Issues in Current Research

The Quinacrine Controversy Continues

Marge Berer

Quinacrine is a *non-surgical method of female sterilisation. It has no? been approved by the drug regulatory* authority *in any country as studies* have *not yet shown whether it is safe or effective.1 A small number of individual doctors are continuing to provide this method to poor* women in *developing countries, in spite of* international advice *by the WHO, IPPF and other medical and* scientific experts *in the field. This report includes: 1) a summary of events in the past year, most importantly the finding of mutagenicity in three of the fourpre-clinical toxicology tests* on the *drug and the issues these results raise for further research; 2) a paper by Lezak Shallat on the continuing provision of quinacrine* sterilisa *tion* to *women in Santiago, Chile.*

IN June 1994, a WHO Consultation on Female Sterilisation Methods, called for four now-standard pre-clinical toxicology studies on quinacrine to be completed. These would be required by the US Food and Drug Administration (USFDA) and other drug regulatory agencies as a necessary step before approval of the drug could be considered. One of those four tests (the Ames test) has already been carried out on quinacrine once in the past, and indicated then that quinacrine was mutagenic. These tests are not difficult to carry out and are therefore not expensive.

Family Health International (FHI), an NGO in the US, decided to carry out the four toxicology studies and the US Agency for International Development (USAID) agreed to fund them. USAID had two main reasons for supporting these tests. First, there were a lot of ethical and scientific questions being raised about this method and they considered that having the answers would be in the public good. Second, if at least three of the four toxicological studies were negative for mutagenicity, it might have been worth pursuing this method.

A number of people at USAID feel (as do a number of people at FHI that a safe and effective non-surgical method of sterilisation would be a good thing to make available.* Thus, if the use of quinacrine for sterilisation in'women could be shown to be safe, and if an effective dosage regimen could be determined, they believe that going ahead with quinacrine development through clinical trials in the US would be worth it. If not, something would still be gained. Quinacrine has demonstrated that a non-surgical method may be feasible, whether or not the drug itself is developed further.[2]

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In Vietnam, more than 31,000 women had quinacrine sterilisation between 1989 and 1993.[3] A retrospective study of more than 1600 of them was carried out in 1994. Although a written report of this study was prepared for presentation in Vietnam in February 1995, the information it contains has not yet been published.'

In the meantime, FHI was doing the mutagenicity studies. The September 1995 issue of FHI's newsletter *Network* reports that three of the four studies were positive, that is, they showed quinacrine to be mutagenic. One of the three was a test that had been done previously, the Ames test; hence, this result was confirmed. The other *in vitro* studies were both positive, while the *in vivo* study was negative.[5]

Mutagenicity is indicative of possible carcinogenic@ but not every mutagenic compound turns out to be carcinogenic.'

The USFDA examined the data and said that just because a drug is mutagenic in the tests employed does not necessarily preclude their approving it for human use. However, they would first require a controlled, lifetime carcino-

genicity study in female rodents to exclude the possibility of quinacrine being carcinogenic.[2]

The rodent is the only animal that society will currently allow to be used to test a mutagenic drug for its carcinogenicity. There are many problems to overcome with such a study of quinacrine in order for the conditions to get close enough to what happens in a woman to be of value. The drug has to be inserted in the rat's uterus more than once so that its effect is chronic over the Lifetime of the animal. The rats have to be anaesthetised to do this and they tend to die if they are anaesthetised several times. The drug could be inserted in the vagina instead, but because quinacrine is a sclerosing agent, it could close the vagina and the study would fail to produce the required results.'

In addition, before the study itself was started, a lot of development work would be needed to determine the best formulation, again to ensure that the study would succeed in its aim. This means that the formulation used to study carcinogenicity would have to be the same one that would go on to be used in clinical trials in women. Getting this right would take a good deal of time and cost a lot of money - the dose of quinacrine and the number of times it is inserted would have to be determined. A one-step, highly effective regimen would be the most acceptable.[2]

The development effort so far has been done on a shoestring and perhaps more systematic and resourced input could improve the formulation, but the work may never be done. FHI estimate that it would cost US$ 8 million and take up to eight years. USAID have decided not to fund this next step and FHI have decided not to pursue it.[2,5] Whether others will find funding for this study remains to be seen.

In the event that a carcinogenicity study takes place and the result is positive, that is, if there is an excess of cancer in the treated rodents compared to the controls, then it is probable that no further human studies or human use could be justified.'

If the result of the carcinogenicity study is negative, that is, if there is not an excess of cancer in the treated rodents compared to the controls, the judgement as to whether human studies can and should be conducted would have to be based on an assessment of the relevance of the mutagenicity data to the human. The option also **exists** to conduct pre-clinical toxicology studies in appropriate non-human primates.[2] After that, it would become a matter of judgement whether to pursue development of the drug. A regulatory agency would probably ask questions such as - Is this a crucial addition to the existing range of methods for sterilisation? Is it at least as safe and efficacious as existing methods? If quinacrine were deemed not to be a valuable enough addition, they would probably say there were insufficient grounds to carry on with it.[7]

If the rodent study failed to demonstrate carcinogenicity, there would be still other unresolved issues. For example, no regulatory agency that opens its doors to public scrutiny of its decisions would be able to ignore the history of controversy and questionable ethics attached

Toxicity of Quinacrine

Ralph Heywood

Quinacrine has recently been subject to a battery of mutagenicity tests. Gene mutilation tests on bacteria and mammalian cell systems gave some positive results. A cytogenetic test ***in vitro*** gave **a** positive result, although an ***in vivo*** cytogenicity study was negative.

Although the results of these mutagenicity studies are not clear cut and can be subject to a number of interpretations, it will be necessary to explain why these results seen in vitro are not relevant to humans.

There are many other toxicological issues I have raised with respect to the safety of quinacrine. No work seems to have been conducted on the distribution of the compound within the intended target organ system. Of particular interest would be to know whether the compound binds or is retained within the uterine cavity and if so, for how long? Another major problem is the effect that quinacrine may have on viruses; certainly studies will have to be conducted to see if quinacrine exacerbates viral conditions. The issue of embryotoxicity and teratogenicity remains unresolved. The pre-clinical package of data continues, in my view, to be inadequate to make a proper risk assessment of quinacrine.

I see little point in pursuing these academic toxicological issues, for I am unaware of any substantiated evidence that the compound can be used to sclerose the Fallopian tubes of women.[6]