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Pharmacokinetics of Quinacrine after Intrapleural Instillation in Rabbits and Man

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Abstract—Quinacrine was given by intrapleural instillation or intravenous infusion to 10 rabbits. The uptake of quinacrine from the pleural space was rapid and complete. The mean absorption half-life was approximately 7 min and the mean bioavailability was slightly in excess of 100%. Similar absorption characteristics generally applied in man, in a pilot study on four patients. In three of them, peak quinacrine plasma concentrations were reached that were far above the normal therapeutic range. Known systemic side-effects of quinacrine comprise CNS stimulation, toxic psychosis and convulsions. In view of the high bioavailability and the large doses used for pleural sclerosing (pleurodesis) in patients, neurological disease and psychiatric disturbances that predispose to CNS toxicity should be considered as contraindications to intrapleural quinacrine.

Quinacrine (mepacrine, Atebrin) is an acridine derivative that was synthesized as a substitute for quinine, for the treatment of malaria. More recently, the drug has come into fairly widespread use as an intrapleural sclerosing agent (for a review, see Hausheer & Yarbro 1985). Patients who accumulate large amounts of pleural exudate, generally as a consequence of pleural carcinosis, suffer from respiratory insufficiency and risk of infection. They also lose large amounts of vital proteins by repeated aspirations of the exudate. Effective palliation can generally be achieved by instillation of a sclerosing agent. Probably by eliciting a local inflammatory reaction, the drug causes the lung to adhere to the chest wall, with obliteration of the pleural cavity.

The usual side-effects of this treatment (pleurodesis) are transient fever and pain related to the desired pleural inflammation. Systemic side-effects of intrapleural quinacrine can be expected to occur if a substantial fraction of the dose is absorbed into the general circulation. Adverse effects of quinacrine on the central nervous system have been observed. Toxic psychosis has been reported as a consequence of oral quinacrine treatment (Evans et al 1984, and references cited therein). After intravenous infusion of quinacrine, convulsions and respiratory depression were observed (Shannon et al 1944). Convulsions have also occurred in patients treated with intrapleural quinacrine (Borda & Krant 1967).

We therefore investigated the systemic exposure to intrapleurally administered quinacrine in rabbits and man. Animals had to be used in the basic studies, since intravenous administration of quinacrine to patients without medical indication must be considered as unethical.

Materials and Methods

Drugs

Quinacrine dihydrochloride was purchased from Boots (Nottingham, UK). While the dose is normally expressed in mg of this salt, plasma concentrations are expressed as base (1 mg dihydrochloride = 0·84 mg base). The drugs used in the animal surgery were pentobarbitone sodium (Mebumal vet., ACO, Sweden), lignocaine (Xylocain, Astra, Sweden) and heparin (Heparin, Kabi-Vitrum, Sweden).

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Surgical procedures in the rabbits

Ten Bourgogne rabbits of either sex, 3·1 ± 0·32 kg, were used. Light general anaesthesia was induced with intravenous pentobarbitone sodium, ca 18 mg kg^{-1} and maintained by further injections of 3–6 mg kg^{-1}. The right hemithorax and the groins were shaved. The left iliac artery was freed under local anaesthesia with lignocaine, and a catheter was inserted into the aorta by this route.

Animals that were to receive intrapleural quinacrine were given lignocaine into the 6th intercostal space. Through a minimal thoracotomy in the anterior axillary line of the 6th intercostal space, a polyvinyl catheter of 2 mm outer diameter was introduced. The admitted air was then aspirated. Throughout the experiment, the rabbits were spontaneously breathing room air. This procedure for pleural catheterization has been described in detail by Elisson & Björkman (1988). The quinacrine dihydrochloride solution, 10 mg kg^{-1} in 2–3 mL of physiological saline, was then instilled, immediately followed by 2–3 mL of saline. Blood samples were taken from the aorta catheter before the instillation and 1, 5, 10, 20, 40, 60, 120, 240 and 360 min afterwards.

