*International Journal of Pharmaceutics*, 13 (1983) 353–359
Elsevier Biomedical Press



# Biological model for the study of the digoxin–quinidine drug interaction

Wolfgang A. Ritschel and William Cacini

*University of Cincinnati Medical Center, College of Pharmacy, Cincinnati, OH 45267 (U.S.A.)*

(Received March 1st, 1982)
(Modified version received July 16th, 1982)
(Accepted July 20th, 1982)

It is now well established that administration of the cardiac anti-arrhythmic drug, quinidine, can produce significantly elevated plasma levels of simultaneously administered digoxin in patients (Doering and König, 1978; Leahey et al., 1978, 1979). Although it has been estimated that this interaction may occur in up to 90% of patients receiving therapeutic doses of each drug (Bigger, 1979), the clinical implications of the elevated digoxin levels are unclear.

The chickens used in these experiments were mature, White Leghorn hens weighing 2–2.5 kg, and were housed in air-conditioned quarters with free access to food and water until the day before an experiment when the food was removed. The chicken was unanesthetized, but lightly restrained with a cloth harness that allowed it to remain comfortable in an upright position. A saphenous vein was cannulated using size no. 50 polyethylene tubing which was flushed continuously with 0.9% saline (0.05–0.1 ml/min). A three-way valve attached to the infusion line facilitated blood sampling and injections. Following cannulation the animal was again given free access to food and water. Room lights were adjusted to a 12-h cycle.

A single dose of about 350 ng [$^3$H]digoxin was administered to 6 chickens by i.v. push over a one-minute period. This was followed by a flushing of the catheter with a small volume of saline after which the timed experiment was begun. In 9 experiments, quinidine sulfate was added to the constant saline infusion solution to result in an infusion rate of 180 $\mu$g/kg/h. This rate was calculated using human data for quinidine (therapeutic steady-state concentration, $C_{av}^{ss}$ of 4 $\mu$g/ml; volume of distribution, $V_\beta$, of 0.5 ml $\cdot$ g$^{-1}$; terminal elimination rate constant $\beta$ of 0.09 h$^{-1}$) (Bellet 1971; Guentert et al., 1979). The following two equations were used to calculate the loading dose, DL, and the infusion rate, R°:

$$R° = C_{av}^{ss} \cdot V_\beta \cdot \beta \quad (1)$$

$$DL = C_{av}^{ss} \cdot V_\beta \quad (2)$$

0378-5173/83/0000-0000/$03.00 

In these experiments, the digoxin was injected i.v. one hour after starting the quinidine maintenance infusion. Venous blood samples were taken prior to digoxin dosing and at various times up to 72 h after dosing. A portion of each plasma sample was analyzed for radioactivity by standard techniques of liquid scintillation counting using a Beckman LS 7000 spectrometer and 3a70B cocktail (RPI, Mount Prospect, IL, U.S.A.). Results were expressed as $^3H$ cpm/ml plasma and converted to ng/ml.

To study the effect of quinidine on the renal digoxin clearance, serial urine samples (Sperber, 1948) were collected over a period of 180 min. Midway through each urine collection, a blood sample was drawn. A cross-over design was used by which digoxin clearance was first determined in the absence of quinidine and, 14 days later, during quinidine administration (2 mg/kg prime injection followed by 0.18 mg/kg/h maintenance infusion as described above). Clearance (ml/min) was calculated according to the following equation:

$$Cl_{ren} = \frac{[^3H]_{urine} \cdot ml_{urine}}{[^3H]_{plasma} \cdot min} \tag{3}$$

The digoxin drug concentration–time data were analyzed by a curve-fitting method (RESID program). All data sets could be fitted best to a biexponential model of the general equation:

$$C(t) = B \cdot e^{-\beta \cdot t} + A \cdot e^{-\alpha \cdot t} \tag{4}$$

The important pharmacokinetic parameters are listed in Table 1.

In addition a compartment model-independent analysis was performed based on the terminal disposition slope, the area under the curve by the trapezoidal rule and the dose administered. The volume of distribution by the area method, $V_{area}$, did not differ significantly from the $V_\beta$, and neither did the total clearance differ.

