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Digoxin-Quinidine Interaction in the Neonatal Dog

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The effects of quinidine on steady state serum and tissue digoxin concentrations in the neonatal dog were studied. To determine the effects of quinidine on serum digoxin concentrations, two groups of neonates were evaluated: Group I (n = 11) was digitalized with 40 μg/kg body weight, intramuscularly, and placed on a 10 μg/kg per day maintenance dose; Group II (n = 7) was digitalized with 50 μg/kg per day, intraperitoneally, and placed on a 20 μg/kg per day maintenance dose. After 10 days of digoxin alone, quinidine was coadministered (30 mg/kg per day, intraperitoneally) for 7 days. Serum digoxin concentrations were measured before quinidine and 1, 3 and 7 days after combined digoxin-quinidine therapy. In Group I, the control serum digoxin concentration was 1.38 ± 0.32 ng/ml and after 7 days of combined therapy it was unchanged (1.39 ± 0.31 ng/ml). In Group II, the control serum digoxin concentration measured 2.80 ± 0.49 ng/ml and after 7 days of combined therapy it, too, was unchanged (3.10 ± 0.65 ng/ml).

The effects of combined digoxin-quinidine administration on tissue digoxin concentrations were studied in two other groups of neonates. Group III (n = 6) was given a low maintenance dose of digoxin (10 μg/kg per day, intramuscularly) and a full 7 days of coadministered quinidine; in Group IV (n = 6), digoxin was given at a higher dose (20 μg/kg per day, intraperitoneally) and a shorter duration of combined digoxin-quinidine therapy (3 days). Tissue samples of skeletal muscle, brain, myocardium, liver and kidney were analyzed for digoxin content and compared with tissue levels measured in control neonates given digoxin alone. Brain digoxin concentrations were higher in Group IV (910 ± 437 ng/g) compared with neonates given digoxin alone (530 ± 49 ng/g). In both Groups III and IV, digoxin tissue concentrations in skeletal muscle, liver and brain, normalized for the serum digoxin level, were significantly higher than in control neonates.

In the neonatal dog, quinidine administration results in little or no increase in the steady state serum digoxin concentration. However, quinidine may be associated with higher brain digoxin levels, particularly at higher digoxin doses and serum levels.

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It has become increasingly apparent that a number of pharmacologic agents can alter the pharmacokinetics of digoxin and result in increased serum digoxin concentrations (1–3). The interaction between digoxin and quinidine was the first of such interactions to be recognized and, since the first description in 1978 (4), has been studied extensively both in the clinical setting and in the animal laboratory (5–13). The salient features of the interaction (9) are that quinidine adminstration results in an increase in the serum digoxin concentration as early as a few hours after the first dose of quinidine, usually peaking in a few days. There is often a two- to threefold serum digoxin increase. The interaction appears to be independent of the serum digoxin concentration and occurs even in the presence of low serum quinidine concentrations. It has been hypothesized that quinidine may alter the renal clearance of digoxin by suppressing digoxin renal tubular secretion (9,14).

We have previously reported (15) that in the neonatal dog, no increases in serum digoxin concentrations are observed after 3 days of combined intraperitoneal digoxin and quinidine therapy. Furthermore, Koren (3) has recently reported that although quinidine results in a significant increase in the serum digoxin concentration in children over the age of 5 years, no increases were observed in any of three infants studied at less than 2 months of age. These data suggest that the digoxin-quinidine interaction in the immature human or animal may be qualitatively different from that observed in the adult.

The objectives of this study were to: 1) quantitate changes in steady state serum digoxin concentrations in the neonatal

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puppy given combined digoxin-quinidine therapy over an extended period of time (7 days) and over a range of serum digoxin concentrations; and 2) to document changes in tissue digoxin concentrations in neonatal puppies given combined digoxin-quinidine therapy.

Methods

For both the serum and tissue studies, the experimental subjects were neonatal mongrel puppies. All puppies were digitalized at 10 days of age and placed on 10 days of maintenance digoxin therapy before beginning quinidine therapy. In all studies, maintenance digoxin doses were administered at approximately 5 PM and blood samples for digoxin serum concentrations were obtained at approximately 10 AM (during the elimination phase). Specific protocols for each experiment are described.

Serum digoxin studies (Groups I and II). To quantitate the effects of combined digoxin-quinidine administration on steady state serum digoxin concentrations, two groups of neonates were studied. Group I consisted of 11 neonates that were digitalized with 40 μg/kg body weight, intramuscularly, and subsequently placed on daily maintenance digoxin doses of 10 μg/kg per day, given intramuscularly at rotating sites. Quinidine sulfate was begun after 10 days of maintenance digoxin therapy at a dose of 15 mg/kg twice a day, intraperitoneally.