In the other group of animals, an infusion of 2·0 mg kg^{-1} of quinacrine dihydrochloride in 2·6–3·0 mL of saline was given via a marginal ear vein over 5·0 min, by means of a syringe pump. Arterial blood samples were taken 1 and 3 min after the start of the infusion, immediately before stopping it and 5, 10, 20, 40, 60, 120, 240 and 360 min after the end of the infusion.

Over the sampling period, blood losses were replaced with saline. Approximately 1000 units of heparin were used in each rabbit to keep the aorta catheter patent. After the 6 h observation period, all catheters were removed and the incisions closed. If the rabbit was in good health postoperatively, it was allowed to survive. Further blood samples were taken from an ear vein the next day (or days). Postoperative complications that sometimes necessitated killing of the

animal were poor circulation and stiffness in the paw whose iliac artery had been ligated.

Procedures in the patients

Blood samples for determination of quinacrine were taken from four patients, two with malignant and two with nonmalignant pleural effusion. The blood sampling was permitted by the Ethics Committee of the University of Lund. After removal of all accessible exudate, a test dose of 100 mg of quinacrine dihydrochloride in 20 mL of saline was instilled via the pleural drain, followed 10 to 15 min later by 500 mg in 100 mL of saline. The pleural drain was then clamped, and it remained so for the next 4 h. Then the suction was re-started. Blood samples were taken before treatment and 15, 30 and 60 min and 2, 4, 7 and 24 h after the instillation of the main dose.

Determination of quinacrine

The blood samples were centrifuged for 15 min at 1000 *g*, and the plasma was pipetted off, taking care to avoid the buffy coat. It was then stored at −90° C until analysis by high performance liquid chromatography (Björkman & Elisson 1987).

Pharmacokinetic analysis

The rate of appearance of quinacrine in the general circulation was calculated by poly-exponential curve fitting to the experimental intrapleural and i.v. time-concentration data. The NONLIN program (Statistical Consultants 1986) was used. The area under the plasma concentration curve (AUC) and the total body clearance (CL) were calculated according to standard formulas (Gibaldi & Perrier 1982). Finally, the mean bioavailability (F) of quinacrine on intraplural instillation was estimated as

$$F = \text{mean}\left(\frac{AUC_{pl}}{dose_{pl}}\right) / \text{mean}\left(\frac{AUC_{iv}}{dose_{iv}}\right)$$

Results

Findings in rabbits

The pharmacokinetic parameters of intrapleural and intravenous quinacrine in rabbits are summarized in Table 1. The plasma concentration curves are shown in Figs 1 and 2. The uptake of quinacrine from the pleural space was rapid, with a half-life of appearance in the plasma of 6·9 ± 5·5 min. From the mean values of AUC/dose in the two groups, a bioavailability of 102% was calculated for intrapleural quinacrine.

Table 1. Pharmacokinetic parameters (mean ± s.d.) of quinacrine in rabbits (n = 5 in each group).

	Route of administration	
Parameter	Intravenous	Intrapleural
C_{max}, ng mL^{-1}	633 ± 227	865 ± 311
t_{max}, min	0[a]	20[b]
AUC/dose, min L^{-1} kg^{-1}	7·82 ± 2·43	7·97 ± 1·29
CL, mL min^{-1} kg^{-1}	136 ± 36	—
$t_{\frac{1}{2}}$ (terminal), h	26 ± 4·7	26 ± 3·5

[a] End of infusion.
[b] In all five rabbits.

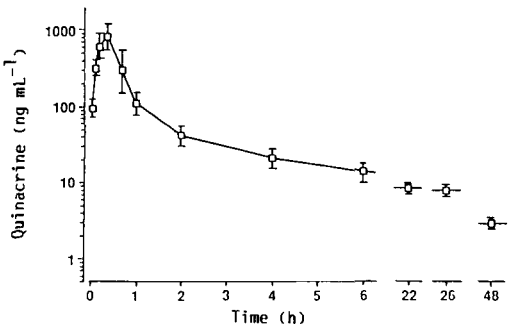

FIG. 1. The average plasma concentration curve of quinacrine (as free base) after intrapleural administration to five rabbits. The bars denote ranges of values. The three last points are based on, respectively, 3, 3 and 2 measurements.

