concentration of quinacrine in solution. This assumption would give a nominal value of 300 mg/hr when the uterine fluid is saturated with quinacrine.

The rate of quinacrine absorption may correlate with the surface area of the uterine cavity. According to data from Lewis and Zuspan,³ the surface area of the uterus follows the slightly curvilinear relationship: area = 8.5 (volume)^{1.115}sq cm over the range of 1 to 6 cu cm volume. This relationship was not used in the model, but the work of Lewis and Zuspan was used as a reference to estimate an upper limit of 1.5 ml for the uterine volume.

FUTURE DIRECTIONS

Kessel and Mumford estimate that only one fourth to one third of the potential demand for sterilization in developing countries, excluding China, can be met by surgical sterilization in the 1980s and that quinacrine methods offer the best hope of meeting the demand.² Although clinical application of QCS and dosage form development for QCS is in an advanced stage, knowledge of the pharmacology of QCS is less developed. Basic research on the pharmacokinetics of intrauterine quinacrine, uterine fluid exchange, cervical discharge, and time integral of quinacrine concentration effects on tubal occlusion would provide a rational basis for selecting an optimum dosage form. It is likely that clinical QCS will continue to be developed outside the United States where surgical sterilization is physically and financially out of reach of those most in need of sterilization.

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