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Pharmacology of Quinacrine Hydrochloride With Emphasis on its Use as a Tubal Occluding Agent

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An intensified program for identification of synthetic antimalarial drugs was conducted in Germany during the 1920s. Quinacrine was one of 12,000 synthetic chemicals found to be effective in treating malaria and was widely used prior to World War II. Quinine remained the chief antimalarial drug, however, until the Japanese invasion of the South Pacific cut supplies and expanded US production of quinacrine became imperative, increasing from a prewar level of 1200 lb/year to almost one ton/day." Much of the pharmacologic knowledge about quinacrine was acquired from observations and studies made during that time.⁶

Quinacrine is a bright yellow crystalline powder. The structure of quinacrine hydrochloride is shown in Figure 6- 1. The metabolic fate of quinacrine is incompletely understood. In humans, urinary products include the un-metabolized form as well as the 0-demethylated derivative, the side-chain-cleaved amine derivative, and an 0-demethylated side-chain-cleaved amine.¹⁶ The pharmacokinetics of quinacrine has been studied primarily in regard to ingestion of the drug.¹⁵ Because the mode of administration may alter the absorption of a drug and its distribution, we investigated the pharmacokinetic properties of quinacrine following intrauterine injection. The data are presented later in this chapter.

Besides its use in the management of malaria, quinacrine has been used to

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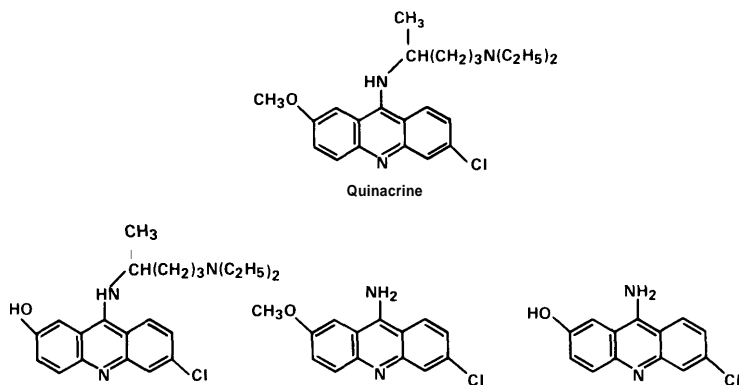


FIG. 6-1. Structure of quinacrine and urinary metabolites.

Metabolites (left to right) are 0-demethylated, side-chain cleaved, and 0-demethylated side-chain cleaved derivative (based on Steck EA: *Chemotherapy of Protozoan Disease*, vol III, pp 23-172.

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treat tapeworm infection, cutaneous leishmaniasis, and lupus erythematosus and to control neoplastic effusions in the pleural and peritoneal cavities.

Numerous toxic effects of quinacrine have been reported, some of which are listed below:

Skin:

- Lemon-yellow pigmentation
- Dermatitis
- Atrophy of sebaceous and sweat glands

Gastrointestinal tract:

- Nausea
- Vomiting
- Abdominal cramps
- Diarrhea

Cardiovascular system:

- Lowering of blood pressure
- Decreased cardiac output
- Bradycardia

Central nervous system:

- Motor acceleration
- Epileptiform convulsions
- Delusions
- Hallucinations

Other:

- Fever
- Headache

The occurrence of these symptoms depends on dose, length of treatment, mode of delivery, and patient susceptibility. For a more detailed discussion

of side-effects, the reader is referred to Goodman and Gilman⁹ and an extensive review by Findlay.⁷ The toxic effects of quinacrine as a tubal occluding agent are discussed later in this chapter.

QUINACRINE ADMINISTRATION TO MONKEYS

INTRAVASCULAR VERSUS INTRAUTERINE INJECTIONS

Quinacrine was administered to cynomolgus monkeys by means of intravascular or intrauterine injections.^{4,5} The cynomolgus monkey was chosen for these studies because its reproductive anatomy is similar to that of the human, and its cervical canal, although more convoluted than that of a woman, can be penetrated by a blunt-end needle.¹³ Thus, quinacrine can be deposited directly into the uterine cavity. A solution of quinacrine was used, so that "worst case" exposure to quinacrine could be evaluated. The dose given (30 mg in 1 ml) is approximately two times the dose, on a body weight basis, that would currently be placed in a woman's uterus at any one time (250 mg is the current human dose).