To study neonates with higher serum digoxin concentrations, as well as to assess the influence of the route of digoxin adminstration on any observed interaction, a second group of neonates was studied (Group II). These neonates (n = 7) were studied in an identical fashion except that digoxin was given intraperitoneally as a 50 μg/kg digitalization dose and a 20 μg/kg per day maintenance dose.

In both Groups I and II, serum digoxin concentrations were measured by radioimmunoassay (Coat-A-Count, Diagnostic Products Corp.) before giving quinidine and 1, 3 and 7 days after starting quinidine. The possibility of digoxin-like substances (16) being detected with this radioimmunoassay was excluded by analyzing serum samples of many of the neonates reported here (and of other neonatal dogs) before digoxin adminstration. These levels were consistently 0. Quinidine levels were also determined and measured by gas-liquid chromatography (17).

Statistical analysis of the effects of quinidine on mean serum digoxin concentration was assessed by analysis of variance. A probability (p) value of less than 0.05 was required to indicate statistical significance.

Tissue studies (Groups III and IV). In the second part of the study, digoxin tissue concentrations were measured in groups of neonates receiving digoxin and quinidine and compared with values obtained in neonates given digoxin alone. Two digoxin-dosing protocols were utilized. In the first group (Group III, n = 6), digoxin and quinidine were coadministered for a total of 7 days. Digoxin was administered intramuscularly at a dose of 10 μg/kg per day. In the second tissue group (Group IV, n = 6), digoxin was given at a higher maintenance dose (20 μg/kg per day) and was administered intraperitoneally. Digoxin and quinidine were coadministered for 3 days.

At the conclusion of the dosing protocols, samples of heart, skeletal muscle, brain, kidney and liver were taken from each of the experimental subjects for analysis of digoxin concentration. Tissue samples were also obtained from groups of control neonates that had received digoxin by the same dosage protocols as Groups III and IV, but without the addition of quinidine. The control neonates for Group III consisted of seven dogs treated with digoxin alone, and the control neonates for Group IV consisted of eight dogs treated with digoxin alone.

All tissue samples were obtained rapidly after death was induced (pentobarbital anesthesia followed by potassium chloride), and were freed of all visible fat and connective tissue. Samples were then lyophylized for 24 hours at −70°C. The freeze-dried tissues were then cleaned of remaining fat and connective tissue and weighed. Digoxin was extracted from the tissue by first shaking the samples in 2 cc of 0.02 *M* phosphate buffer and then adding 5 cc of dichloromethane. The dichloromethane layer was collected (above procedure repeated twice) and evaporated in a water bath at 50°C until dry. After drying, the residue was resuspended in 0.5 cc of digoxin-free human serum and assayed by radioimmunoassay. Extraction efficiencies were determined by adding 0.1 cc of 8 ng/ml of digoxin standard to digoxin-free canine heart tissue and assaying these samples in each extraction procedure. Extraction efficiencies ranged from 75 to 100%; all radioimmunoassay determinations (serum and tissue) were performed in duplicate and percent coefficients of variance of less than 10 were considered acceptable. A detailed description of this method of tissue analysis has been previously described (18).

Statistics. Statistical comparisons of tissue digoxin concentrations (expressed both as an absolute value in nanograms per gram dry weight and as a ratio to the serum digoxin concentration in milliliters per gram) were made between the digoxin-quinidine and control group neonates utilizing a standard *t* test. A p value of less than 0.05 was required to indicate significance.

Results

Serum digoxin studies. The serum digoxin determinations (and corresponding quinidine levels) before and during the 7 days of combined digoxin-quinidine therapy are presented for Groups I and II in Table 1. In Group I (low dose digoxin), the control serum digoxin concentration, after 10 days of maintenance digoxin, measured 1.38 ± 0.32 (mean ± SD). After a full 7 days of coadministered quin-

Table 1. Digoxin-Quinidine Interaction in the Neonate

	Control	Days After Quinidine 1	3	7
Group I (n = 11)				
Digoxin (ng/ml)	1.38 ± 0.32	1.43 ± 0.23	1.71 ± 0.30*	1.39 ± 0.31
Quinidine (mg/liter)	—	4.25 ± 0.86	4.35 ± 1.12	3.58 ± 0.54
Group II (n = 7)				
Digoxin (ng/ml)	2.80 ± 0.49	2.60 ± 0.48	2.60 ± 0.53	3.10 ± 0.65
Quinidine (mg/liter)	—	4.10 ± 1.00	2.70 ± 1.47	3.70 ± 1.67

