

PRESENTATION GIVEN AT EXPERTS PANEL DISCUSSION
ON
QUINACRINE AS A METHOD OF FEMALE
STERILIZATION
HELD AT THE AVSC OFFICES IN NEW YORK CITY
ON
DECEMBER 2, 1993
BY
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Introduction:

Family Health International (FHI) has a long history of working with quinacrine as an agent for effecting nonsurgical tubal occlusion.

I will present a short review of the human Toxicology information available for quinacrine. Animal Toxicology studies completed in the 1970s and early 1980s are included in the literature that you were provided.

My presentation will be followed by a short presentation by Dr. David Sokal on cancer risks among women in Chile who have been treated with quinacrine.

After lunch the remaining FHI presentations on the Vietnam studies will be presented by Ms. Carol Connell and Ms. Cindy Waszak.

Human Toxicity of Quinacrine

First, I will briefly explain why FHI has been interested in
[SLIDE] the development of nonsurgical sterilization. A Population Reports monograph estimated in 1985 that maternal mortality rates for women in poor, developing countries averaged 400 per 100,000 births and unfortunately this rate has probably not changed much since then. Surgical sterilization is much safer than that, with reported mortality rates in the range of about 3 to 10 per 100,000 in developed countries (United States and the United Kingdom), and 5 to 20 per 100,000 in developing countries, though a few studies have shown higher rates. Population Reports estimated that in Bangladesh, every 100,000 sterilizations prevent 1,000 maternal deaths.

However surgical sterilization, even with the simplified techniques used in developing countries, requires highly
[SLIDE] trained personnel and substantial resources. The potential advantages of a nonsurgical sterilization method include: eliminating the risks and fears of surgery; it can be performed by health workers who know how to do IUD insertions; it would provide another alternative for women; it would be much less expensive, and would probably lead to greater access to sterilization for women as part of a national health service.

When FHI interrupted its work with quinacrine for several years due to concerns about a cluster of cancers in Chile, we

began looking at iodine as another agent which might be used for nonsurgical sterilization and we presently have permission from the FDA (an IND) to study iodine for use in nonsurgical sterilization. Dr. Ralph Richart's efforts have been essential for iodine.

[SLIDE] One advantage of the use of quinacrine is that we have data on toxicity from both chronic and acute administration of large doses of quinacrine in humans. During World War II, with the cut-off of supplies of quinine by the Japanese, and the high rate of malaria in the Pacific theater, an emergency research program was mounted to test various substitutes for quinine, and quinacrine was chosen for the prevention and treatment of malaria. Roughly one million soldiers received quinacrine for one or more years during their service in the Pacific, at doses much higher than used in quinacrine pellet sterilization.

We also have data on acute toxicity for several routes of administration from studies associated with the World War II malaria effort and from other medical uses. There is no question that at high doses, quinacrine is very toxic. When chloroquine became available shortly after World War II, quinacrine was dropped as an antimalarial. The good news is that the doses used for quinacrine pellet sterilization (252 mg per insertion) are very low compared to those used for other purposes, and appear to be quite safe, perhaps even

safer than surgical sterilization.

[SLIDE] As Paracelsus said in the 16th century, "All substances are poisons..." In the United States, aspirin killed thousands of children before childproof caps became mandatory. In high doses Tylenol causes irreversible liver damage, and it is one of the most common causes of death by suicide in Great Britain.

[SLIDE] In World War II, soldiers usually took 100 mg of quinacrine per day for malaria prevention, though sometimes 200 mg per day was used. Treatment for malaria involved a loading dose of about 1,000 mg on the first day and then a smaller dose for six days for a total dose of 2,800 mg in a week.

[SLIDE] Major toxicity due to long-term, high-dose quinacrine was well documented among soldiers. Quinacrine is eliminated from the body very slowly and levels build up with long-term administration. In soldiers, toxicity was not reported with less than a month of exposure or ingestion of about 3,000 mg. Toxic psychoses occasionally occurred during treatment for malaria. They sometimes lasted for several months before suddenly disappearing.

Various types of skin rashes were the most common side effect of quinacrine therapy, occurring in 1 in 2,000 soldiers taking 100 mg per day and in 1 in 500 soldiers taking 200 mg per day. Some of the rashes were quite severe, leaving

permanent sequellae, and there were a small number of fatal cases of exfoliative dermatitis. The average cumulative dose of quinacrine before onset of a rash that left permanent sequellae was 24,800 mg, about 50 times the total dose used for 2 quinacrine pellet insertions.

Aplastic anemia was also noted and occurred at a rate of about 2 per 100,000 soldiers. About half of the cases were preceded by a skin rash.

[SLIDE] Toxicity data from acute administration of quinacrine is available for the following routes: oral, intravenous, intrauterine and intra-peritoneal (intra-abdominal) . In a well-controlled study of

[SLIDE] oral administration, high doses given over 7 to 10 days were shown to produce CNS stimulation resulting in sleeplessness, nightmares, and transient brain wave (EEG) changes. Low dose oral administration often produces headache, dizziness or GI symptoms, but these usually disappear with continued administration or lowering of the dose.

[SLIDE] A small study of intravenous administration was tried for malarial therapy, but was quickly abandoned. Among six men who received 500 mg intravenously, two developed transient but severe toxicity, including depressed respiration and a seizure.

