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Chloroquine–digoxin interaction

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Summary

A study in dogs indicated that there was an interaction between chloroquine (daily oral dose) and digoxin (i.v. loading dose plus daily oral dose). An increase in digoxin serum concentrations due to chloroquine (one-third human dosage for treatment of malaria attack) was gradual but gave rise to significantly increased levels by the third day of chloroquine dosage. This represented approximately a 77% increase over peak levels before chloroquine was started. A similar interaction has previously been reported between quinidine and digoxin and the presently reported interaction is likely to be due to a similar mechanism. A build-up of a chloroquine metabolite may also have played a role in the present interaction since maximal increases in digoxin serum levels were noted when metabolite concentrations were highest. The clinical potential of the interaction is postulated.

Introduction

The interaction between digoxin and quinidine is now well established. In 1978, three groups (Leahey et al., 1978; Ejvinsson, 1978; Doering and Konig, 1978) independently described the drug interaction. They found that when quinidine was given to patients taking digoxin, serum digoxin concentrations were increased, often

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above the upper limit of the therapeutic range. Quinine, the levorotatory stereoisomer of quinidine, has also been found to cause a significant increase in digoxin plasma levels, i.e. 63.5% on the first day of its administration and 74.6% on day 4 of its administration (Aronson and Carver, 1981). In addition, Leden (1982) found that the anti-rheumatoid use of hydroxychloroquine, caused a hazardous increase in digoxin serum concentrations when administered to two patients stabilized on digoxin therapy.

The chemical similarities between quinidine, quinine, hydroxychloroquine and chloroquine prompted the present study which has examined the effect of chloroquine on steady-state digoxin serum concentrations. The clinical significance of such an interaction is of potential importance in malaria endemic areas of the 'Third World', where digoxin is also frequently used, and where the malaria attack is routinely treated with chloroquine. Chloroquine is also the drug of choice in the treatment of hepatic amoebiasis.

The present study was carried out in the dog since this species is a good predictive animal model of digoxin–drug interaction; for example, Wilkerson et al. (1980) showed that ibuprofen interacted with digoxin in the dog, and this prediction was subsequently confirmed in man (Quattrocchi et al., 1983).

Materials and Methods

Experimental protocol

Six greyhound dogs weighing 22.8 ± 0.9 kg were used in the present study. The dogs were given an intravenous loading dose of digoxin (25 μg/kg) on day 1 and then dosed orally each morning thereafter using Lanoxin Syrup (14 μg/kg of digoxin). This dosage regimen was suggested by Button et al. (1980) for canines; they found that such a dosage regimen produced digoxin serum concentrations which were similar to those used therapeutically in man.

After 8 days of digoxin treatment (to ensure steady-state serum levels), the dogs were given oral chloroquine at a dosage of one-third the quantity used in the normal human adult treatment regimen for a malaria attack. Each dog received chloroquine phosphate 333 mg stat. on day 9 followed by 167 mg after 6 h on the same day. This was followed by 167 mg each morning on days 10 and 11. Reference venous blood samples (10 ml) were taken from each dog on day 1 before the intravenous loading dose of digoxin. Sampling was re-started on day 7, i.e. after 6 days treatment with digoxin. Venous blood samples (10 ml) were taken from each dog in the morning just prior to digoxin dosing and at 2, 3, 4, 6 and 10 h after the digoxin dose. This sampling protocol was adhered to on day 8 and during concomitant chloroquine therapy on days 9 and 11. Trough digoxin samples were taken on days 10 and 12. The samples were immediately centrifuged and the separated serum was stored at $-20°C$ until assay for both digoxin and chloroquine content.

Assay methods

Assay for digoxin content was carried out using a radioimmunoassay technique (Amerlex, Radiochemical Centre, Amersham, U.K.). Chloroquine was shown not to

interfere with this assay for digoxin. Assay for chloroquine content was carried out using a sensitive specific HPLC technique, with fluorescence detection, based on that of Alván et al. (1982).

Statistical comparisons

Two parameters were used to compare the plasma digoxin profiles on the sampling days, i.e. 7, 8, 9, and 11, namely the peak plasma digoxin concentration measured and the AUC (measured by the trapezoidal method over each 24-h sampling period). Comparisons were made using the paired *t*-test.