*$p < 0.03$. Data are reported as mean ± SD. n = number of subjects.

idine, and despite achievement of adequate serum quinidine concentrations during the entire period of time, the serum digoxin concentration remained unchanged, measuring 1.39 ± 0.31 ng/ml (Fig. 1). After 3 days of combined digoxin-quinidine adminstration, a small mean increase of 0.30 ng/ml in the serum digoxin concentration was observed. This small increase results in a significant p value (0.03) for the overall relation by analysis of variance. However, apart from the very modest (and unsustained) increase at day 3, no apparent overall increase was observed in the serum digoxin concentrations in this group of neonates after the addition of quinidine.

In Group II, the control serum digoxin concentration measured 2.80 ± 0.49 ng/ml (Fig. 2). No increases were observed in the serum digoxin concentration over the entire 7 days of combined digoxin-quinidine therapy (serum digoxin concentration 3.10 ± 0.65 ng/ml after 7 days of combined therapy). Again, serum quinidine concentrations achieved during this period of combined therapy were all well above the value of 1.9 mg/liter, thought to be the threshold quinidine concentration at which the interaction between digoxin and quinidine is observed (19). Thus in both neonate Groups I and II, no significant quinidine-related rise in the serum digoxin concentration could be demonstrated after 1 week of combined therapy.

Tissue digoxin studies. Tissue digoxin concentrations and tissue digoxin concentrations normalized for serum digoxin concentration (tissue/serum ratio) for Group III are presented in Table 2A. For comparison, digoxin tissue levels obtained from a group of seven neonates treated identically to Group III except for the omission of quinidine are also presented. At the time of tissue collection, the serum digoxin concentration in the digoxin-quinidine group was 1.19 ± 0.13 ng/ml and in the control group was 2.00 ± 0.28 ng/ml.

Inspection of the absolute digoxin tissue levels reveals no significant differences between the digoxin-quinidine and digoxin alone groups in brain, heart, kidney, liver or skeletal muscle digoxin concentrations. However, when the data are normalized for the attained serum digoxin concentration (tissue/serum ratio) a significantly higher normalized digoxin tissue concentration is observed in the digoxin-quinidine neonates for the brain (254 ± 70 versus 156 ± 42 ml/g), liver (112 ± 13 versus 72 ± 10 ml/g) and skeletal muscle (180 ± 11 versus 108 ± 24 ml/g) (Fig. 3). Thus, despite attainment of a lower serum digoxin concentration in the neonates receiving digoxin plus quinidine, tissue

Figure 1. Group I serum digoxin (D) determinations before (C) administering quinidine (Q) and 1, 3 and 7 days after adding quinidine. IM = intramuscular; IP = intraperitoneal.

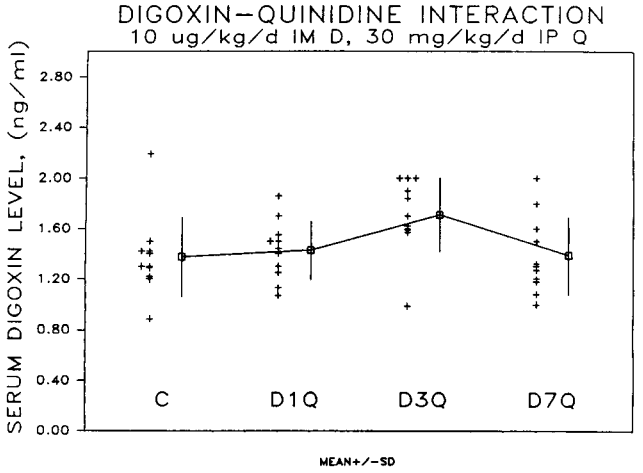

Figure 2. Group II serum digoxin determinations before (C) and 1, 3 and 7 days after adding quinidine. Abbreviations as in Figure 1.

