



Quinacrine: sclerosing agent of the utero-tubal junction in women, with anticarcinogenic actions in transplanted tumors in mice

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Abstract

Quinacrine, an acridine derivative that was in widespread use as an anti-malarial, has been shown to have both sclerosant and anticarcinogenic actions. The sclerosant action of quinacrine has been used to produce occlusion of Fallopian tube in both experimental animals and women, and several clinical studies are reviewed. Both actions of quinacrine are potentiated by steroidal and non-steroidal antiprostaglandins as well as by ionic copper. Combinations of quinacrine with antiprostaglandin drugs, and also with copper, improved the efficacy of quinacrine when used for female sterilization and reduced side effects. A review of the experimental and epidemiological evidence suggests that quinacrine has no carcinogenic effects.

Keywords: Quinacrine; Sclerosant; Anticarcinogen; Tubal sterilization; Antiprostaglandins

1. Introduction

Quinacrine is an acridine derivative described in 1932 by Schulemann for the treatment of malaria [1]. It was discovered in an intensive research program on synthetic **antimalarials** carried out in the German laboratories of I.G. Farbenindustrie. The program covered the preparation and trial of over 12 040 compounds resulting in the identification of pamaquine and quinacrine as potential therapeutic agents.

Even though quinacrine was widely used before the Second World War, quinine was mainly used for the treatment of malaria [2]. When the supply of quinine from Germany was interrupted during hostilities, it became imperative to manufacture a substitute in the United States. Technical problems were soon solved, and the **American** substitute (quinacrine) turned out to be chemically and pharmacologically identical to the German chemical. Before the War, the United States produced about 540 kg per year of quinacrine, but war necessities resulted in the production of about 900 kg per day. The experience in the Armed Forces soon demonstrated the superiority of quinacrine

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for malaria prophylaxis, and quinacrine became the official drug [3]. Impressive follow-up studies by US Armed Forces physicians provided detailed information on its side effects and toxicity, ranking it among the best studied drugs ever introduced [4,5].

Quinacrine is 6-chloro-9(1-methyl-4-diethylamino) butylamino-2-methoxyacridine ($M_w = 508.9$). It is available as the dihydrochloride (quinacrine hydrochloride, USP). Quinacrine differs from chloroquine in having an acridine nucleus instead of quinoline [6].

In 1989, Wallace [7] published an extensive review on the use of quinacrine in rheumatic diseases, mentioning all known actions of the drug, including sclerosis of the human uterotubal junction [8]. The pharmacological actions of quinacrine are numerous and some of them are anticarcinogenic.

The more important actions of quinacrine include: antiprostaglandin action [9-12]; antioxidant effects [13,14]; antiproliferative and antimutagenic effects [15-20]; antimicrobial properties [21-23]; DNA and RNA polymerase inhibition and suppression of lupus erythematosus cell factor [24-29]; induction of sclerosis [30-35].

I. 1. Sclerosing actions

Quinacrine is a locally effective sclerosing

Table 1

Summary of sclerosant action of substances used alone in aqueous solution in the rat uterus

Substance	Concntration	Effect
Quinacrine	190 mg/ml	+++
Quinacrine	50 mg/ml	++-
Betamethasone	0.6 mg/ml	-
Diclofenac	25 mg/ml	-
Indomethacin	25 mg/ml	-
Copper	0.5×10^{-7} M	-
Zinc	0.5×10^{-7} M	-

+ to + + + = intensity of damage; ++ = moderate damage; - = no or minimal lesion.

agent. Its intracavitary administration is capable of preventing recurrent pleural and pericardial effusions, as well as pneumothoraces [30-32]. In women, quinacrine pellet instillation into the uterus results in occlusion of the Fallopian tubes. A fibrotic and granulomatous tissue is formed by quinacrine-induced fibroblastic cells which become active in the human tubal epithelium. Several studies on rats and rabbits [33-35] have demonstrated the granulomatous and obstructive effects produced by the topical action of quinacrine in the tubal and uterine epithelium. This fibroblastic action of quinacrine is locally potentiated by antiprostaglandins and copper [36,37]. Tables 1 and 2 summarize the histopatho-

Table 2

Summary of sclerosant action of combinations of substances instilled in aqueous solution into the rat uterus

Combination of substances	Effect on uterus	Effect on tube
Quinacrine + copper	++++	++
Quinacrine 100 mg/ml + zinc	+++	
Quinacrine + betamethasone 1.2 mg/ml	+++	
Quinacrine + betamethasone + zinc	++++	++
Quinacrine + diclofenac	+++	
Quinacrine + diclofenac + copper	++-	
Quinacrine + diclofenac + zinc	++	
Quinacrine + diclofenac + betamethasone + copper	++	
Quinacrine + diclofenac + betamethasone + zinc	++-	
Quinacrine + indomethacin	++++	+ -
Quinacrine + indomethacin + copper	++	

Except where specified the concentrations of substances are as in Table 1.