Following intravascular injection of a 1-ml solution of 30 mg quinacrine, 149 ± 42 ng/ml ($n = 3$) was observed in the plasma at 0.5 hours (Fig. 6-2). The level declined during the next 3% hours, with an estimated half-life of 2 hours. Less than 1% of the administered drug was found in the urine over

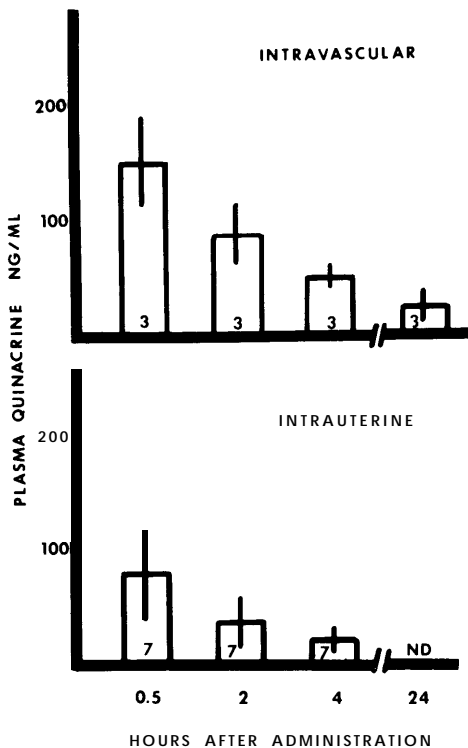


FIG. 6-2. Plasma quinacrine concentrations at various times after intravascular or intrauterine administration of 30 mg quinacrine hydrochloride solution to nonpregnant monkeys. (ND, not detectable; number in bars represents number of observations; Vertical line is \pm SEM)

the first 4-hour interval. At 24 hours, the plasma level was 23.5 ± 8.5 ng/ml. Tissues obtained following necropsy at this time were found to have high concentrations of quinacrine. The tissue-plasma ratios are indicated in Table 6-1.

Following intrauterine injections of the 30 mg quinacrine solution, plasma quinacrine levels were 77.1 ± 37.0 ng/ml ($n = 7$) and declined at a rate similar to that in the group receiving intravascular injections. Thus, quinacrine rapidly enters the circulation when deposited into the uterine cavity. Twenty-four hours after administration, quinacrine was found not only in the uterus and other reproductive organs but also in all organs listed in Table 6-1, except cerebellum and skeletal muscle. It is significant that high concentrations of quinacrine could be detected in the isthmus and ampulla of the oviduct, indicating the possibility of spill into the peritoneal cavity. Many of the tissues from animals that received intrauterine quinacrine and were necropsied 1 week later also contained significant amounts of quinacrine; however, these concentrations were, in general, significantly less than those concentrations found at 24 hours. By 28 days, all tissues had undetectable levels of quinacrine or levels near the limit of detection.

Following both intravascular and intrauterine injection of quinacrine, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and lactic dehydrogenase showed significant elevations compared with these measurements in control monkeys receiving 1 ml physiologic saline by way of the intrauterine route. The elevations were moderate and transient, re-

TABLE 6-1. Tissue-Plasma Ratio of Quinacrine 24 Hours After Intravascular Administration of 30 mg Quinacrine to Cynomolgus Monkeys

TISSUE	RATIO
Lung	1676:1
Adrenal	1345:1
Kidney	1211:1
Pancreas	1041:1
Liver	994:1
Spleen	904:1
Heart	723:1
Bone marrow	445:1
Lymph node	378:1
Myometrium	256:1
Ovary	219:1
Hypothalamus	200:1
Endometrium	184:1
Cerebellum	171:1
Uterine cervix	158:1
Midbrain	138:1
Isthmus (oviduct)	131 :1
Ampulla (oviduct)	94:1
Skeletal muscle	68:1

turning to preinjection levels within 48 hours. Histologic examination of tissues listed in Table 6-1 revealed no pathology, except for the reproductive tissue in those animals receiving intrauterine injections of quinacrine.⁵

Following intravascular injection of 30 mg quinacrine, two of three monkeys vomited or retched within 3 minutes of the injection. While nausea has been reported following oral administration of quinacrine in humans, this has implied a direct gastrointestinal effect. Since in these monkeys, the symptoms were seen following intravascular administration, this effect appears to be indirect, possibly acting through the central nervous system. No other toxic effects were observed in these animals that could be attributed to quinacrine administration.