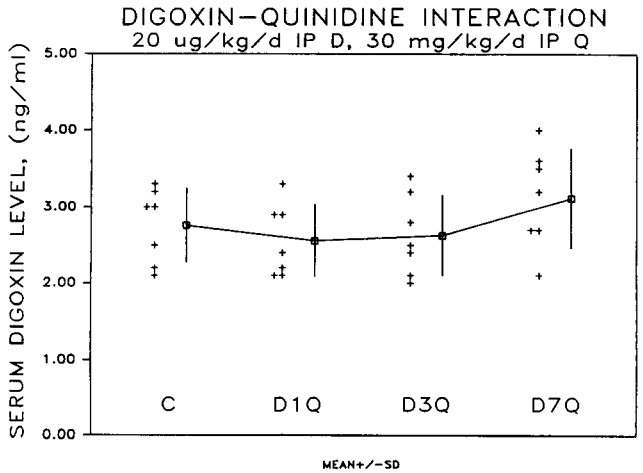

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Table 2. Digoxin-Quinidine Interaction in the Neonate Tissue Study

	Digoxin Tissue Level (ng/g dry weight)*		Tissue/Serum Ratio (ml/g)*	
	D,Q	D	D,Q	D
A. Group III (D,Q) Versus Control (D)				
Brain	306 ± 104	304 ± 61	254 ± 70†	156 ± 42
Heart	374 ± 82	537 ± 178	315 ± 73	272 ± 89
Kidney	1,796 ± 469	2,125 ± 457	1,524 ± 473	1,065 ± 185
Liver	134 ± 25	142 ± 16	112 ± 13†	72 ± 10
Skeletal muscle	130 ± 35	156 ± 28	180 ± 11†	108 ± 24
B. Group IV (D,Q) Versus Control (D)				
Brain	910 ± 437†	530 ± 49	229 ± 106†	100 ± 20
Heart	892 ± 167	991 ± 112	222 ± 33†	185 ± 18
Kidney	5,179 ± 465	4,634 ± 1,220	1,297 ± 163†	873 ± 241
Liver	368 ± 86	356 ± 89	93 ± 28†	66 ± 11
Skeletal muscle	267 ± 40	248 ± 46	67 ± 14†	46 ± 9

*Mean ± SD; †$p < 0.05$, *t* test comparison of tissue/serum ratio. D = digoxin; Q = quinidine.

levels in this group were comparable with those observed in the control group. When normalized for the serum digoxin level, relatively higher tissue digoxin concentrations were observed in liver, muscle and brain.

Tissue concentrations and corrected digoxin tissue concentrations for Group IV are presented in Table 2B. Again, for comparison, digoxin tissue levels obtained from a group of neonates (n = 8) treated identically except without quinidine are shown. As in Group III, the attained serum digoxin concentration in the digoxin-quinidine group was lower than that measured in the control group (4.03 ± 0.47 versus 5.41 ± 0.77 ng/ml) ($p < 0.002$). Absolute tissue digoxin concentrations in the digoxin-quinidine and control neonates were not significantly different for heart, kidney, liver or skeletal muscle. However, in the digoxin-quinidine–treated neonates, a significantly *higher* brain digoxin concentration was measured (910 ± 437 versus 530 ± 49 ng/g) ($p < 0.03$) (Fig. 4). Inspection of the graph shows that five of the six neonates had a greater brain digoxin concentration than *all* of the values measured in the control (digoxin only) group.

When normalized for the serum digoxin concentration, tissue concentrations (tissue/serum ratio) were significantly

Figure 3. Brain digoxin (D) concentrations normalized for serum digoxin level are plotted for Group III neonates (digoxin and quinidine group) on the **right** and a group of control neonates (digoxin only) on the **left**. A higher digoxin tissue to serum ratio is observed in the neonates receiving combined digoxin-quinidine (Q) therapy. Similar findings were observed for liver and skeletal muscle in these groups. Abbreviations as in Figure 1.

