QUINIDINE: ARTERIAL, VENOUS, CORONARY SINUS AND MYOCARDIAL CONCENTRATIONS *

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Most of the current knowledge of relationships between blood levels of quinidine and therapeutic or toxic effects were ascertained by determining peripheral venous levels following oral administration. After single oral administration of quinidine sulfate to patients with atrial fibrillation, Wegria and Boyle (1) observed that the intensity of the cardiac effect of the drug and its plasma concentration were grossly parallel but not parallel in a strictly quantitative manner. Discrepancies were found between the intensity of cardiac effect and quinidine plasma concentration, the plasma level of the drug decreasing faster than the intensity of its cardiac effect. Some investigators utilize quinidine concentration of venous blood as a guide in determining optimal therapy (2–6). Wegria and Boyle (1) reported no significant difference between the arterial and venous concentration of quinidine a few hours after oral administration. Higher levels were found in the myocardium than in the peripheral venous blood. A recent publication (7) contains a review of the pertinent literature on the subject. In spite of the clinical practice of administering quinidine intravenously to patients with certain life-threatening arrhythmias for immediate therapeutic effects, there is a paucity of data relative to blood levels and these are limited to venous blood (4, 8).

In the present study of the cardiovascular effects of quinidine given intravenously, levels were determined in specimens obtained from a peripheral vein, artery, coronary sinus and myocardium. Quinidine given intravenously reaches the heart directly, thus bypassing the gastrointestinal tract and liver. We attempted to determine whether a gradient could be demonstrated across the myocardium following such administration.

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METHODS

Quinidine gluconate was injected within 1 minute into a cannulated foreleg vein of mongrel dogs anesthetized with sodium pentobarbital. The cannula was kept patent by a drip of heparinized normal saline which was used to flush the injected quinidine into the circulation. Cannulas were inserted into the femoral artery and femoral vein of opposite hind legs for a distance of 5 cm to permit proper collection of specimens. Following cannulation of the opposite femoral artery, the blood pressure was recorded constantly with a Sanborn water manometer or Statham strain gage. Electrocardiograms were continuously recorded. The chest was opened in the right third or fourth intercostal space and a polyethylene tube, small enough not to obstruct the coronary sinus, was inserted into the right atrial appendage and guided into the coronary sinus. After insertion, the tube was sutured to the right atrial wall at a distance from the coronary sinus. The cannula was initially kept patent by a slow drip of heparinized normal saline. In later studies, coronary sinus blood was often permitted to drip constantly. With the help of 3 observers, specimens were withdrawn simultaneously from the femoral vein, femoral artery and coronary sinus at 1, 3, 5, 10, 15 and 30-minute intervals following injection. The collection of samples was completed within 10 seconds. In some instances, the effects of repeated and prolonged injections were determined. In 5 dogs, ventricular biopsies were obtained at varying intervals following the injection of quinidine.

Quinidine levels were determined on whole blood samples by measuring the fluorescence of trichloroacetic acid filtrates, employing the principles of the Linenthal, Ulick and Patterson (9, 10) modification of the Brodie, Udenfriend and Baer technique (11, 12). In each animal, blood samples obtained prior to the administration of quinidine were used as blanks. Minimal to no fluorescence was detected. Initially, an Aminco-Bowman spectrophotofluorometer was employed at an activation wave length of 360 mμ and an emission wave length of 450 mμ. Subsequently, a photofluorometer (Electronic model 12C, Coleman Instrument Co.) was used with a primary and a secondary filter, Corning nos. 5874 and 3389-4308.

A solution of quinidine gluconate containing 100 mg per 100 ml as quinidine base was prepared. One-tenth milliliter of this solution was added to various volumes of blood so that the final theoretical concentration of quinidine base was from 1 to 20 μg per ml blood. These

bloods were analyzed as blind samples and were reported as differences between blood blank and quinidine sample. The mean recovery was 94 per cent, SE 3.9 per cent. Forty specimens were run in quintuplicate. The mean difference of an individual specimen from the mean value of its group was ± 2.93 per cent, SD 2.57 per cent. To ascertain that the measured fluorescence represented unconjugated quinidine, parallel samples of the same blood were extracted according to standard procedure in 10 dogs (9–12). The results indicated that over the period of observation there had been no significant conjugation of the quinidine.