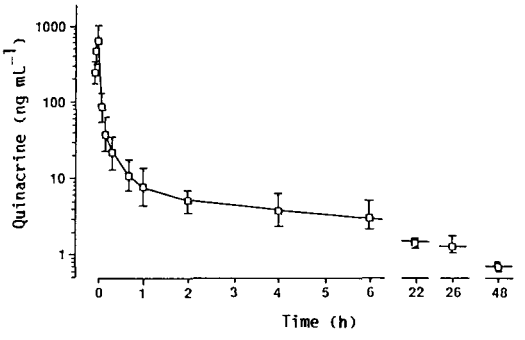

FIG. 2. The average plasma concentration curve of quinacrine after intravenous administration to five rabbits. The three last points are based on, respectively, 4, 3 and 2 measurements.

Rabbit no. 2 was killed four months after the quinacrine treatment and an autopsy was performed. Thin, fibrous adhesions were present throughout the right pleural cavity. There was no exudate. The left pleural cavity, as well as heart, lungs, liver, kidneys and spleen were macroscopically normal. Autopsy on rabbit no. 4, after two months, showed minimal adhesions between the lung and diaphragm.

In a preliminary experiment, intravenous infusion of quinacrine dihydrochloride at a dose of 10 mg kg^{-1} over 1 min was immediately fatal to the rabbit. The infusion of 2 mg kg^{-1} over 5 min had no visible effect on the animals.

Findings in the patients

The plasma concentrations of quinacrine found in the patients are summarized in Table 2 and Fig. 3. Apparently, the absorption of intrapleurally administered quinacrine can also be fast in man.

Patients nos. 1 and 2 had pleurisy of non-malignant origin and absorbed quinacrine rapidly. Patient no. 3 had terminal

Table 2. Plasma concentrations of quinacrine found in patients.

Patient no.	C_{max} ng mL^{-1}	t_{max} min	Hours with $C_{pl} > 100$ ng mL^{-1}
1	543	15	3
2	450	30	2·5
3	15	120	0
4	970	15	3·5

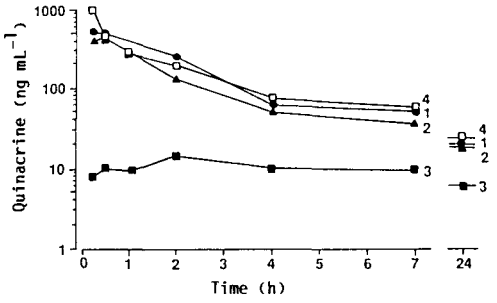

FIG. 3. Individual plasma concentration curves of quinacrine after intrapleural administration to four patients. The numbering of the patients is as in Table 2.

cancer and died 8 days after the pleurodesis. The autopsy showed a very thick parietal pleura (approximately 6 cm) and extensive tumor involvement of the lungs. In his case the absorption of quinacrine was slow and incomplete. Patient no. 4 had adenocystic carcinoma which affected only a minor part of the pleural surface, as found by thoracoscopy. She is still alive, 10 months after the pleurodesis. The absorption of quinacrine was in her case quick and extensive.

Discussion

The basic pharmacokinetic characteristics of quinacrine in man can be estimated from the data given by Shannon et al (1944). From blood concentrations measured over one week after intravenous infusions in six patients, a mean blood clearance of 0·32 L kg^{-1} h^{-1} and a mean terminal half-life of 5 days can be calculated. The plasma clearance of quinacrine is not known, but, with a blood/plasma concentration ratio of four, it can be estimated at 1·3 L kg^{-1} h^{-1} (cf Rowland & Tozer 1980). The clearance is extensively metabolic, with very little renal excretion of unchanged drug.

The usual oral dose of quinacrine dihydrochloride in the treatment of malaria is five times 200 mg the first day followed by 100 mg thrice daily (Goodman & Gilman 1955). An intrapleural dose of 600 mg is thus numerically equal to 3–6 single oral doses. However, in view of the high metabolic clearance of quinacrine, its oral bioavailability is probably low. An intrapleural dose, with a high bioavailability, might thus in terms of systemic exposure correspond to a much higher oral dose.