INTRAUTERINE INJECTIONS DURING PREGNANCY

Intrauterine injections of quinacrine were also administered to pregnant monkeys between pregnancy days 34 and 46. Administration of 30 mg quinacrine resulted in plasma concentrations that were at least comparable to those in nonpregnant monkeys receiving intravascular administration of the same dose (Fig. 6-3). This may reflect increased vascularity of the uterus during pregnancy, and more rapid absorption of the drug. Following intrauterine administration of 3 mg of the drug, plasma concentrations were approximately 10-fold less than those in monkeys receiving the 30-mg dose.

One pregnant monkey was found dead in its cage 48 hours after intrauterine administration of 30 mg quinacrine. Autopsy did not reveal the cause of death. While there was no direct or statistical evidence that quinacrine was the cause of death, we were concerned, since we have never had a death in a pregnant monkey following intrauterine injections in our studies involving other drugs.^{2,3} Also the plasma quinacrine concentration at 30 minutes was 445 ng/ml, which was higher than any other 30-minute concentration, including concentrations following intravascular injections in nonpregnant monkeys. It is also significant that we were not able to obtain any urine from this animal, although its bladder was catheterized for the 4-hour postinjection collection period. Thus, impaired clearance of the drug may account in part for high plasma levels.

The effect of quinacrine administration on the fetuses of these pregnant monkeys is discussed in Chapter 7.

INTRAPERITONEAL ADMINISTRATION

A danger of intrauterine administration of drugs is either spill of the drug through the oviducts into the peritoneal cavity or perforation of the uterus with direct application of the drug into this cavity. To determine toxicity in case such an event occurs, the following study was performed.

Under ketamine anesthesia, a needle was inserted through the cervical canal and the uterus was punctured. A 1-ml solution containing 30 mg quinacrine was then applied directly into the peritoneal cavity. Three monkeys were subsequently observed for 3 days and showed no abnormal behavior. Laparotomy performed on day 3 revealed slight adhesion of one tube to the uterus in one monkey, but no other effects were observed.

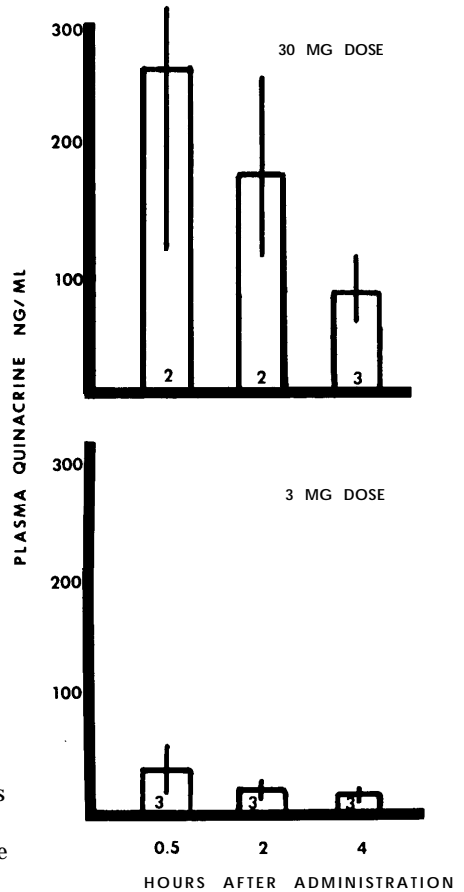


FIG. 6-3. Plasma quinacrine concentrations following intrauterine administration of either 30 or 3 mg quinacrine hydrochloride solution to pregnant monkeys.

A report by Chandra and Malaviya indicated that when high intraperitoneal doses of quinacrine suspension were administered to rhesus monkeys, death occurred within 10 minutes; lower doses caused hyperactivity. The same doses, placed in the uterus of those animals, had no effect.*

These studies prompted us to test higher doses of quinacrine in the peritoneal cavity of cynomolgus monkeys. Since pellets are the current form in which the drug is used in women, we elected to use pellets in this study. Three monkeys were studied at one time. Each was immobilized with ketamine and placed under halothane anesthesia. Each received a midabdominal incision and a pellet applicator (supplied by IFRP) was inserted through the incision and pellets were released into the peritoneal cavity. One applicator contained seven pellets (250 mg total dose), one contained 3½ pellets (125 mg), and one contained no pellets (sham control). The animals were then allowed to recover from anesthesia. Periodically, blood was taken from the femoral vein for quinacrine determination. This experimental procedure was repeated on different monkeys on two other occasions, so that each treatment group consisted of three animals.