All findings are expressed in terms of quinidine base.

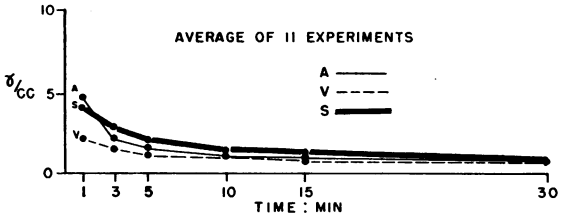

FIG. 1. ARTERIAL, VENOUS AND CORONARY SINUS CONCENTRATIONS OF QUINIDINE BASE (MICROGRAMS PER MILLILITER) AFTER THE RAPID INTRAVENOUS INJECTION OF 4.1 TO 6.0 MG PER KG.

RESULTS

Quinidine gluconate was administered rapidly in amounts varying from 2.0 to 15.0 mg per kg body weight.

A. Dosage levels of 2.0 to 4.0 mg per kg body weight. Four dogs in this group received one injection and two received a second similar dose 15 to 30 minutes after the 30-minute specimen had been obtained. The peak level was reached in the 1-minute arterial specimen with a range of 1.1 to 4.7 μg per ml. The levels then fell abruptly in the first few minutes with plateaus obtained within 5 to 10 minutes. The arterial, venous and coronary sinus levels were essentially similar by 10 minutes with a range from 0.2 to 1.7 μg per ml at 30 minutes. The venous level of quinidine was somewhat lower than the arterial and coronary sinus specimens for the first 5 minutes. There was no significant difference between the arterial and coronary sinus levels. With the second injection, there was an increase in the early levels of quinidine as compared with those following the first injection. The peak arterial level was 5.3 μg per ml and the 30-minute level 2.2 μg per ml. In the subsequent samples, no significant difference was demonstrated as compared with the first injection except for slightly higher levels.

B. Dosage levels of 4.1 to 6.0 mg per kg body weight (Figure 1). The 11 dogs in this group received an initial injection of 4.1 to 6.0 mg per kg body weight, and 6 received a similar dose repeated 15 to 30 minutes after the 30-minute specimen was obtained. The peak levels were found in the 1-minute arterial specimens and varied from 2.1 to 12.0 μg per ml. The levels fell abruptly to approximately one-half the peak concentration in the first 5 minutes with a plateau obtained in 10 minutes and little change noted by 30 minutes. The arterial, venous and coronary sinus levels were similar in 10 minutes for any one dog with the levels varying from 0.3 to 3.8 μg per ml by 30 minutes. In six dogs, the quinidine level in the coronary sinus specimen was greater than in the arterial or venous specimens at 3 and 5 minutes. The concentration of quinidine in the venous specimen was consistently lower than that in the arterial or coronary sinus specimens for the first 3 to 5 minutes. In the six dogs which received a second injection of quinidine, the peak arterial level was 2.7 to 12 μg per ml with a 30-minute level of 0.3 to 4.2 μg per ml. In two of these dogs, the concentration of quinidine in the coronary sinus was greater than in the arterial sample obtained at 1 and 3 or 3 and 5 minutes. Each of these dogs showed similar results following the initial injections.