Results

The digoxin dosage regimen suggested by Button et al. (1980) for canine digitalization and subsequently used in the present study gave rise to digoxin serum concentrations similar to those obtained during normal clinical usage of digoxin in man (0.8–2.0 ng · ml^{-1}). The mean peak concentration of chloroquine (3 h post-drug administration) recorded in dogs was 382.1 ng · ml^{-1}. This was much higher than that found in healthy volunteers in these laboratories after receiving 1 g of chloroquine diphosphate (184.5 ng · ml^{-1}; McElnay et al., 1982). In the healthy volunteers peak concentrations did not occur until 6 h post-dosing and therefore it appears that the rate of chloroquine absorption was faster in the dog. During the remainder of the chloroquine treatment regimen serum concentrations ranged from approximately 100–220 ng · ml^{-1} (Fig. 1). During analysis of the serum samples for chloroquine a peak of unknown origin occurred with an R_f value of 2.4 times that of chloroquine. Since the peak size increased during the chloroquine therapy (Fig. 2) it was assumed that this was a metabolite of chloroquine which was building up in the bloodstream.

The peak corresponded exactly in R_f value to the major chloroquine metabolite in a serum sample obtained from a human subject who had received chloroquine. Although the evidence is not conclusive, the metabolite in the dog was likely to be

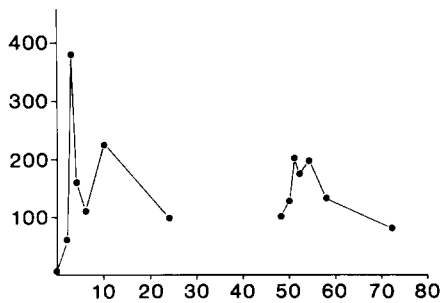

Fig. 1. Mean serum concentrations of chloroquine in 6 dogs obtained during the chloroquine treatment days, i.e. days 9, 10 and 11 of the study. (N.B. time 0 is the time of administration of the first chloroquine dose).

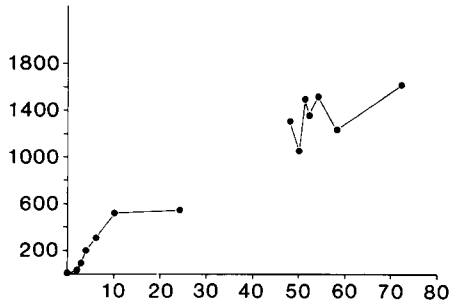

Fig. 2. Mean serum concentrations * in 6 dogs of unidentified chloroquine metabolite obtained during the chloroquine treatment days, i.e. days 9, 10 and 11 of the study. (N.B. time 0 is the time of administration of the first chloroquine dose).

* $ng \cdot ml^{-1}$ assuming similar fluorescent characteristics to the parent chloroquine; see text for details.

desethyl chloroquine, the major metabolite in man. Since no standard was available for this metabolite, its concentration in plasma was not directly measurable; however, assuming similar extraction and fluorescent characteristics to the parent compound, the metabolite reached much higher concentrations than chloroquine in plasma (Fig. 2). There was a gradual build-up of metabolite concentration during the chloroquine treatment periods.

Regarding digoxin serum concentrations there was no significant increase in recorded mean peak values during the first day of concomitant treatment with chloroquine (day 9; mean peak 1.67 ± 0.15 $ng \cdot ml^{-1}$) but mean peak values increased significantly ($P < 0.05$) to 2.78 ± 0.32 $ng \cdot ml^{-1}$ (Table 1; Fig. 3) on the

TABLE 1

THE EFFECT OF CHLOROQUINE THERAPY ON RECORDED PEAK SERUM CONCENTRATIONS OF DIGOXIN (ON DAYS 7 AND 8 DIGOXIN ALONE WAS ADMINISTERED WHILE ON DAYS 9 AND 11 CONCOMITANT CHLOROQUINE WAS ADMINISTERED; SERUM SAMPLES WERE TAKEN FROM 2 h POST-DOSAGE)

Dog	Peak values ($ng \cdot ml^{-1}$)			
	Day 7	8	9	11
1	1.99	2.15	2.06	2.93
2	1.69	1.69	1.33	3.48
3	1.56	1.40	1.20	2.60
4	1.62	1.83	2.05	1.75
5	1.40	1.41	1.60	3.78
6	1.14	1.46	1.78	2.16
Mean + S.E.	1.57 ± 0.11	1.66 ± 0.12	1.67 ± 0.15	2.78 ± 0.32

* For statistical significances of results see text.