66 I Female Transcervical Sterilization

Of the three monkeys receiving 250 mg quinacrine, two died approximately 2 hours after administration. The third had a seizure, beginning at 2 hours after treatment, which lasted for approximately 1 hour. This animal recovered and appeared to be healthy thereafter. The three monkeys receiving 125 mg quinacrine all survived. One demonstrated slight tremors of the limbs while recovering from anesthesia. All animals receiving intraperitoneal quinacrine pellets, regardless of dose, demonstrated crouching behavior that may have been indicative of abdominal pain. No hyperactivity was observed. The sham monkeys showed more activity than did the treated animals during a 4-hour observation period following treatment.

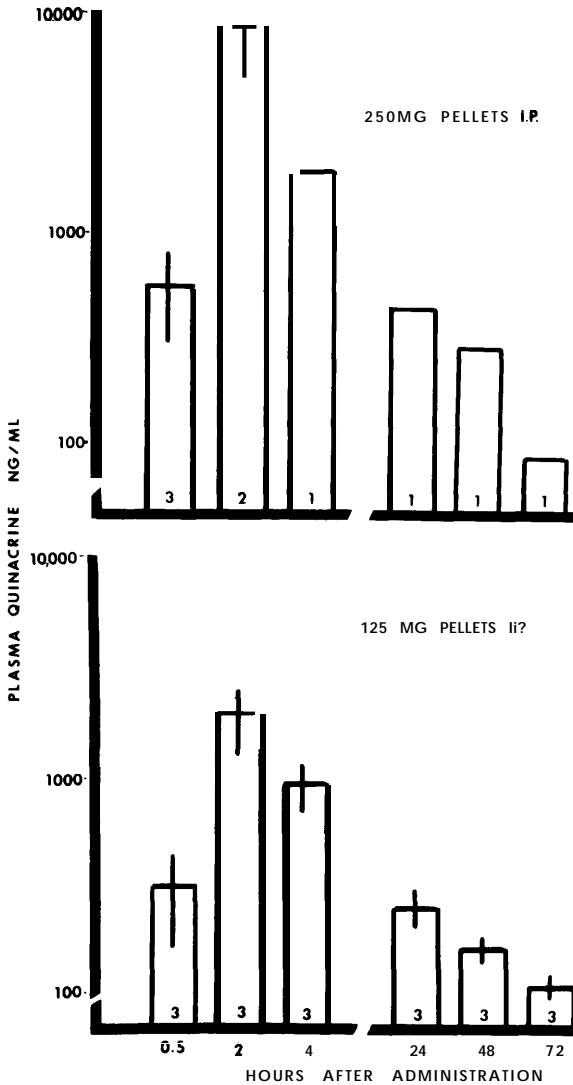


FIG. 6-4. Plasma quinacrine concentration following intraperitoneal administration of 250 or 125 mg quinacrine hydrochloride pellets to nonpregnant monkeys. Note that ordinate is logarithmic.