C. Dosage levels of 6.1 to 10.0 mg per kg body weight. Eleven dogs received 6.1 to 10.0 mg of quinidine base per kg body weight as an initial injection. The peak arterial level ranged from 4.6 to 22.2 μg per ml. The levels fell abruptly in 3 minutes with a plateau obtained within 15 to 30 minutes. The arterial, venous and coronary sinus levels in any one dog were similar in 30 minutes, with the levels ranging from 0.5 to 5.7 μg per ml. In eight dogs, the quinidine blood levels were greater in the coronary sinus than in the artery or vein in the 3 to 10-minute specimens. Seven dogs received a second injection of quinidine 15 to 30 minutes after the last 30-minute specimen had been obtained. In three of these dogs, the quinidine level in the coronary sinus blood was greater than in the artery or vein in the 1 and 3 or 3 and 5-minute specimens. The peak arterial level ranged from 0.8 to 14.3 μg per ml and the residual

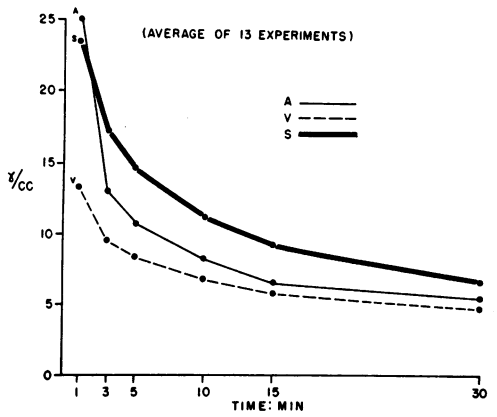

FIG. 2. ARTERIAL, VENOUS AND CORONARY SINUS CONCENTRATIONS OF QUINIDINE BASE (MICROGRAMS PER MILLILITER) AFTER THE RAPID INTRAVENOUS INJECTION OF 15.0 MG PER KG. The concentration of quinidine in the coronary sinus is greater than in the arterial and venous specimens in the 3 to 15-minute samples.

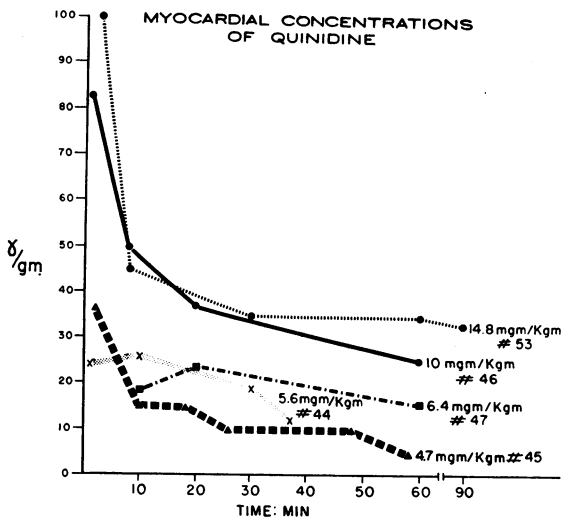

FIG. 3. THE MYOCARDIAL CONCENTRATIONS OF QUINIDINE FOLLOWING VARIOUS INTRAVENOUSLY INJECTED AMOUNTS. The concentration varies directly with the amount injected.

levels at 30 minutes were 1.1 to 5.7 μg per ml. The rapid fall within a few minutes was similar to that observed following the initial injection.

D. Dosage levels of 15.0 mg per kg body weight. Thirteen dogs received 15.0 mg per kg as an initial injection (Figure 2). The peak arterial levels ranged from 11.5 to 59.0 μg per ml. The levels fell abruptly in 3 to 5 minutes with a plateau appearing by 10 to 15 minutes in most instances. In 30 minutes, the arterial, venous and coronary sinus concentrations approached one another; the levels varied from 2.3 to 10.5 μg per ml. In each instance the quinidine level was greater in the coronary sinus blood of the 3-minute specimen and this usually persisted for 10 to 15 minutes. The 1-minute coronary sinus sample showed a higher concentration of quinidine than the arterial specimen in 8 of the 13 dogs. Eight of the dogs received a subsequent repeat injection of 15.0 mg of quinidine base per kg. The peak arterial level ranged from 18.0 to 54.0 μg per ml with 30-minute residual levels of 6.4 to 16.0 μg per ml. In seven trials the 3-minute level of quinidine was highest in the coronary sinus. In the remaining dog, the 5-minute coronary sinus concentration of quinidine was highest. In five studies the 1-minute coronary sinus specimen showed a higher concentration of quinidine than the arterial sample.