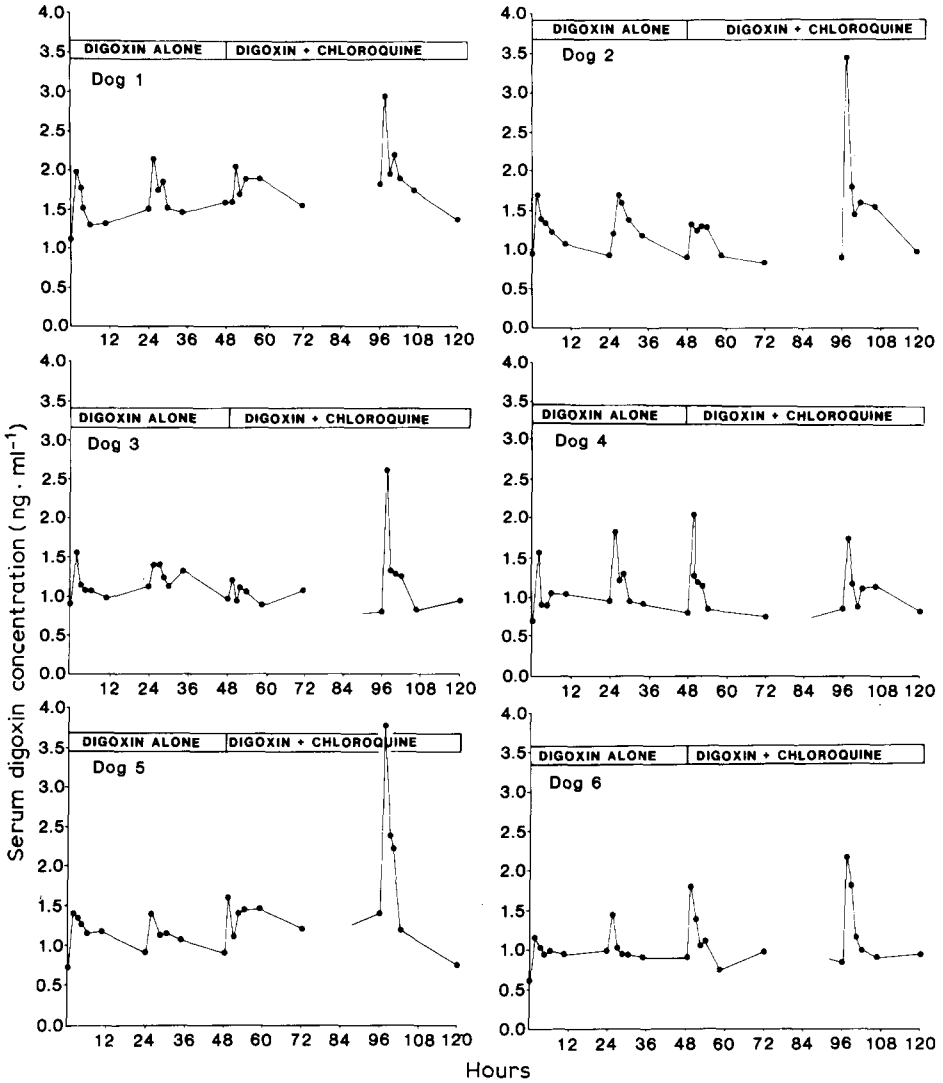

Fig. 3. Digoxin serum profiles for the 6 dogs during the final 5 days of digoxin therapy (days 7–11). Concomitant chloroquine therapy was administered as per described protocol on days 9, 10 and 11, i.e. beginning at 48 h on the time axis.

third day. It is stressed that in all cases the data were not fitted to a pharmacokinetic model and that the recorded peak values are those which were actually measured from 2 h post-drug administration. A 2-h initial sampling time was chosen to allow absorption and initial distribution of the dose to take place. Similarly the AUC values (calculated by the trapezoidal rule over the 24-h dosage interval) showed a significant increase ($P < 0.05$) on the third day of chloroquine therapy of approximately 20% over that of day 7 (digoxin alone), and a similar increase over the mean

TABLE 2

THE EFFECT OF CHLOROQUINE THERAPY ON AUC OF DIGOXIN OVER THE 24-h DIGOXIN DOSING INTERVALS (ON DAYS 7 AND 8 DIGOXIN ALONE WAS ADMINISTERED WHILE ON DAYS 9 AND 11 CONCOMITANT CHLOROQUINE WAS ADMINISTERED)

Dog	AUC * ($ng \cdot ml^{-1} \cdot h$)			
	Day 7	8	9	11
1	35.01	38.46	42.55	42.72
2	26.75	28.23	24.09	36.03
3	26.02	28.60	23.56	25.55
4	24.42	23.90	23.65	25.69
5	27.18	25.60	32.47	36.73
6	23.36	22.86	23.45	26.41
Mean ± S.E.	27.12 ± 1.68	27.94 ± 2.30	28.30 ± 3.19	32.19 ± 2.98

* For statistical significances of results see text.