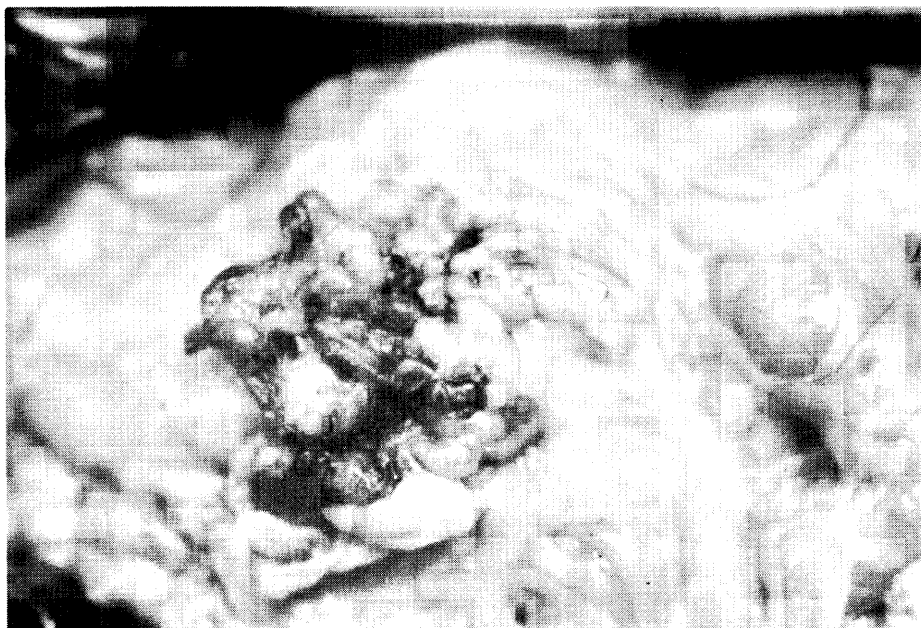


FIG. 6-5. Peritoneal inflammation and adhesions in monkey 3 days following intraperitoneal administration of 125 mg quinacrine pellets.

Plasma quinacrine levels were very high at 30 minutes after treatment (Fig. 6-4). These concentrations increased and we observed the highest levels at 2 hours, the time when the monkeys treated with the high dose died or had convulsions. A blood sample, obtained from one monkey at the time of its death, revealed a quinacrine level of 11,700 ng/ml. In the surviving monkeys treated with quinacrine, plasma concentrations of the drug remained elevated for 3 days after treatment, although they demonstrated a declining trend (see Fig. 6-4).

Surviving animals were autopsied 3 days after treatment. No pellet material could be identified in the peritoneal cavities. One monkey receiving 250 mg quinacrine and another receiving 125 mg quinacrine had an area of inflammation and adhesion directly below the area of incision, corresponding to the area of drug application (Fig. 6-5). Such a reaction could be a source of pain.

COMMENTS

The studies with cynomolgus monkeys indicated three effects that cause concern about the use of quinacrine as a tubal occlusion agent: (1) abdominal pain, (2) central nervous system (CNS) stimulation, and (3) death following administration of the drug.

Some indication of the effect of applying quinacrine directly to the intraperitoneal cavity of humans can be acquired from studies in which quinacrine

was used in the control of neoplastic effusions. In one study, 400-mg doses placed directly into the peritoneal cavity caused abdominal pain. The pain is thought to be due to an inflammatory response of the peritoneum to the drug.⁸ In another study, instillation of less than 1200 mg resulted in minor toxic symptoms, such as pain or nausea.¹⁴ As the dose exceeded 1200 mg, however, more severe toxic effects were reported, including transient CNS symptoms, such as hallucinatory episodes and "other cerebral difficulties."

The convulsions that occurred in one monkey in our study are of particular significance, because CNS effects were previously reported in people receiving oral quinacrine for treatment of malaria and in women receiving intrauterine quinacrine as a tubal occlusive agent." CNS excitation following treatment of malaria with quinacrine had been noticed and characterized variously as psychic stimulation, motor acceleration, restlessness, insomnia, increased work capacity, and epileptiform convulsions.⁹

A "toxic psychosis" seems to be of two distinct types. In one, there is a sudden increase in motor activity, auditory and visual hallucinations, and delusions. The other type is characterized by gradual clouding of the sensorium, disorientation, amnesia for recent events, and confabulation.⁹ That quinacrine, and not the disease, is the source of the symptoms has been demonstrated by the following studies using healthy subjects. In one study, 31 people who had never suffered from malaria were given increasing doses of quinacrine (from 100 mg to 1200 mg daily, orally).¹⁰ Twenty-four reported CNS disturbances of varying degrees. Severe psychic disturbances occurred in 12 subjects, 3 of whom developed frank psychoses, with hallucinations and delusions. Control subjects receiving a placebo reported only mild symptoms, such as insomnia and tension.

In another study, five subjects were given oral doses of quinacrine, ranging from 200 to 1200 mg/day, until plasma levels of the drug exceeded 100 ng/ml.⁶ Electroencephalograms were obtained from bipolar fronto-occipital tracings. Frequency of brain waves accelerated when the plasma level of drug exceeded 30 ng/ml. Psychological symptoms, from restlessness to acute panic reaction, occurred concurrent with acceleration in the electroencephalographic patterns.

Following instillation of quinacrine suspension into the uterus, "CNS excitation" was reported in 2% of the patients. However, the symptom has not been reported when pellets are administered."

To date, more than 1000 women have received intrauterine administration of quinacrine, either in solutions or pellets, with no drug-related deaths reported. The studies in cynomolgus monkeys described above, and those in rhesus monkeys, emphasize that the pellet dose that caused death in the cynomolgus monkey was, on a body weight basis, 17 times the dose normally given to women, and the drug was placed directly into the peritoneal cavity.