The mean digoxin blood concentration–time curves after i.v. push injection in the presence and absence of quinidine infusion are shown in Fig. 1. Significant differences between the two treatments exist at all time points between 1.5 and 30 h after i.v. digoxin injection.

Significant differences (see Table 1) were found for the volume of distribution at steady-state ($V_{ss}$), and the apparent volume of distribution, ($V_\beta$ or $V_{area}$), the total clearance, ($Cl_{tot}$), and the area under the curve (AUC). The elimination half-life ($t_{1/2\beta}$) was practically identical in both groups. Since the clearance is the product of $V_\beta \times (0.693/t_{1/2\beta})$, the decrease in total clearance of digoxin in presence of quinidine seems to be caused predominantly or exclusively by the decrease in volume of distribution.

The renal clearance of digoxin decreased from 2.21 ml/min/kg in the absence of quinidine to 1.16 ml/min/kg, during quinidine infusion ($0.1 > P > 0.05$).

In spite of extensive research, the mechanism of the digoxin–quinidine drug interaction has not been fully elucidated. To be most meaningful, further studies should be carried out with pharmacokinetic digoxin disposition similar to that in

TABLE 1

PHARMACOKINETIC PARAMETERS OF DIGOXIN WITHOUT AND WITH COADMINISTRATION OF QUINIDINE

| Parameter | Control (n = 6) | | | With quinidine (n = 9) | | | Unpaired *t*-test for S ($P < 0.05$) |
|---|---|---|---|---|---|---|---|
| | $\bar{x}$ | ±S.D. | ±S.E.M. | $\bar{x}$ | ±S.D. | ±S.E.M. | |
| Body weight BW (kg) | 2.33 | 1.7 | 0.7 | 2.75 | 0.8 | 0.26 | |
| Dose (ng) | 368.7 | 50.9 | 20.8 | 344.5 | 46 0 | 15.4 | |
| Distribution half-life | | | | | | | |
| $t_{1/2\alpha}$ (h) | 0.34 | 0.25 | 0.10 | 0.55 | 0.85 | 0.28 | N.S. |
| Elimination half-life | | | | | | | |
| $t_{1/2\beta}$ (h) | 31.92 | 9.2 | 3.7 | 29.23 | 22.8 | 7.6 | N.S. |
| Microconstants | | | | | | | |
| $k_{12}$ (1/h) | 2.16 | 1.10 | 0.45 | 2.06 | 1.49 | 0.50 | N.S. |
| $k_{21}$ (1/h) | 0.22 | 0.05 | 0.02 | 0.21 | 0.12 | 0.04 | N.S. |
| $k_{13}$ (1/h) | 0.27 | 0.13 | 0.05 | 0.93 | 1.5 | 0.49 | N.S. |
| Volume of distribution | | | | | | | |
| $V_c$ (1/kg) | 0.91 | 0.71 | 0.29 | 0.41 | 0.33 | 0.11 | N.S. |
| $V_{ss}$ (1/kg) | 7.79 | 2.90 | 1.20 | 2.82 | 1.91 | 0.64 | S. |
| $V_\beta$ (1/kg) | 8.60 | 3.10 | 1.30 | 3.30 | 2.12 | 0.71 | S. |
| Total clearance | | | | | | | |
| $Cl_{tot}$ (ml/min/kg) | 6.76 | 1.31 | 0.74 | 3.42 | 1.88 | 0.63 | S. |
| Area under curve | | | | | | | |
| $AUC_{(0-\infty)}$ ((ng/ml)h) | 0.944 | 0.36 | 0.15 | 1.89 | 0.88 | 0.29 | S. |

