

TOXIC EFFECTS OF QUINACRINE HYDROCHLORIDE
IN RHESUS MONKEYS

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Abstract

The toxic effects of intraperitoneal, intrauterine and intravenous administration of quinacrine hydrochloride solution were evaluated in female adult rhesus monkeys (*Macaca mulatta*). A single intraperitoneal injection of 400 mg and above resulted in the development of toxic manifestations leading to death of monkeys. Intrauterine instillation of 500 mg of quinacrine was well tolerated and did not produce any toxic effects. However, intravenous injection of 100 and 75 mg was lethal to the animals.

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Introduction

In an attempt to create a refractory uterine endometrium for fertility control, Zipper *et al.* instilled various cytotoxic and antienzymatic chemical agents into the rat uterus and identified quinacrine hydrochloride as a potent chemical agent for such purposes. Dose-dependent histological changes were observed in the endometrium. A single instillation of 200 mg/ml of quinacrine hydrochloride produced irreversible, occlusive-type changes in the rat uterus (1). Tubal occlusion and infertility have also been reported after intrauterine instillation of this chemical in rhesus monkeys and women (2, 3). However, transcervical delivery of such agents, either blindly or through a hysteroscope, into the uterine cavity in a mass sterilization programme has an inherent possibility of spillage into the peritoneal cavity leading to peritoneal complications including chemical peritonitis. SUCH toxicity has been reported in rodents and other laboratory animals (4, 5). An increased interest in the use of such chemical agents delivered either as suspension or as a pellet has prompted us to generate additional information on toxicity with quinacrine hydrochloride in rhesus monkeys.

Material and Method

Adult female rhesus monkeys of the Institute's primate colony were used in this study. The animals were maintained under uniform husbandry conditions and received pellet diet (Hind Lever, Ltd.) supplemented with soaked gram and seasonal fruits. Eight groups of three monkeys were divided into control, intraperitoneal, intravenous and intrauterine quinacrine-treated schedule. Pretreatment body weight and food intake was recorded for each animal.

Three groups of three animals each received a single intraperitoneal injection of 500, 400 and 250 mg of quinacrine hydrochloride in water as suspension. Intrauterine instillation of 500 mg was carried out in another three animals. Another batch of 3 monkeys each were injected intravenously with 100, 75 and 50 mg quinacrine. The control group of monkeys received 1 ml of solvent only.

The animals were observed for any changes in their gross behavior, food consumption and body weight alterations. The animals which died immediately after treatment were autopsied and the visceral peritoneal organs were examined for any gross morphological changes. The uterus and Fallopian tubes were fixed in Bouin's fluid and serial sections were cut for histological evaluation.

Results

Toxicity due to quinacrine hydrochloride treatment was apparently noted in all the monkeys receiving 500 and 400 mg of quinacrine intraperitoneally. All the animals immediately after injection showed signs of pronounced depression and extreme exhaustion as evidenced by increased breathlessness, which was followed by signs of anaphylactoid-type reactions resulting in excitement and convulsions without any discharge from the mouth. The animals showed increased signs of breathing difficulty and appeared to die due to respiratory failure. Autopsy of these animals indicated a generalized distribution of yellow-staining quinacrine solution throughout the visceral peritoneal cavity. No gross abnormal changes could be observed in the peritoneal organs. There were no signs of haemorrhage or haemolysis from the peritoneal structures. It was thus noted that quinacrine hydrochloride was highly toxic when placed directly into the peritoneal cavity at 500 and 400 mg in 1 ml aqueous solution since all the monkeys died within 10 minutes of receiving the injections. The monkeys receiving 250 mg in 1 ml of water intraperitoneally did not show any signs of toxicity except some initial depression lasting for about 10-20 minutes after which they recovered.

The group of monkeys which received 100 and 75 mg of quinacrine hydrochloride intravenously demonstrated similar type of toxic manifestations as observed with the group receiving 500 and 400 mg intraperitoneally and died instantaneously. However, three monkeys receiving 50 mg of quinacrine intravenously tolerated the dose and showed no signs of toxicity except colouration of conjunctiva and other mucosal linings of the body.

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Another group of animals which received 500 mg of quinacrine hydrochloride dissolved in 1 ml of water and injected transcervically into the uterine cavity did not show any sign of toxicity throughout the observation period of 60 days after instillation. Autopsy of these animals did not show any sign of peritoneal involvement. Histological examination of the uterine endometrium and the Fallopian tubes presented a normal histoarchitecture.

All the animals who survived the initial shock or death were observed for 90 days following treatment. The monkeys were laparotomised and peritoneal visceral organs were examined. No gross change could be observed. There was no loss or gain of body weight or any alteration in their food intake. No other visual signs of toxicity were noted during this period.