The rapid absorption of intrapleural quinacrine in the rabbits is in keeping with the lipophilic character of the drug (its octanol—pH 7·4 buffer partition coefficient is approximately 80; Unger & Chiang 1981) and with the large surface and good blood perfusion of the healthy pleura. The fibrous adhesions found in the pleura of rabbits no. 2 and 4 testify that the catheter tip was indeed in the pleural space.

Rapid uptake of quinacrine was also observed in the three patients with fairly normal pleuras. This is somewhat at variance with the limited data available on intrapleural pharmacokinetics of other drugs. Instillation of doxorubicin in four patients with pleural carcinosis gave a rather slow, and apparently incomplete, absorption of drug into the circulation (Eksborg et al 1984). Also, after intrapleural administration of etoposide to a single patient, the peak plasma concentration was found after 4 h, and the clearance from the pleural space was only 0·2 mL min^{-1} (Jones et al 1985). Also in our pilot study on four patients, the absorption of quinacrine from the pleural space was low in a patient with extensive tumour involvement of the pleura. The rapid drug absorption seen in the rabbits and in the other three patients should therefore not be considered as clinically ubiquitous but as examples of what may be found in patients with comparatively healthy pleuras.

Systemic peak concentrations of quinacrine after intrapleural administration that are in the range of 400–1000 ng mL^{-1} should be compared with the upper therapeutic limit of approximately 100 ng mL^{-1} advocated in the treatment of malaria (Shannon et al 1944; Goodman & Gilman 1955). Quinacrine caused plasma concentration-dependent changes in the EEG in an early study on volunteers, and apparently it acts as a CNS stimulant at ordinary oral dosage (Engel et al 1947). In keeping with this, oral quinacrine has been reported to cause toxic psychosis (Evans et al 1984, and references cited therein). Whether this effect is due to excessive plasma concentrations of quinacrine, however, has not been elucidated.

Adverse effects attributable to actions on the CNS have also been observed after parenteral administration. Respiratory depression was noted in two malaria patients who received intravenous quinacrine, at whole blood concentrations of 760–1080 ng mL^{-1} (Shannon et al 1944). These blood concentrations may be tentatively translated to plasma concentrations of 200–300 ng mL^{-1}. One of these patients also experienced mild convulsions. Severe convulsions were observed in two cancer patients who had received quinacrine intrapleurally (Borda & Krant 1967). One of these patients had a grossly abnormal EEG before the treatment, and she experienced a grand mal seizure 3 h after the second of two consecutive instillations of 400 mg of quinacrine dihydrochloride. The other one died in status epilepticus 13 h after the instillation of 400 mg, which, in view of our findings, probably did not coincide with a high plasma concentration of quinacrine. Both patients were on long-term corticosteroid treatment, which might have lowered their seizure threshold.

Taken together, these case reports afford circumstantial evidence that quinacrine affects the CNS and that plasma concentrations in excess of 100 ng mL^{-1} may be hazardous in sensitive patients.

An inhibition of cholinesterase has been proposed as the mechanism of toxicity (Waelsch & Nachmansohn 1943). However, the free concentration of quinacrine necessary for 50% inhibition of cholinesterase from human blood was 3 μg mL^{-1}. With a 70–90% plasma protein binding of quinacrine (Shannon et al 1944), this would correspond to a total plasma concentration of 10–30 μg mL^{-1}, which is clearly far above the concentrations obtained in-vivo under any clinical condition. In the rabbit that received 10 mg kg^{-1} of quinacrine dihydrochloride intravenously over 1 min, such plasma concentrations may have been reached and caused cardiac paralysis.

Irrespective of the mode of action of quinacrine on the CNS, in view of our pharmacokinetic findings, we suggest that neurological conditions such as latent psychosis, lowered seizure threshold, parkinsonism and possibly cerebral arteriosclerosis should be considered as contraindications to intrapleural quinacrine.

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