

# CONTRACEPTIVE TECHNOLOGY

U P D A T E<sup>TM</sup>

A Monthly Newsletter for Health Professionals

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### Special Report

## **Quinacrine pellets have potential for simple, low-cost female sterilizations**

Family planning researchers have spent the last two decades teaching an old drug new tricks: quinacrine, initially developed in the 1920s to treat malaria, is being used to provide simple, low-cost, nonsurgical sterilization to thousands of women in developing countries.

But in the United States, Quinacrine-type drugs are used solely to treat Giardiasis and tapeworm, not for sterilization. No pharmaceutical companies have petitioned the U.S. Food and Drug Administration in Rockville, MD, to approve quinacrine for contraception, and it appears unlikely that any company will step forward. Quinacrine cannot be patented, and therefore any financial investments could not be protected, sources tell

*Contraceptive Technology Update.*

Although it has been successfully used around the world, the method has come under fire by U.S. family planners. Critics say quinacrine has been introduced into service-delivery programs without following tried-and-true testing procedures, but the drug's proponents can supply tomes of data supporting its safety, pointing out that quinacrine is one of the world's most studied drugs. Used for sterilization, it can prevent maternal deaths and provide effective permanent contraception at a fraction of the cost of surgical sterilization, they say.

Many reproductive health professionals, especially those in the United States, know little about quinacrine and how it is used for family planning. Researchers and clinicians interviewed by *CTU* for this special report expect to see more attention paid to — and controversy over — this method as

## **Cast your vote for top contraceptive methods**

This month's issue of *Contraceptive Technology Update* includes our most comprehensive survey questionnaire for family planning professionals. We realize how busy you are, and that's why this year's annual survey combines our Annual Pill Survey of family planners with our Annual Reader Survey. Your answers are extremely important and will be included in upcoming issues of the newsletter. Please take a few minutes to complete this important survey and let your voice be heard! ■

family planners learn more about the contraceptive use of the drug and results of studies conducted overseas.

## What is quinacrine?

Quinacrine has been used to treat malaria, Giardia, tapeworm, lung conditions such as cancer, and most recently, to block a woman's fallopian tubes.

Quinacrine has sclerosing properties, which means the chemical causes an inflammatory response resulting in the build-up of scar tissue. If painted on the lung and pleural cavity of a patient experiencing a collapsed lung, for example, the drug causes the lung to adhere to the pleural wall and keeps it from caving in. Additionally, intentional scarring of the lung cavities of advanced lung cancer patients can prevent repeated fluid buildup.

If a modified copper T IUD inserter is used to place quinacrine pellets high up in the uterus, the drug dissolves (in about 30 minutes) and mixes with uterine fluids. These fluids then travel a short way into the portion of the tubes inside the wall of the uterus — usually a few millimeters to a few centimeters — and cause a fibrotic plug of scar tissue that blocks the tubes and results in sterilization. A 36 mg pellet costs about one penny, making each application of seven pellets less than a dime.

Although malaria treatment requires 2,800 mg per week, two to three applications a month apart of seven pellets (252 mg) of quinacrine seem to do the trick for female sterilization, says **Stephen D. Mumford**, DrPH, president of the nonprofit Center for Research on Population and Security in Research Triangle Park, NC. Mumford, a 15-year veteran of quinacrine research, says more than 20,000 scientific papers

relate to quinacrine as a treatment for malaria, the balance of which attest to its safety. No deaths have been reported in more than 80,000 women who have used the pelletized nonsurgical sterilization approach, he says.

## Liquid form of drug leads to deaths

Quinacrine was first used as a sterilizing agent in the 1970s by Chilean gynecologist **Jaime Zipper**, MD, at the Hospital Sotero del Rio in Puente Alto, Chile. The liquid form of the drug he used caused some toxic side effects, notably a condition called "toxic psychosis," which translates to "intense mental irritability." The liquid form also was related to three deaths. Zipper then switched to the pellet form of the drug, which has been used by other researchers in 13 countries — Bangladesh, China, Costa Rica, Croatia, Egypt, India, Indonesia, Iran, Pakistan, the Philippines, Venezuela, Chile, and Vietnam.

Phase I clinical trials in Chilean women given either two or three applications produced failure rates from 2.0% to 3.3% after one year, depending on different doses of the drug; after two years, a subset of women given three insertions experienced a failure rate of 6.7%.<sup>2</sup> No two-year figure was reported for the women receiving two insertions.

Family Health International (FHI), a reproductive health research organization in Research Triangle Park, NC, funded the Chilean studies and a small-scale study<sup>3</sup> in Texas in the 1980s under an Investigational New Drug (IND) application granted by the FDA.

While the organization's IND was still in effect, 17 of 1,492 Chilean quinacrine users developed cancer. Although based on age-specific incidence rates from the cancer registry in Cali, Colombia, 18.4 cancers could have been expected

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from this group of women,<sup>4</sup> FHI dropped the IND at the hint that quinacrine could have caused the cancers.

Researchers at FHI looked back at the data from the Chilean studies, and later reported after 15 years of follow-up that “no evidence was found of excess cancer risk associated with quinacrine pellet transcervical sterilization.”<sup>4</sup> The women will continue to be monitored for five more years.

Some quinacrine proponents were perplexed by the possible association between the drug and the cancer cases, and believe its origin is not scientific.

“You know, this drug is used every day in American children for giardiasis treatment,” Mumford says. “It’s been used in America for 60 years. Now comes along this fertility control application of the drug, and suddenly it causes cancer. I’ve heard this before and I know it comes from the opposition to family planning.”