E. Myocardial concentrations. Five dogs received 4.7 to 14.8 mg quinidine per kg intravenously (Figure 3). In addition to arterial, venous and coronary sinus samples, biopsies were obtained from the ventricular myocardium at varying intervals up to 90 minutes. The myocardial concentrations of quinidine were four- to tenfold

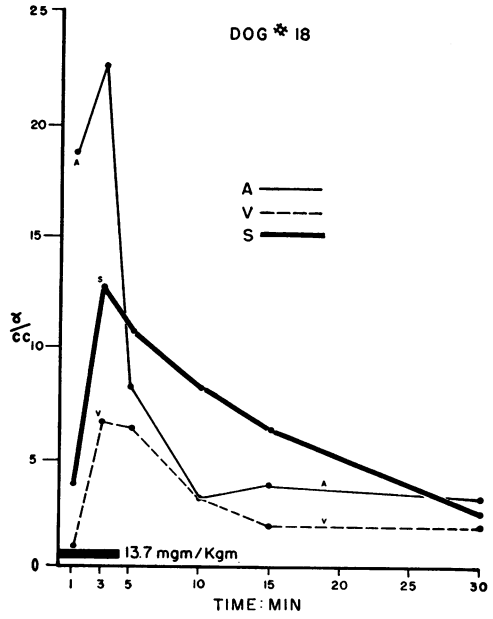

FIG. 4. ARTERIAL, VENOUS AND CORONARY SINUS CONCENTRATIONS FOLLOWING THE INJECTION OF 13.7 MG PER KG OVER A 4.5-MINUTE PERIOD. The concentration of quinidine increases rapidly during the period of injection and then decreases after the injection is stopped. The coronary sinus concentration is greater than the arterial and venous samples until the 20-minute specimen.

higher than the corresponding blood specimens. Three to 6 per cent of the injected amount was initially localized in the myocardium. The myocardial concentrations varied directly with the amount of quinidine injected.

F. Blood pressure. Within 30 to 60 seconds after the injection of 5 or more mg per kg, the blood pressure fell abruptly to two-thirds or less of the control value. A less marked drop usually occurred with smaller injections. The duration of reduced pressure persisted for varying periods depending upon the dosage, and usually for at least 15 minutes. Vasopressors such as Levophed and Aramine effectively prevented this drop in pressure.

G. Prolonged injection. When quinidine is given more slowly, there is a gradual rise in the arterial, venous and coronary sinus concentrations until the injection is discontinued (Figure 4). This results in a more rapid decline in the arterial concentration as compared with the coronary sinus. The level of quinidine in the coronary sinus exceeds the arterial specimen for several minutes. This was observed in three dogs given 11.0 to 14.0 mg per kg over a period of 5 minutes.

DISCUSSION

The intravenous administration of quinidine is usually reserved for emergency use in those patients with certain life-threatening arrhythmias in whom a prompt therapeutic result is required. Most of the available data pertaining to quinidine assay has been obtained after oral, intramuscular or rectal administration (2–4, 9, 13–19). Wegria and Boyle (1) reported no significant differences between the arterial and peripheral venous specimens obtained a few hours after oral administration. Several dogs were sacrificed at hourly intervals following orally administered quinidine. Maximal plasma and tissue quinidine concentrations were reached within 3 hours after ingestion of the drug. Myocardial levels were higher than those of peripheral venous blood. The concentration of quinidine in the left ventricle was 148.6 mg per kg, and in the plasma, 12.5 mg per L 3 hours after 50 mg per kg of quinidine sulfate was given orally. A marked difference persisted up to the final determination at 14 hours.

Sokolow (4) reported that intravenous administration in humans produced high venous levels in a few minutes with the peak subsiding in 5 to 10 minutes. Weisman (20) noted that with a single intravenous dose, less than 6 per cent remained in the blood after 7 minutes. Weiss and Hatcher (21) showed in cats that 95 per cent of an intravenous dose was cleared from the blood in 5 minutes. Kelsey, Oldham and Geiling (22) observed myocardial concentrations of quinidine six times greater than in blood in the rabbit 10 minutes after intravenous injection.