[SLIDE] Acute toxicity data from intrauterine administration is available from nearly 20 years of studies. In the 1970s a number of studies were done with quinacrine suspensions, and at one time the Population Council had an IND for the testing of this form of quinacrine. The use of suspensions was abandoned due to their toxicity, especially when it was found that much lower doses of quinacrine in the form of pellets were safer and more effective. Most of this early work was pioneered by Dr. Jaime Zipper in Chile, who developed an animal model and has done numerous animal studies.

[SLIDE] I will first present the data on the relatively high doses used as suspensions, and then some data on the use of pellets. From 1970 to 1979, about 1109 cases treated with quinacrine suspension were reported in the literature. Doses ranged from 250 to 3000 mg, and various adjuvants were used. Most of the patients were done by Dr. Zipper, but at least five other investigators in four countries were also involved.

[SLIDE] CNS excitation was noted in 2% of patients in one well controlled trial, and a number of other serious adverse events were reported.

[SLIDE] Although no deaths were reported in the literature, FHI is aware of three deaths which did occur, two in the United States and one in Bangladesh. At least two of the deaths reportedly involved the use of xylocaine either as a spinal

anesthetic or as a diluant for the quinacrine, and it was not clear whether the deaths might have been due to intravascular spill of the anesthetic or the quinacrine.

Due to the toxicity of quinacrine suspensions, FHI worked with Dr. Zipper to develop less toxic preparations. One abandoned approach involved the application of quinacrine to the arms of an IUD. The quinacrine pellet method appeared to be the most promising, and in 1981 FHI received permission from the FDA to begin safety studies of quinacrine pellets in women in the United States.

[SLIDE] Between 1977 and 1992, approximately 50,000 insertions of quinacrine have been performed. Doses ranging from about 180 mg to 300 mg have been used, and from one to three insertions are usually given, at one month intervals in the proliferative phase of the menstrual cycle. The most commonly used protocol in recent years has involved two insertions of 250 mg, occasionally with adjuvants. These studies have been performed in numerous countries including two Phase I, safety studies in the United States sponsored by FHI (with funding from USAID). Reports from a number of quinacrine pellet studies are included in the background materials.

[SLIDE] The acute morbidity of quinacrine pellet insertion is similar to that experienced during an IUD insertion. About 9

to 15% of women complain of cramping pains following the insertion. The leakage of quinacrine from the uterus into the vagina causes vaginal pruritus in many women, and headaches and dizziness are also commonly reported. Amenorrhea of several months duration has been reported in 1 to 15% of women, and appears to be more frequent in women who have had three insertions.

[SLIDE] Major complications from the use of quinacrine pellets are rare. Data from the two studies shown here are meant to be illustrative of the range of reported occurrences observed following quinacrine pellet insertions. Data from Zipper include a high rate of clinical follow-up at a single clinic and include all events noted within 12 months of sterilization. The causative relationship between quinacrine and these events is not always clear. Drs. Hieu and Zipper have reported instances of PID and synechia and hematometra following quinacrine insertion. Zipper has reported an instance of presumed uterine perforation which resulted in about 48 hours of severe pelvic pain. Hieu reported two cases of severe bleeding, one immediately following quinacrine insertion and one a year later. The allergic reaction he reported consisted of severe pruritus. One woman in Zipper's series was noted to have a uterine myoma (fibroid) on follow-up, and four women had hematometra. Three of the women with hematometra were treated with simple cervical dilatation, and one was hospitalized and had

cervical dilatation performed under anesthesia. Three of the women in Hieu's series had hysterectomies due to their complications, two of the women with synechia and one of the women with chronic pain.

[SLIDE] Most important, there have been no reported cases of CNS excitation with the use of quinacrine pellets, and no deaths have been reported following quinacrine pellet insertions. In 50,000 surgical sterilizations in the developing world, about 3 to 10 fatalities would have been expected.

[SLIDE] One of the concerns that has been raised about the use of quinacrine pellets is the possible toxicity that might result if the inserter perforated the uterus, and the pellets were deposited in the abdominal cavity instead of the uterus. There is some data relevant to this concern in the cancer literature. Quinacrine solutions have been injected into the abdomen of cancer patients for the treatment of recurrent fluid accumulations (ascites) due to cancer. The dosage of 400 mg is greater than that used for female sterilization and it is dissolved in saline before administration, which would lead to much more rapid absorption than in the case of quinacrine pellets. In Rochlin's 1964 study, treatments were administered on successive days for 1 to 6 days.

[SLIDE] Patients who received one or two injections (800 mg or less) had relatively mild toxicity. Most patients who received

three or more injections (1200 mg or more) had severe abdominal pain with ileus and fever, and some of them also experienced CNS toxicity. The fact that there were only relatively mild side effects after one or two injections is reassuring. However, some concern is raised by the occurrence of intra-abdominal adhesions caused by these treatments.

[SLIDE] This completes my review of the human data on the toxicity of quinacrine from chronic and acute administration. Based on this data and on FHI's past experience with quinacrine, here is a list of some of the issues that deserve further research. We need more data on the long-term safety of the method, and on a number of other factors including the insertion technique, the number of insertions, the need for contraception between insertions, whether anti-prostaglandins or other adjuvants increase efficacy, and whether ectopic pregnancies are increased with this method and tubal occlusion.

[SLIDE] Though more research is needed in several areas, I think we can come to two tentative conclusions. First, the immediate mortality from quinacrine pellet insertion is lower than from surgical sterilization. Second, regulatory approval should be sought from a developed country such as the United States or the United Kingdom. Seeking regulatory approval will involve the performance of additional studies and may prove

quite costly, but approval from an objective, respected regulatory body would help legitimize this method in the eyes of many.

TMK/sj/18653