+ to + + + + = intensity of damage; ++ = moderate damage; - = no or minimal lesion.

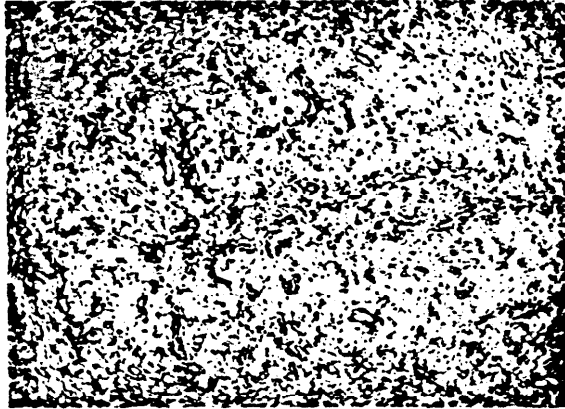


Fig. 1. Histological section of rat uterus treated with 50 mg/ml quinacrine and 25 mg/ml diclofenac. Section at middle level shows uterus obstructed by fibrotic and granulomatous tissue ($\times 40$).

logical changes observed in the uterus of the rat when various combinations of antiprostaglandins and ionic copper and zinc are instilled into the uterine lumen (see also Fig. 1).

Quinacrine, depending on its concentration or association with antiprostaglandins or ionic copper as co-factors, can produce a reversible inflammatory state, or permanent fibrosis.

The association of quinacrine with copper potentiates the fibroblastic action of quinacrine alone. Copper alone in the same concentrations, 1×10^{-2} M or 1×10^{-3} M, produces only functional changes in the endometrium.

Recently, the structures of DNA binding domains of glucocorticoid and estrogen receptors have been determined, as well as the position of zinc atoms in them [38]. Copper may replace the zinc resulting in altered biochemical function.

Research conducted in rat and rabbit [33-35] demonstrated that the instillation of different pharmacological agents into the uterine cavity could modify the physiology and morphology of the endometrium, thus altering reproductive processes. For example, β -adrenergic blockers produced long periods of infertility [39]. The uterus becomes refractory to implantation. The same was observed with instillations of copper salts [40]. These substances did not alter the uterine morphology or histology. Another compound in-

vestigated was quinacrine. Different concentrations from 50 up to 200 mg/ml of quinacrine in water were instilled into the rat uterus in a volume of 0.1 ml and kept in contact with the endometrium for 20-30 min. The epithelial tissue was replaced by fibrous and granulomatous tissue that blocked the uterine lumen. Similar experiments in the rabbit showed that both the uterine and tubal mucosa were refractory to the fibrosing action of quinacrine. From other studies in the rabbit it was concluded that the high content of Zn^{2+} in both uterus and tube in this species made them refractory to the action of quinacrine [33]. When the research was extended to the human, it was observed that 250 mg of quinacrine inserted as pellets into the uterine cavity twice, with one month between insertions, produced bilateral tubal obstruction in 97% of the cases in the first year following instillation [8].

Quinacrine produces a granuloma in the tubal ostium because in this area a low tissue concentration of zinc exists [41,42]. The high concentration of zinc in the endometrium may reduce or prevent the action of quinacrine on this epithelium.

The series of experiments summarized in Tables 1 and 2 demonstrated the effects produced by the associations of quinacrine with betamethasone, diclofenac, indomethacin, copper and zinc. They showed that the fibrosing and sclerosing action is highly selective, and specific. The most effective obstructive combination at the uterine and tubal level in the rat is the association of copper with quinacrine. In the human the most effective obstructive combination at the uterotubal level is the association of quinacrine, copper and betamethasone.

2. The development of a non-surgical technique for female sterilization with endouterine quinacrine plus adjuvants

The development of a non-surgical, ambulatory sterilization technique that is as effective as present surgical techniques is a priority and could provide a partial solution for the explosive growth of population and its catastrophic secondary consequences [43,44].