A 250-mg dose of intraperitoneal quinacrine resulted in the deaths of two of the three monkeys. Assuming an approximate weight of 3 kg for a cynomolgus monkey, this would be about 80 mg/kg. In rats, the maximal tolerable dose is reported to be 250 mg/kg following intraperitoneal administration.¹² A 40-mg dose of quinacrine injected into the rat uterus resulted in a 32% death rate.¹¹ The mechanism by which death occurs in response to quinacrine is not known, but it appears to be related to the circulating levels of the drug.

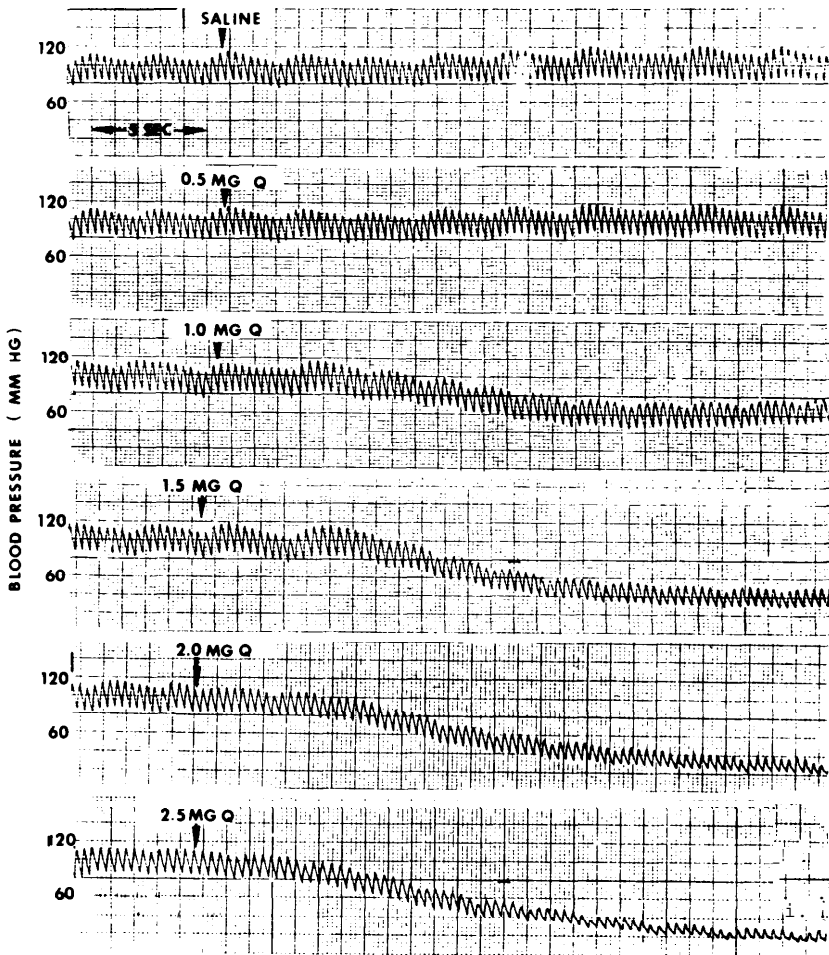


FIG. 6-6. Blood pressure in rat in response to increasing doses of intravascular quinacrine. Injection was made into jugular vein, and pressure recording was made from carotid artery by way of pressure transducer attached to polygraph. Each vertical division is 20 mm Hg. Recovery to preinjection pressure was allowed to occur before next dose was given. With 2.5 mg quinacrine, there was no recovery and animal died. (Q, quinacrine hydrochloride)

We have done preliminary studies in rats demonstrating that intravascular injections of quinacrine, beginning with 1 mg, will cause a decrease in blood pressure from 115/80 mm Hg (systolic/diastolic) to 70/45 mm Hg (Fig. 6-6). This occurs after a lag period of 6 or 7 seconds and is followed by complete recovery after 25 seconds. With increasing doses, there is a greater depression in blood pressure, with prolonged recovery time. Following a dose of 2.5 mg, however, blood pressure dropped to 20/15 mm Hg, there was no recovery,

and the animal died. This experiment was replicated in a second animal with the same outcome.

Clearly, there is some risk in the use of quinacrine as a tubal occlusion agent. The importance of these risks relative to the future use of this drug in fertility regulation will be discussed in Chapter 15.

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