Discussion

The results of the present study thus clearly indicate that quinacrine hydrochloride injection administered either intraperitoneally or intravenously induces toxic manifestations which may be fatal at a particular dose. The deaths following both routes of administration occurred either immediately or within 10 minutes of injection. Presumably, death occurred in these animals due to either cardiac or respiratory failure. Similar toxic observations have been made by Ciaccio *et al.* in rodents (6) where it was shown that an intraperitoneal injection of quinacrine hydrochloride at 200 mg/kg body weight when administered to white mice was fatal. Zipper advocated the use of quinacrine hydrochloride for sterilization of women and advised one or more applications in order to achieve a high percentage of success (7). During the transcervical delivery of this agent, an aqueous suspension spillage of this material into the peritoneal cavity is always possible. Although Israngkun *et al.* (8) found that a massive dose of 1 gram of quinacrine hydrochloride injected into the peritoneal cavity of rhesus monkeys was safe, as there was no local effects six weeks later, the high percentage of mortality observed in our studies are contradictory to these findings. In point of fact, toxicity, enteromegaly and steatorrhea have been reported by Keeler *et al.* in rats (9) after a single intraperitoneal injection of quinacrine. Similar toxic manifestations have been observed in hamsters, gerbils and *peromyscus* sp. (6). The non-toxicity observed

after instillation of 500 mg of quinacrine into the uterus is in contrast to the findings of Ciaccio et al. (6) who showed toxicity leading to death of mice after receiving quinacrine. Autopsy of these animals indicated peritoneal spillage of quinacrine as a possible cause of death in mice. It is now known that quinacrine, proflavine and other acridines inhibit numerous enzyme reactions, most particularly those which require either a nucleic acid template or utilizes flavin **coenzyme**; for example, d-amino acid oxidase or coenzyme reductase, which might probably account for the respiratory failures as observed in our monkeys (10). The colouration of the conjunctiva and other mucosal linings has been attributed to the accumulation of quinacrine in the epithelial and keratinous tissues (11, 12). The drug was preferentially found to be concentrated in the liver, spleen and kidneys and is eliminated slowly from the body over a period of weeks (13). The convulsions observed in our study are very much similar to those reported by Newell and Lidz in human subjects (14).

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References

1. Zipper, J.A., Medel, M. and Prager, R.: Alterations in fertility induced by unilateral intrauterine instillation of cytotoxic compounds in rats. *Amer. J. Obstet. Gynecol.* 101:971 (1968).
2. Chandra, H., Malaviya, B. and Kar, A.B.: Chemical occlusion of rhesus monkey oviducts with quinacrine. *Ind. J. Expl. Biol.* 12:1 (1974)
3. Zipper, J.A., Medel, M., Pastene, L. and Rivera, M.: Intrauterine instillation of chemical cytotoxic agents for tubal sterilisation and treatment of functional metrorrhagia. *Inter. J. Fertil.* 14:280 (1969)
4. Joseph, A.A. and Kincl, F.A.: Toxic and antifertility effects of quinacrine hydrochloride in rats. *Amer. J. Obstet. Gynecol.* 119:978 (1974)

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5. Ratna, K. Nair, Sahni, S.K. and Devi, P.K.: Peritoneal reactions with some of the tubal occlusive agents. *Ind. J. Expl. Biol.* 13:558 (1975)
6. Ciaccio, L.A., Hill, J.L. and Kincl, F.A.: Observations on quinacrine hydrochloride (in rodents). *Contraception* 17:231 (1978)
7. Zipper, J.A., Stachetti, E. and Medel, M.: Human fertility control by transvaginal application of quinacrine in the fallopian tube. *Fert. Steril.* 21:581 (1970)
8. Israngkun, C., Pharosavadi, S., Newirth, R.S. and Richart, R.M.: Clinical evaluation of quinacrine hydrochloride for sterilisation of the human female. *Contraception* 14:75 (1976)
9. Keeler, R., Richardson, H. and Watson, A.J.: Enteromegaly and steatarrhea in the rat following intraperitoneal quinacrine (Atebrine). *Lab. Invest.* 15:1253 (1966)
10. Neville, R., Jr. and Davies, D.R.: The interaction of acridine dyes with DNA. *J. Mol. Biol.* 17:57 (1966)
11. Gerke, P.Y.: Analysis of quinacrine deposits in human skin. *Vestn. Venerol. Dermatol.* 5:21, (1948)
12. Miller, O.B., Herrmann, F. and Rubin, J.: The effects of mepacrine hydrochloride (Atebrine) upon the human skin. *J. Invest. Dermatol.* 15:445 (1950)
13. Tropp, C. and Weise, W.: The excretion of atebrine in the urine and faeces. *Naunyn-Schmiedebergs. Arch. Exptl. Pathol. Pharmacol.* 170:339 (1953)
14. Newell, H.W. and Lifz, T.: The toxicity of atebrine to the central nervous system. *Amer. J. Psychiat.* 102:805 (1946)