Table 3
pregnancy rates/100 woman-years in women completing three intrauterine instillations of 252 mg quinacrine

Reference	Women	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Zipper et al. [45]	148	4.2	6.4	8.8	8.8	8.8	8.8
Zipper et al. [8]	123	3.3	6.7	6.7	7.6	7.6	7.6
Guzman-Serani [46]	149	0.7	3.4	4.1	5.6	5.6	6.4
Bhatt et al. [47]	81	0.0	1.2	3.7	3.7	—	—
Agoestina et al. [48]	100	3.1	—	—	—	—	—
Total women	601						
Mean pregnancy rates ^a		2.8	4.4	5.8	6.2	7.3	7.6

^a76% of all the pregnancies occur during the first 3 years.

The technique using endouterine quinacrine pellets consists in the insertion of quinacrine as pellets, each of 36 mg, into the uterine cavity. The pellets have a controlled dissolution rate from 10 to 100 min, thus reducing toxicity and avoiding expulsion through the cervical os. The total doses used for sterilization have varied from 180 to 288 mg.

Five studies done by four investigators are summarized in Table 3. Side effects attributed to quinacrine were found, but they were mostly of a minor nature and disappeared between 1 and 7 days. The most important side effects included general malaise, fever and headaches. The cumulative percentage of these reactions to the drug was 15%. Uterine pain or uterine infection, endometritis or adnexitis, were rare side effects. The pellets currently in use have a dissolution half-life of about 30 min.

The follow-up data of Table 3 demonstrate that the rates for the first, second and third year are reliable only with high numbers. Experiences with 100-200 cases require a follow-up of 3 years to obtain true rates.

A recent study, carried out in Viet Nam, reported experience with 3 1781 cases [49]. One or two insertions of 252 mg of quinacrine alone were used. There were 818 pregnancies following the procedures. The pregnancy rate for the group with two insertions was 2.63 per 100 woman-years. There was no maternal mortality and only eight complications were reported. A similar but surgical study might have shown up to 30 cases of death, and from 540 to 18 12 serious complica-

tions. All reported side effects were minor and of short duration. The ectopic pregnancy incidence was 0.89 per 1000 woman-years of use. An estimated 242 maternal deaths may be averted by these 31 781 sterilizations.

2.1. Antiprostaglandins as adjuvant substances to quinacrine

Because of the unwanted iatrogenic effects attributed to quinacrine alone, it was decided to add intrauterine or intramuscular antiprostaglandins to the quinacrine pellets to minimize these effects. Two types were used: steroidal, betamethasone [37], and non-steroidal, diclofenac [50]. The dose of each insertion has varied from 180 to 288 mg of quinacrine. The follow-up of these patients led to the following conclusions:

- all iatrogenic effects disappear when inserting quinacrine together with the antiprostaglandin, betamethasone or diclofenac;
- the trend in the pregnancy rate seems to be smaller in the three groups with antiprostaglandins (Table 4).

2.2. Quinacrine, antiprostaglandins and copper

It has been demonstrated that copper can stop the phosphatidylinositol cycle and interfere with the regulation of arachidonic acid production [52]. In the binding of some hormonal receptors, such as those for estrogens and glucocorticoids, to DNA, there are three Zn²⁺ ions for each binding site, that are coordinated in a tetrahedral bind of cysteine ligation, called 'zinc fingers' [38]. Copper could displace the zinc ions altering the receptor

Table 4

Pregnancy rates 100 woman-years in women treated with quinacrine pellets plus antiprostaglandins: 3-year follow-up

Group	Number of women	Year 1	Year 2	Year 3
(A) Trujillo et al. [50]	157	2.1	3.0	3.6
(B) Zipper et al. [37]	217	0.9	1.4	1.8
(C) Zipper et al. [51]	114	—	0.9	0.9
Total women	488			
Mean pregnancy rate		1.0	1.8	2.1

A: 216 mg quinacrine + 50 mg diclofenac + 150 mg diclofenac, i.m. (two administrations). B: 250 mg quinacrine + 1.2 mg betamethasone (three administrations). C: 288 mg quinacrine + 1.2 mg betamethasone + 0.5 mg copper sulfate (two administrations).