AUC value of day 8 (digoxin alone) of the trial, which just failed to reach statistical significance. The increase in the AUC value on day 9 (first day of chloroquine therapy), however, was small (4.4%) and statistically insignificant ($P > 0.05$). The individual serum digoxin profiles for the 6 separate dogs are shown in Fig. 3.

Discussion

It is now well established that the dog shows a pharmacokinetic profile for digoxin which closely resembles the human situation, in absorption (Button et al., 1980), toxic threshold (Hahn 1977; Teske et al., 1976) and therapeutic range (De Rick et al., 1978). Harrison and Gibaldi (1977) found that the dog model could be scaled to the human situation by simply considering differences in organ volumes, organ blood flow and digoxin clearances. Good predictions of plasma digoxin concentration, urinary digoxin excretion, and steady-state plasma, heart and skeletal muscle digoxin concentrations were obtained by these latter authors after a single dose. The dog has also been used by previous authors to examine digoxin pharmacokinetic drug interactions, e.g. Wilkerson et al. (1980) used the dog as a model to examine the effects of several drugs, including ibuprofen, on digoxin serum concentrations.

The results of the present study indicated that there was an interaction between chloroquine and digoxin. The increase in digoxin serum concentrations due to administration of chloroquine was gradual, i.e. the increase in digoxin serum peak levels was insignificant on the first day of chloroquine therapy, but gave rise to significantly increased concentrations of 2.78 ± 0.32 $ng \cdot ml^{-1}$ on the third day of chloroquine dosage. This represented an approximate 77% increase over the peak level attained before chloroquine was administered.

Similar interaction data have been described for the digoxin/quinidine interaction. Doering (1979), for example, found that the magnitude of the increase in serum

digoxin concentration was dependent on the dosage of quinidine, with higher doses leading to higher serum digoxin concentrations. He also found that digoxin serum concentrations started to rise on the first day of treatment with quinidine and continued to rise until a new steady-state was reached at about 5 days. These results were confirmed by Leahey et al. (1979b). The latter group suggested that the interaction occurred due to the displacement of digoxin from its binding sites in tissues by quinidine. Earlier work by Hooymans and Merkus (1978) showed that quinidine decreased the renal clearance of digoxin. Hager et al. (1979) found that the interaction led to a fall in digoxin volume of distribution, due to its displacement from tissue binding sites, without any change in the elimination half-life. They concluded that the total clearance must therefore have decreased. Similar results were obtained by Leahey et al. (1979a).

The mechanism of the chloroquine/digoxin interaction presently described is likely to be due to similar mechanisms as the digoxin/quinidine interaction. The build-up of the chloroquine metabolite may also have played a role in the presently reported interaction since maximal increases in digoxin serum levels were noted when metabolite concentrations were highest.

The significance of a chloroquine/digoxin interaction is of likely importance in malaria endemic regions, where both drugs are used routinely in the treatment of malaria and congestive heart failure, respectively. There have, however, been some conflicting views about the nature of the toxic effects caused by high serum digoxin levels. Moysey et al. (1981) have suggested that if the high digoxin serum concentrations were not associated with increases in myocardial muscle concentrations then those high levels were expected to cause neurotoxicity rather than direct cardiac toxicity. The heart rhythm may, however, be influenced by both mechanisms (Gillis et al., 1975).

Bigger (1979) suggested that an increase in serum digoxin levels, which is accompanied by displacement of digoxin from the myocardium, does not necessarily lead to an increase in its effects on the heart. Leahey et al. (1979b) showed, however, that increased serum levels of digoxin caused by co-administration of quinidine led to an intensification of toxic digitalis effects on the heart which was reflected by associated ECG changes. All these toxic symptoms disappeared when digoxin serum concentration normalized after quinidine withdrawal. Walker et al. (1983) suggested that adverse effects of the digoxin/quinidine interaction may be limited to elderly patients.

In conclusion, although there is some disagreement as to the occurrence of digoxin toxicity what remains clear is that toxic effects of digoxin have been reported in the literature after digoxin–drug interactions. Therefore, since the dog has been shown to be a good animal model of digoxin pharmacokinetics, it would appear prudent, based on the present results, to recommend that patients on combined digoxin/chloroquine therapy should be monitored very carefully for raised serum digoxin concentrations. The clinical potential of the interaction, however, awaits controlled trials in patients using this drug combination.

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