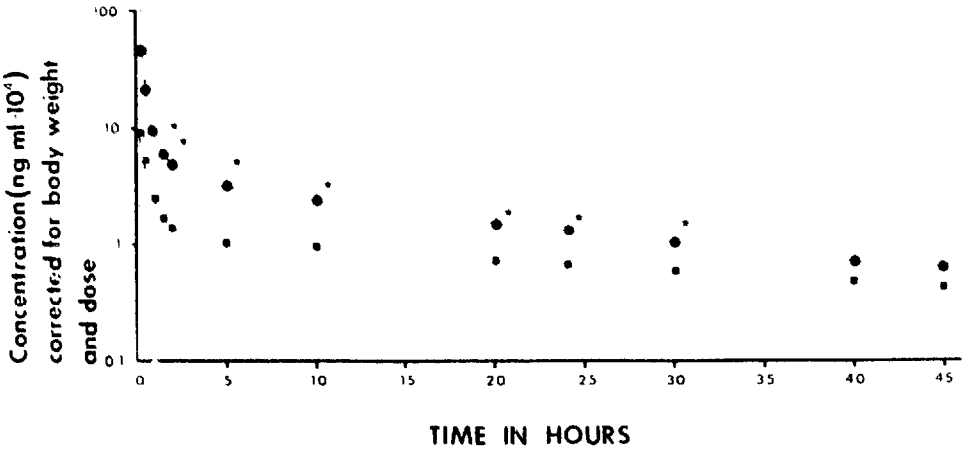


Fig. 1. Digoxin plasma concentration–time profile (means and S.D.) upon i.v. injection of digoxin alone (solid line) and in the presence of quinidine (dashed line). * indicates significant differences in concentration at the appropriate time ($P < 0.05$).

man. A comparison of the major pharmacokinetic parameters of digoxin in man with those obtained in various animal species is presented in Table 2. It is evident that the chicken may serve as a valid model for further studies. The i.v. injection of digoxin during i v. infusion of quinidine was chosen in our studies because a change in digoxin absorption by quinidine has been ruled out as a significant contributor to the drug interaction (Hager et al., 1979; Hooymans and Merkus, 1978).

In most studies in man a reduction in the volume of distribution of digoxin has been observed (Schenk-Gustafsson et al., 1981; Leahey, 1980; Hager et al., 1979). Similar results have beer obtained in the dog (Gibson et al., 1981). Our results are consistent with these findings. We found a reduction of $V_\beta$ from 8.6 l $kg^{-1}$ to 3.3 l $kg^{-1}$ ($P < 0.005$). A decrease in the volume of distribution to 70% has been found by Hager et al. (1979), suggesting that quinidine may displace digoxin from tissue binding sites. In the present study using the chicken, we observed no significant difference in the digoxin volume of distribution of the central compartment in the presence or absence of quinidine, whereas $V_{ss}$ and $V_\beta$ were decreased significantly by quinidine. This indicates that the change in volume of distribution was associated with peripheral tissues. Where such a peripheral distribution volume change occurs needs further investigation. Results published to date have been contradictory. Whereas Straub et al. (1978) found that digoxin was displaced by quinidine from beef heart ATPase, no such displacement was observed by Doering (1979) in the

TABLE 2

PHARMACOKINETIC PARAMETERS OF DIGOXIN IN VARIOUS SPECIES ± S.D. OR (RANGE)

| Species | $t_{1/2\alpha}$ (h) | $t_{1/2\beta}$ (h) | $V_c$ (l/kg) | $V_{ss}$ (l/kg) |
|---|---|---|---|---|
| Man | | | | |
| Adult | 0.35 (0.27–0.50) | 39.1 (26–60) | 0.48 (0.24–0.78) | 6.4 (4.8–8.1) |
| Newborn | 0.59 (0.58–0.61) | 49.3 (35–69) | 1.1 ± 0.16 | 8.6 (7.5–9.9) |
| Infant | 0.52 ± 0.1 | 29.8 ± 15.6 | 1.3 ± 0.16 | 9.96 ± 0.97 |
| Elderly | | 69.6 ± 13.1 | | |
| Dog | | 25 (23–30) | | 9.11 |
| Cat | | 57.8 ± 14.45 | | |
| Rat | 0.25 (0.18–0.4) | 2.5 ± 0.26 | 2.4 (1.9–2.9) | |
| Turkey | 0.65 ± 0.63 | 11.03 ± 3.77 | 1.54 ± 0.54 | 4.56 ± 1.26 |
| Chicken | 0.34 ± 0.25 | 31.9 ± 9.2 | 0.91 ± 0.71 | 7.79 ± 2.9 |

sarcolemma fraction of lamb myocardium, or by Kim et al. (1981) in the Langendorff preparation of guinea pig heart. Also, in the presence of quinidine no change was observed in the amount of bound digoxin in kidney, cardiac muscle, liver, skeletal muscle and brain by the latter authors. Despite the lack of definitive data, the fact that digoxin does bind extensively to tissues, could mean that even minor decreases of binding in individual tissues could theoretically result in an overall effect of increased plasma concentrations.