*All patients completed 4 years of follow-up without additional pregnancies.

or subjacent gene. These two observations, and the experimental observations in the rabbit where copper sulfate and zinc chelates potentiate fibrosis and granuloma formation [33], led us to add copper to quinacrine pellets.

A group of 118 women received intrauterine pellets containing 288 mg of quinacrine, 1 mg bethametasone and 0.5 mg of copper sulfate and was compared with a second group of 95 women who received two instillations of 250 mg quinacrine plus 75 mg diclofenac.

In the first group there were no pregnancies at the end of one year and one pregnancy at 19 months of follow-up. In the second group there were three pregnancies during 25 months of follow-up. In both groups combined, 6.8% of women reported one or more of the following symptoms: fever; headache; discomfort; pelvic pain; vaginitis; and endometritis following the first instillation of pellets, and 16% reported a similar range of symptoms and signs following the second instillation [51].

The fibroblastic action of quinacrine is related to its antiprostaglandin activity. The addition of compounds that potentiate the quinacrine antiprostaglandin action, like copper or other antiprostaglandin agents, improves its tubal sclerosing effect. This is demonstrated in clinical trials by the reduced pregnancy rates (Tables 3 and 4). Another effect seen with the addition of antiprostaglandins is the significant reduction in the iatrogenic reactions observed with quinacrine alone.

3. The anticarcinogenic properties of quinacrine alone or in combination with other agents

Non-steroidal antiinflammatory drugs (NSAIDs), such as aspirin, indomethacin, piroxicam, and sulindac, inhibit the growth of colon tumors induced by chemical carcinogens in rodents [53-56]. The mechanism is unknown, but it may involve the suppression of cell proliferation or the stimulation of an immune response, due to an inhibitory effect on prostaglandin synthesis. A similar effect in humans has been suggested [57]. Antiprostaglandin compounds also have inhibitory properties on viral tumors [58,59]. One of these antiprostaglandins, quinacrine, has multiple additional properties.

A great number of nucleoproteins related to DNA transcription and the role played by zinc, in the replication and transcription have been described [60]. They have specific roles in the regulation of genes. The replacement of zinc by other metals such as copper and cobalt can lead to functional changes [33,61]. Copper plays an important role in the organism; its excess can displace zinc from its various binding sites, including zinc fingers [38].

Zinc is not carcinogenic, mutagenic or teratogenic [62], but a relative increase in the zinc concentration modifies two important properties of quinacrine: the drug loses its fibroblastic and anticarcinogenic functions.

Many of the quinacrine mechanisms of action as an antiprostaglandin [10,111, antioxidant [13,291,

anti-proliferative [17], anti-mutagenic [16,20], and DNA-RNA polymerase-inhibiting substance [24,63], are oriented toward an anticarcinogenic function. Since many non-steroidal anti-prostaglandins such as indomethacin, piroxicam, sulindac, aspirin, etc., act as antineoplastic agents [53-56], quinacrine, also a non-steroidal anti-prostaglandin, should have a similar action [9].

4. Experimental studies in animals and epidemiological studies in the human

McCormick [17] found that quinacrine reduced cancer incidence and carcinoma multiplicity of mammary tumors in rats. Glade and Brown [64] demonstrated that quinacrine is active as an antileukemic agent in a culture medium of monoblastic leukemia cells, and Fitzhugh showed that quinacrine included in meals given to rats for 2 years did not have any toxic or carcinogenic effect [65].

4.1. Experimental anticarcinogenic functions of quinacrine in mice

To study the anticarcinogenic activity of quinacrine, three types of malignant tumors in mice were used: TA3, TA3-MTXR (methotrexate resistant variant) and MMT (Bittner's retro-viral tumor from C3H strain). TA3 tumor corresponds to a mammary carcinoma of ascitic growth, maintained by transferring every 7 days in the peritoneal cavity of the same strain. MMT corresponds to a retrovirus which is transmitted to the offspring by lactation. Genetic, hormonal and viral (RNA retrovirus) factors are required in these spontaneous mammary tumors. They have a great malignant potential and are resistant to many chemotherapeutic agents.

A common protocol was followed for the three experimental tumors. Several groups of male AJ mice were inoculated intramuscularly in the right thigh with 1 000 000 neoplastic cells of the three types of tumor. Each group was made up of five to ten AJ mice weighing from 20 to 25 g each. In order to test for a correlation between the fibroblastic and anticarcinogenic actions of quinacrine we used the same pharmacological compounds that improve the sclerosing properties of

quinacrine, namely betamethasone, diclofenac, indomethacin and ionic copper.

