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## Quinacrine Hydrochloride: Future Research

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Without doubt, there is a need and a demand for a chemical method of tubal sterilization. Chemicals of various categories, including caustic, sclerosing, granuloma-producing, and cytotoxic agents and tissue adhesives have been tested in both animal models and humans.<sup>2</sup> The most effective agent appears to be quinacrine, and, depending on the mode of delivery, it can cause bilateral tubal closure rates in excess of 90%. Clinically, quinacrine has been used in several developing countries.

Efforts have been directed toward improving the efficacy of quinacrine by manipulating the mode of delivery. One approach has been a change from its administration as a slurry to a compacted pellet. V- or T-shaped IUD vectors, with quinacrine located at the tips, have been especially designed to ensure delivery of the drug to the cornual region of the uterus near the uterotubal junction.

As efficacy of quinacrine sterilization improves, safety comes to the fore. In evaluating the elusive risk/benefit ratio of a drug treatment, the therapeutic index is an important consideration. The therapeutic index is the relationship between the dose of a drug that produces an undesirable effect, compared with the dose that produces the desired effect. That index represents, in essence, the "margin of safety" of the drug. A low index, that is, one in which the toxic dose is very close to the effective dose, may be acceptable in the treatment of a life-threatening disease. Thus, digitalis, which has a very low therapeutic index, is nevertheless an acceptable agent for the treatment of congestive heart failure.

In regard to quinacrine, there are numerous known toxic effects; yet, these were of minor importance when this agent was used to treat patients with malaria. However, the risk/benefit assessment of a drug for the treatment or prevention of a debilitating disease like malaria may not be the same as when the agent is used for voluntary tubal sterilization. As an agent for chemical sterilization, it must be assessed against the risks of current methods of surgical contraception, as well as against the risks of other methods of contraception, and of pregnancy itself.

Most of our experience with quinacrine toxicity was gained through its widespread use as an antimalarial during World War II. More pertinent, however, is consideration of potential effects that may occur following intrauterine administration of the drug. Solutions of the drug administered into the uterus are known to be quickly absorbed into the blood and distributed throughout the body. This appears not to cause any toxicity as long as the plasma levels do not exceed some critical level.

That some of the more serious toxic effects of quinacrine are related to elevated plasma levels is shown by the following findings:

Accelerations in electroencephalograms and physiological symptoms occurred in quinacrine-treated human subjects when plasma levels of the drug exceeded 30 ng/ml.

In monkey studies, death or convulsions occurred after quinacrine administration, at the time when plasma levels were at peak concentrations.

In rat studies, a decrease in blood pressure occurred immediately after intravenous infusion of quinacrine, with recovery occurring a short time later, unless the decrease was so severe as to result in death (see Chapter 6).

Central nervous system (CNS) excitation syndromes have been reported following intrauterine administration of quinacrine solutions in 2% of treated women.<sup>1</sup> Studies using pellets suggest a lower incidence of this CNS effect.<sup>3</sup> Possibly, the plasma level achieved in women receiving pellets is less than in those women receiving solutions, but this has not been documented. High plasma levels of quinacrine could also result from inadvertent administration of the drug to pregnant women. Increased plasma levels were observed when the same dose of quinacrine was administered to pregnant as compared with nonpregnant monkeys.

Another consideration is that perforation of the uterus is an inevitable complication, if an intrauterine instrument is used for drug delivery. The subsequent administration of the drug directly into the peritoneal cavity might be expected to result in more rapid absorption of the drug into the blood, and hence higher plasma levels and greater likelihood of toxic reaction (see Chapter 6).

A separate issue is that of potential carcinogenicity of the drug. It is known that quinacrine binds to deoxyribonucleic acid (DNA) and that it acts as a frame shift mutagen in bacterial mutagenicity tests (see Chapter 7). However, no association of quinacrine with mutagenicity or cancer has been demonstrated in mammals, and, theoretically, a single exposure would cause less concern than would a long-term exposure. However, such potential hazards must be considered. It is notable that other analogues of quinacrine were found not to be mutagenic in bacterial test systems (see Chapter 7). However, the efficacy of these drugs as tubal occluding agents has not been documented.

By what mechanism quinacrine closes the tube is still not known. It has been suggested that quinacrine action is related to its ability to intercalate with DNA, and its failure to work in some species, such as the rabbit, is related to the concentration of zinc in the tissue, which inhibits binding with DNA. It is possible, however, that the species differences in response to quinacrine

may involve anatomical rather than biochemical factors. For instance, it may be that the close apposition of the luminal surfaces of the uterotubal junction of some species may be more conducive to fibrotic connections between surfaces, rather than to reepithelialization (see Chapter 8).

Furthermore, tubal occlusion may not be the sole *modus operandi* in the antifertility property of quinacrine. It is conceivable that quinacrine affects the reproductive tract in some as yet unknown way to impair the function of the tube, endometrium, or uterine environment.

Further research on quinacrine is needed. Such research might include the following:

Development of a timed release system for quinacrine to give a rate of release that would ensure low plasma levels of this agent, even if it is accidentally placed in the peritoneal cavity, while at the same time yielding high efficacy in causing tubal occlusion

Determination of the tubal occlusion efficacy of nonmutagenic drugs chemically related to quinacrine

Continued testing of alternative drugs with potentially better therapeutic indices for their ability to cause tubal occlusion

More precise definition of the process by which quinacrine results in decreased fertility

Determination of the mechanism by which quinacrine causes tubal closure

On development of improved drug and/or delivery systems, institution of clinical trials, so that such a sterilization technique would ultimately become available.

## REFERENCES

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