To our knowledge, this is the first attempt to measure and demonstrate quinidine arteriovenous and coronary-sinus arterial differences after intravenous injection of quinidine. There was a fairly wide variation in the blood levels of each animal in spite of the standardization of dose. The variation in the initial arterial level is probably secondary to the rapid change in concentration that occurs shortly after injection. Variations occur in man after the oral administration of quinidine for therapeutic purposes. With increased doses and repeated injections, the blood levels increased and the same general curves resulted. In each dog, the relationships of arterial, venous and coronary sinus levels persisted as described.

The detection of a transient gradient between the coronary sinus and arterial samples suggests several possible alternative explanations. The concentration in the coronary sinus may be higher because of the technique of collection. Conceivably, the catheter partially blocked the coronary sinus so that the specimen reflected the earlier higher arterial level. To obviate this artifact, various sizes of catheters were employed, and similar results were obtained. Moreover, the catheter remained patent in several dogs during the continuous collection of blood. The results were similar whether this technique or a constant slow perfusion with heparinized saline was used. Every effort was made to obtain simultaneously collected specimens.

The concentration of quinidine in the myocardium far exceeded that of the blood. A tentative explanation for the higher concentration in the coronary sinus is based upon the hypothesis that the quinidine is initially bound or pooled in the myocardium and is subsequently washed out by the perfusing blood. The higher coronary sinus concentration may thus represent a washing

out of this bound or pooled quinidine. Preliminary studies indicate that appreciable amounts of quinidine are recovered in the coronary sinus specimens after perfusion of the coronary arteries with saline or whole blood. Quinidine is thus washed out from the myocardium by the perfusing fluid. Weiss and Hatcher (21) interpreted their data as showing that the capillaries of certain organs fix quinidine loosely initially and that much of the fixed drug can be removed by perfusion. Chen and Geiling (23) found that the capillaries of the lungs may be the site of absorption for removal of quinine from the circulation.

Following the intravenous administration of large doses of quinidine, hypotension results uniformly (24, 25). Conceivably, the transient higher concentration of quinidine in the coronary sinus as compared with the arterial blood may be associated with the subsequent hypotension that might promote pooling in the myocardium. Preliminary studies in five dogs indicate that when hypotension is prevented by vasopressor substances, the coronary sinus concentration continues to exceed the arterial levels from the 3 to 5 or 10-minute period. Another factor to be considered is that altered coronary flow may be related to varying quinidine content in the coronary sinus blood, since only limited amounts of quinidine may be released to the perfusing blood in any given period of time. The possibility remains that the increased coronary artery perfusion during higher arterial pressures may reduce the concentration of quinidine in the myocardium.

The extremely high myocardial concentration of quinidine occurs shortly after injection, as demonstrated by the extremely high initial peak and the subsequent rapid decline. Apparently the quinidine is bound rapidly in the myocardium after the initial period of perfusion and subsequently declines as the blood continues to perfuse the myocardium. Quinidine is also found in high concentrations in other tissues, but the presence of arteriovenous differences across these tissues has not been determined.

SUMMARY

1. The rapid intravenous administration of quinidine gluconate in doses of 4.1 to 6.0 mg per kg body weight produces a peak arterial level in 1 minute with a rapid decline within 3 to 5 minutes. In three of six dogs, the quinidine level in the coronary sinus transiently exceeded that in arterial blood following the 1-minute specimen.

2. With the injection of higher doses, the quinidine level in the coronary sinus usually exceeded the arterial level after the first minute.

3. The myocardial concentration of quinidine, following examination of biopsy specimens taken serially in the same animal, exceeded the concentration in the blood from four- to tenfold.

4. It is suggested that quinidine is pooled transiently or bound in the myocardium and is subsequently washed into the coronary sinus.

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