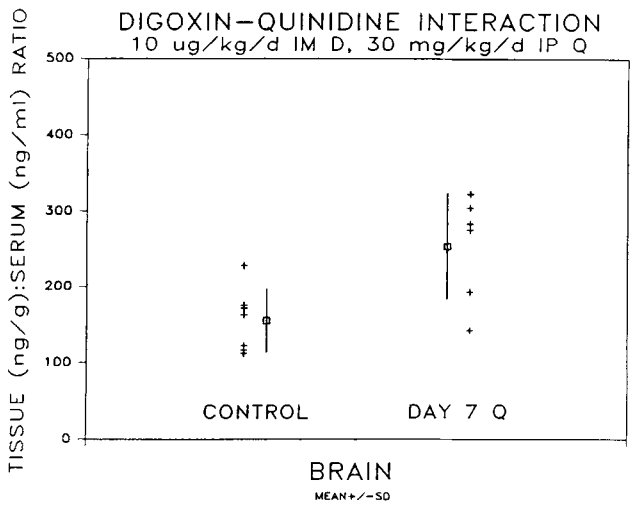
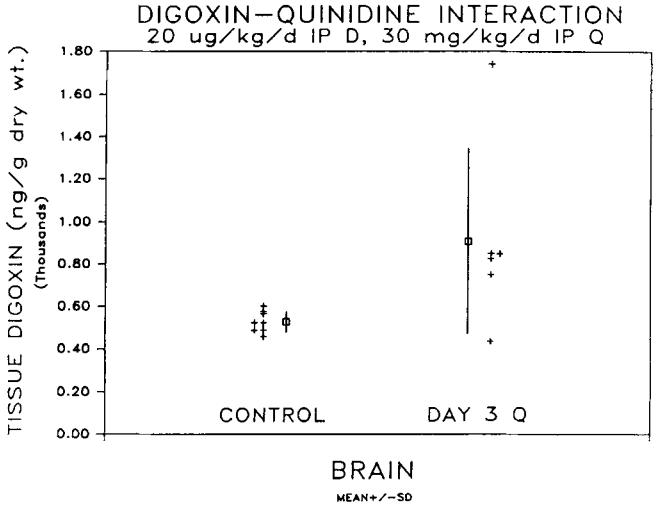


Figure 4. Brain digoxin (D) concentrations are plotted for Group IV neonates (digoxin and quinidine) on the **right** and a group of control neonates (digoxin only) on the **left**. A higher brain digoxin concentration is observed in the experimental group. Abbreviations as in Figure 1.



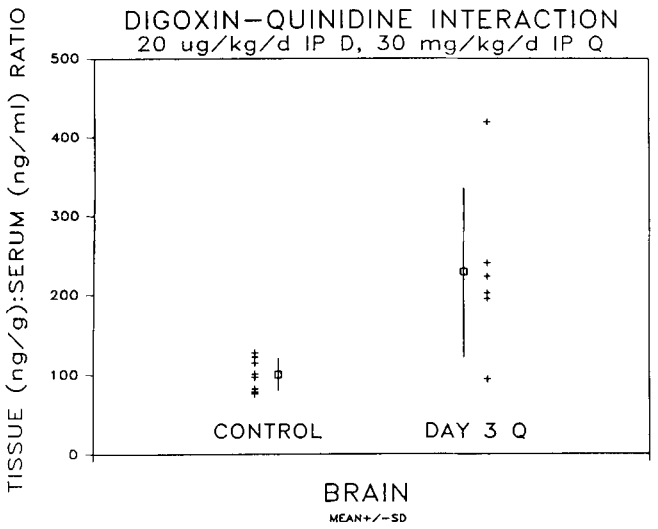


Figure 5. Brain digoxin (D) concentrations, normalized for serum digoxin level, are plotted for Group IV neonates on the **right** and control neonates on the **left**. A higher digoxin tissue to serum ratio is observed in the neonates receiving combined digoxin-quinidine therapy. Abbreviations as in Figure 1.

higher in the digoxin-quinidine group not only in the brain (Fig. 5) but in all of the other tissue sites as well (Table 2B).

Discussion

Previous studies in the adult dog have clearly demonstrated that, as in the adult human, the administration of quinidine can result in a substantial increase in the steady state serum digoxin concentration (10,11,13,20). Increases in the serum digoxin concentration have been observed within days of beginning quinidine therapy and have been observed utilizing drug-dosing protocols employing intravenous (11,13), oral (10) or combined (20) methods of drug adminstration. The magnitude of the increases in serum digoxin concentration has been variable, but increases as high as 100% (doubling of the serum digoxin concentration) are commonly reported. Pharmacokinetic studies in the dog (20) have suggested that the increase in the serum digoxin concentration may, at least in part, be due to a quinidine-mediated reduction in the clearance of digoxin. Thus, it seems that the adult dog provides a suitable animal model for studying the digoxin-quinidine interaction, exhibiting essentially the same pharmacokinetic characteristics of the drug interaction as described in the adult human.

Effects of quinidine on serum digoxin concentration. The major finding of our study is that over at least 7 days of coadministration, quinidine results in little or no appreciable increases in the serum digoxin concentration in the neonatal dog. Despite achieving adequate digoxin and quinidine serum concentrations and examining two different routes of administration (intramuscular and intraperitoneal), we were unable to demonstrate a quinidine-mediated increase in the serum digoxin concentration in the neonate. The results of this investigation, as well as the recent clinical observations by Koren (3) in which *no* increases were observed in the serum digoxin concentration of three infant humans given combined digoxin-quinidine therapy, raise the important question of whether there is a *lack* of an interaction in the neonate or whether, in fact, the interaction occurs and is quantitatively or qualitatively different from that described in the adult. Considering the multitude of differences known to exist in drug distribution, protein binding, metabolism and excretion in the neonate (21,22), it is not at all improbable that drug interactions in the neonate may also be quite different.