But some family planning experts disagree. **Amy E. Pollack**, MD, MPH, medical director of the Association for Voluntary Surgical Contraception in New York City says quinacrine is not in frequent use; in fact, it is only used by infectious disease specialists when conventional giardiasis treatment fails. And because quinacrine is used in a different form — pellets deposited in a body cavity — researchers can’t conclude that the pellets will not cause localized cancer.

### **Toxicology shows quinacrine is a mutagen**

Laboratory studies to show quinacrine’s toxicology, teratology, and mutagenicity were conducted in the late 1970s at The Johns Hopkins University School of Medicine in Baltimore.<sup>5-7</sup> Although quinacrine was found to be potentially toxic, teratogenic, and mutagenic, the studies were still used as the basis for the IND granted for the Texas study. When the results of these toxicology studies were presented to the Toxicology Panel of the World Health Organization (WHO) in 1991, WHO representatives deemed them inadequate and recommended the studies be repeated and extended.

Researchers wonder whether the delivery system for the intrauterine quinacrine application will differ significantly in toxicity from the oral delivery system for malaria, and whether the liquid form of quinacrine could produce

toxic effects that won’t be seen with the pelletized form of the drug. Whether as liquid or pellet, quinacrine almost certainly is mutagenic, but that doesn’t mean it is going to cause harm to a woman using it, says **Pouru Bhiwandi**, MD, MPH, former medical director of FHI and now a gynecologist in private practice in Raleigh, NC. The toxicology studies have been done in bacteria and in animal models, the results of which aren’t always applicable to humans, she says.

Bhiwandi, who took part in several small clinical trials of intrauterine quinacrine in India and Indonesia during her 10 years with FHI, indicates that there are two ways the drug could leak into the body after it has been placed in the uterus. Some will get into the body via the bloodstream when the drug is absorbed by blood vessels in the uterine cavity, but the amount would be significantly less than what enters the body when the drug is taken orally, as with malaria treatment, she explains.

The drug could also leak into the peritoneal cavity through the fallopian tubes, causing damaging adhesions, Bhiwandi continues. This mode of leakage is unlikely, based on experiences with women who were about to have hysterectomies and who agreed to use quinacrine several months before their surgery; subsequent histology studies showed that the drug didn’t penetrate far enough into the tubes to leak into the body, she says.

Even if quinacrine proves to be toxic to humans, if the benefits outweigh the risks, the drug could still be made available, Bhiwandi says, pointing out that several drugs to treat cardiac conditions and cancer are toxic but are still approved by the FDA. More studies are needed to determine the drug’s safety profile, she adds.

Women’s health advocates are concerned about the toxicology results, and agree that more studies are needed.

“I’m unconvinced from what I’ve seen that any clinical trials should go forward without better toxicology work,” says **Judy Norsigian** of the Boston Women’s Health Book Collective. “I’m not a scientist, but I’ve seen things that have made me very concerned about the potential carcinogenic risk. I don’t think that question has been resolved enough.”

Although this simple sterilization method has definite advantages over the surgical method, calling the quinacrine procedure

nonsurgical is inappropriate, Norsigian says. Rather, it should be referred to as chemical sterilization, she notes, adding that the chemical's mode of action is to cause damage, she says.

"I think the idea of a sterilization procedure that did not involve surgery of some sort is very appealing," Norsigian says. "However, I suspect that anything capable of being an efficient sterilizer is probably going to be efficient at destroying other material in the body."

### Population control vs. individual risk?

Even if the eventual toxicology studies allow quinacrine to be studied further in American women, the efficacy of the method so far is dubious, Norsigian says. Although failures as high as 6.7% (after two years) have been reported, a recent study in Vietnam shows failure rates between 2% and 3%.<sup>8</sup> (See related story, p. 34.)

"We're not talking about something that is as effective as it needs to be to be called sterilization," she notes.

Some women's activists and concerned American scientists suspect that a population control policy may be driving the enthusiasm about quinacrine, which — given its failure rate and still unproven safety — may be a second-rate option. But those championing the quinacrine cause point to the drug's ability to prevent life-threatening conditions that can arise from surgical sterilization in developing countries. The drug's supporters agree that the nonsurgical method is associated with higher failure rates, but when the benefits and risks are considered together, the benefits win out, says **Elton Kessel**, MD, secretary general of the International Federation for Family Health in Carlton, OR.

People who think quinacrine is a second-rate option "are incapable of following the logic that you can justify the use of this method because it will save the lives of women of reproductive age," says Kessel, who has been working on the quinacrine issue for 13 years. "To me, it's an absolute mathematical fact that it will save the lives of women where there are high mortality rates."

Case fatality rates from surgical sterilization in the United States are reported as one to four per 100,000 women,<sup>9</sup> but in the developing world can be as high as 21 per 100,000 women.<sup>10</sup> Additionally, maternal death in the developing world is high, compared to the United States; 570

women die from childbirth or abortion per 100,000 live births in Bangladesh" while 7.9 women per 100,000 live births die from childbirth or abortion in America.<sup>12</sup>

Many family planning providers say American women also will like the nonsurgical approach to sterilization. The number of Americans relying on sterilization for birth control in the United States is increasing every year, with most couples choosing female tubal ligation rather than male vasectomy. Tubal ligations are still more dangerous than vasectomy, especially for women at high risk. (See related story, p. 48.)

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