Thirty-one experimental groups were studied. The control group received common food and tap water. The other groups received the same regime with the addition of different compounds that had been used as adjuvants or inhibitors (ionic zinc) of the fibroblastic action of quinacrine. The tumoral-node growth was evaluated by measuring its largest and smallest diameter every 3-4 days. The observation period lasted one month, a period in which most untreated control animals died. The results showed that quinacrine, alone or in combination with one or more of the potentiating agents, resulted in a significant increase in the number of animals surviving for one month following tumor inoculation [66,67]. The assumption is that quinacrine has a significant anticarcinogenic action.

4.2. Epidemiological studies in the human

There is no evidence that quinacrine can be carcinogenic in humans or rodents. Bauer [68] reported two cases of quinacrine hydrochloride palmar drug eruption (tropical lichenoid dermatitis) that underwent malignant transformation. The population of patients was slightly over 120 000 Australian servicemen, taking 100 or 200 mg of quinacrine daily for many months, even after the onset of their drug eruption. The latent period between the late sequelae of drug eruption and its malignant change can be as much as 34 years after quinacrine use, and it would depend mainly on the skin reaction of the patient and his sensitivity to the drug. No other case of cancer attributed to quinacrine has apparently been described [69].

Two recent studies demonstrated that quinacrine shows no carcinogenic activity in the groups of women analyzed. In the first study [70], the incidence rate of high grade intraepithelial squamous cell lesions, a precursor of cervical carcinoma, in 1061 patients treated with quinacrine was not higher than the incidence rate of the control group. The second study [71] found no evidence of excess cancer risk associated with quinacrine hydrochloride transcervical sterilization in 1491 women who provided 7941 person-years of follow-up. A panel of experts,

commissioned by Family Health International to evaluate quinacrine's toxicology, concluded that quinacrine was mutagenic in prokaryotic organisms (bacteria), but that it was very unlikely that quinacrine was a rodent or human carcinogen.

In 1956, Lacassagne [72] studied the relation between physical and chemical properties of angular benzacridines and their possible carcinogenic activity. He confirmed that **acridine** and its derivative have no carcinogenic activity, probably due to its special configuration with methyl group in position 9 and nitrogen in position 10. Nitrogen in position 12 increased the electronic density and the molecule became highly carcinogenic. Quinacrine has nitrogen located in position 10.

The International Agency for Research on Cancer (IARC) investigated the carcinogenic risk of acridine orange, a compound that has the same basic acridine structure of quinacrine but not the **alkyl** side chain. It was concluded that there was no evidence of acridine orange **carcinogenicity** in the long-term carcinogenic assays in rodents [73].

5. Conclusions

1. Quinacrine, in some concentrations, produces an obstructive granuloma of the lumen of the intramural Fallopian tube when introduced into the human uterus.

2. Two transcervical insertions of slow dissolution pellets containing 250 mg of quinacrine, produce a cumulative pregnancy rate of 7% at 8 years of follow-up.

3. The addition of steroidal or non-steroidal anti-prostaglandins (betamethasone, **indomethacin**, diclofenac) to quinacrine potentiated the sclerosing action of this compound and reduced the pregnancy rates in the first 3 years of follow-up in all groups studied.

4. The use of betamethasone and copper as adjuvants to quinacrine produces an obstructive occlusion, equivalent to mechanical surgical occlusion.

5. Experimentally, quinacrine acts as a curative agent for some transplantable carcinomas in the rat. In the transplantable tumors TA3, TA3-MTXR and MMT, it not only diminishes the size

and rate of growth of tumors but also some tumors regress.

6. The combination of quinacrine with betamethasone and copper increases the **anticarcinogenic** potential of quinacrine. The most active combinations are quinacrine-indomethacin and quinacrine-copper.

7. Quinacrine is an essential substance for triggering the process of **tumoral** disappearance, since none of the adjuvants were effective when used alone. Anti-prostaglandins used alone had no effect on decreasing tumor size or on the rate of tumor growth.

8. Zinc cations antagonize some of the effects of copper and the fibroblastic and anticarcinogenic actions of quinacrine.

9. Epidemiological studies have shown that there is no evidence of excess risk of cancer (cervical or other) associated with transcervical quinacrine sterilization compared with control groups.

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