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Department of Reproductive Health and Research

Statement

The safety of quinacrine when used as a method of non-surgical sterilization in women

Department of Reproductive Health and Research
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Special Programme of Research, Development and Research Training in Human Reproduction

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Interim statement

Background

Quinacrine hydrochloride ("quinacrine")*, when formulated into pellets and inserted into the uterus of women, causes scarring and blockage of the fallopian tubes. It is estimated that at least 140,000 women in 34 countries have undergone this procedure as a method of non-surgical sterilization.

Numerous reports of short-term safety and efficacy of quinacrine sterilization in women have been published. Prompted by the recent availability of pre-clinical toxicology and long-term human safety data, WHO convened a technical consultation on 8-10 October 2008, in order to assess the relationship between quinacrine, when used for intrauterine administration for non-surgical sterilization in women, and cancer risk. The consultation brought together 21 technical experts and four observers. The experts included toxicologists, pathologists, genetic toxicologists, epidemiologists, clinicians and national regulatory body scientists. Among these experts, ten Panelists were responsible for drafting the recommendations and eleven specialists were on hand to present technical information and provide support. All participants were asked to declare any conflicts of interest; none of the Panelists declared any conflict of interest relevant to the subject matter of the meeting.

The consultation considered data from animals and humans as related to cancer risk, particularly gynecological cancer risk. Experts were provided with original study reports and a library of publications prior to the consultation; the most recent laboratory and epidemiological data were presented and discussed at the meeting. The Panel arrived at its recommendations through consensus. The recommendations stated here will inform the final WHO statement and recommendations on the safety of quinacrine for use in women for non-surgical sterilization, to be developed following a thorough review of human safety data. It is anticipated that the recommendations in this interim statement will remain valid until late 2009, or until such a time as the review can be completed. The Department of Reproductive Health and Research at WHO Headquarters in Geneva will be responsible for initiating a review of these recommendations at that time.

Panel conclusions

Currently available genetic toxicity data are sufficient to support the conclusion that quinacrine is genotoxic (able to cause damage to the genetic material of cells) *in vitro* (1-4). However, there is some discordance in the literature regarding genotoxicity in various animal assay systems (5-11). No additional *in vivo* genetic toxicity studies are recommended at this time because negative results would not negate positive *in vitro* study results that suggest a genotoxic effect of quinacrine.

Two recently completed animal cancer studies were reviewed by the panel. In a neonatal mouse study designed to identify genotoxic carcinogens, no increase in the incidence of malignant tumors was observed at any dose of quinacrine (12, 13). In a study in rats designed to mimic human exposure, quinacrine was administered into the uteri of the test animals on two occasions at approximately three weeks apart, at one of four different dose levels; the animals were evaluated for cancer and other pathological findings at the end of two years (14). A dose-related increased incidence of both benign and malignant tumors of the vagina, cervix and uterus was observed. However, changes such as inflammation, necrosis and cystic dilata-

*The Panel recognized that different studies have used different formulations of the active ingredient. The term "quinacrine" is used here as a generic term to refer to any and all of these formulations.

tion of the uterus were also observed in the quinacrine-exposed animals. Thus, the findings did not allow the Panel to distinguish between a direct genotoxic effect of quinacrine, a secondary effect of inflammation and tissue regeneration, or a combination of the two, in the genesis of observed tumors in the rat.

The epidemiological studies reviewed at the consultation examining cancer following quinacrine sterilization were well conducted. They showed no excess risk of cancers of the uterus or elsewhere in the female genital tract, or any other site, but had limited statistical power. This was because the prevalence of exposure to quinacrine in the population studied was low in the case-control study (15) and few women developed cancer in the follow-up studies (16, 17). This means that the Panel could not exclude a modest increased risk in gynecologic cancers. It could, however, exclude a large increased risk. The Panelists did not review safety data related to outcomes other than cancer during the meeting.

Recommendations

The Panel is aware of ongoing analyses of epidemiological data. When these data become available, a thorough review of all human safety data should be conducted.

If the epidemiological data cannot exclude an association between quinacrine exposure and cancer, the molecular mechanisms of induction of cancer by quinacrine in the rat model should be investigated.

There should be continued surveillance of women who have received quinacrine sterilization in the past for risk of gynecologic cancer and other health complications, such as ectopic pregnancy, adhesion-related morbidity, or adverse maternal and fetal outcomes related to unintended pregnancies (method failures).

Until the totality of safety, effectiveness and epidemiological data has been reviewed, quinacrine should not be used for non-surgical sterilization of women in either clinical or research settings.

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