Effects of quinidine on tissue digoxin concentrations. We believe that the question of whether a digoxin-quinidine interaction occurs in the neonatal dog is best answered by considering the results of the tissue digoxin analyses. In examining the tissue digoxin data, it is first necessary to appreciate that previous studies in adult dogs have reported somewhat variable findings. Doherty et al. (11) compared the tissue digoxin concentrations in dogs given 4 days of digoxin alone and in dogs given 3 days of coadministered quinidine. They reported a significant increase in the brain digoxin concentration (51%) in the digoxin-quinidine group in association with significantly lower digoxin concentrations in left and right ventricular myocardium (20%), kidney (27%) and skeletal muscle (30%). When the tissue/serum ratios were analyzed, in addition to a significant increase in the brain digoxin concentration, a significant decrease in skeletal muscle digoxin concentration was again calculated. Doherty et al. concluded that quinidine may have resulted in a displacement of digoxin from certain tissue sites (specifically skeletal muscle) to the brain and pointed out the potential role of an increased brain digoxin concentration in mediating digoxin intoxication.

Warner et al. (13) recently reported the results of digoxin tissue analyses in dogs receiving digoxin alone and in dogs given 4 to 7 days of digoxin with quinidine. In contrast to the previous study, *higher* tissue digoxin concentrations were measured in myocardium, liver, kidney and skeletal muscle in dogs treated with digoxin and quinidine. These investigators also found a significantly increased digoxin concentration in the cerebral gray matter, cerebellum and pons but concluded, based on analysis of the tissue/serum ratio, that the increased brain digoxin concentrations (as well as myocardium, liver, kidney and skeletal muscle concentrations) were explained by the increased serum digoxin concentrations achieved in the digoxin-quinidine group.

In our tissue studies, neonates given high doses of digoxin (20 μg/kg per day) and 3 days of combined digoxin-quinidine therapy had a significantly higher brain digoxin concentration than that found in neonates given digoxin alone (Table 2B, Fig. 4). This increased brain digoxin con-

centration was observed despite achievement of serum digoxin concentrations that were actually lower in the digoxin-quinidine group. As a result of the lower serum digoxin concentration, tissue/serum ratios of not only brain but also heart, kidney, liver and skeletal muscle were significantly higher in the digoxin-quinidine–treated neonates. Similarly, although no significant differences were observed in the tissue concentrations of neonates given 7 days of low dose digoxin (10 μg/kg per day) plus quinidine and those given digoxin alone, the tissue/serum ratios of brain, liver and skeletal muscle were significantly higher in the digoxin-quinidine group than in the neonates receiving only digoxin; this is because of the lower serum digoxin concentrations achieved in the digoxin-quinidine group.

Thus, despite the inability to show a significant change in the serum digoxin concentration in neonates given combined digoxin and quinidine, the tissue data are strongly suggestive of an interaction in which relatively higher tissue digoxin concentrations are achieved, particularly in the brain, in neonates given combined digoxin-quinidine therapy. The exact mechanisms by which quinidine results in a relative or absolute increase in the digoxin concentration of the brain despite little or no increase in serum digoxin concentration cannot be determined from our study. Nevertheless, our data are concordant with the observations of Doherty et al. (11), who also observed increased brain digoxin concentrations with no apparent increases in the serum digoxin concentration. More detailed pharmacokinetic studies, including studies looking for transient shifts in digoxin tissue content (as hypothesized by Doherty et al. [11]) as well as studies investigating specific tissue-binding characteristics of digoxin with and without quinidine, would be required to fully describe and characterize the neonatal digoxin-quinidine interaction.

Conclusions. This study demonstrates that in the neonatal dog, little or no increase in the serum digoxin concentration is observed during combined digoxin-quinidine therapy. Nevertheless, quinidine administration may result in higher digoxin concentrations in the brain (as well as other tissue sites), particularly at higher serum digoxin levels. Because higher brain digoxin concentrations may be important in mediating the clinical manifestations of digoxin intoxication, caution is still indicated when digoxin and quinidine are utilized together in the neonatal period.

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