Ochs and Greenblatt (1981) found a 64% decrease in $Cl_{tot}$ of digoxin from a value of 6.06 ml/min/kg to 2.18 ml/min/kg in the presence of quinidine. In our chicken model, a similar decrease in $Cl_{tot}$ was found from 6.76 ml/min/kg to 3.42 ml/min/kg (−51%).

The decrease in renal clearance of digoxin in presence of quinidine was first reported by Hooymans and Merkus (1978), who noted a decrease from 94 to 62 ml/min/1.73 $m^2$, or 34%. These results have been supported by studies in man (Doering, 1979; Hager et al., 1979; Leahey et al., 1980). Our studies in chickens demonstrated a decrease in digoxin renal clearance from 2.21 to 1.16 ml/min/kg, or 52%. The limited number of observations does not warrant a statistical evaluation; however, the results are qualitatively similar to observations in man.

Based on the comparison given above, we propose the chicken as a potential model for further digoxin–quinidine interaction studies.

| $V_\beta$ (l/kg) | $Cl_{tot}$ (ml/min/kg) * (ml/min/1.73 $m^2$) | $Cl_{ren}$ (ml/min/kg) * (ml/min/1.73 $m^2$) | References |
|---|---|---|---|
| 6.8 (3–17) | 5 (2.4–8)<br>188 ± 44 * | 2.1<br>144 ± 41 | Ochs et al., 1981; Koup et al., 1975; Turner et al., 1977; Lloyd et al., 1978; Reunig et al., 1973; Nyberg et al., 1974; Bonelli et al., 1978; Kramer et al., 1979; Rabkin et al., 1975; Gault et al., 1976; Ochs et al., 1979 |
| 11.1 | 3<br>45 (25–65) * | | Wettrell, 1977; Morselli et al., 1975 |
| 12.1 ± 1.46 | 8.2<br>163 ± 98 * | | Wettrell, 1977; Morselli et al., 1975; Dungan et al., 1972 |
| 4.1 | 0.8 ± 0.2 | | Cusack et al., 1979; Ewy et al., 1969 |
| 19 (17–21) | 4.57 | | Doherty et al., 1966; Wilkerson et al., 1980 |
| 20.4 ± 5.34 | 4.05 ± 1.4 | | Weidler et al., 1978 |
| 3.5 (2.5–4.5) | 5.77 ± 1.9 | 2.9 | Harrison et al., 1976 |
| 5.55 | 5.81 ± 1.5 | | Park et al., 1981 |
| 8.6 ± 3.1 | 6.76 ± 1.81 | 2.21 | present study |

The authors would like to thank Mr. Karl Grummich for technical assistance. This study was supported in part by the University of Cincinnati Office of Geriatric Programs.

## References

Bellet, S., Disorders of the Heart Beat, 3rd Edn., Lea and Febiger, Philadelphia, 1971, PA 980–1007.

Bigger, J.T., The quinidine–digoxin interaction. N. Engl. J. Med., 301 (1979) 779–781.

Bonelli, J., Haydl, H., Hruby, K. and Kaik, G., The pharmacokinetics of digoxin in patients with hyperthyroidism and after normalization of thyroid function. Int. J. Clin. Pharmacol., 16 (1978) 302–306.

Cusack, B., Kelly, J., O'Mally, K., Noel, J., Lavan, J. and Horgan, J., Digoxin in the elderly: pharmacokinetic consequences of old age. Clin. Pharmacol. Ther., 25 (1979) 772–776.

Doering, W. and Konig, E., Anstieg der Digoxinkonzentration im Serum unter Chinidinmedikation. Med. Klin., 73 (1978) 1085–1088.

Doering, W., Quinidine–digoxin interaction. Pharmacokinetics, underlying mechanism and clinical implications. N. Engl. J. Med., 301 (1979) 400–404.

Doherty, J.E. and Perkins, W.H., Tissue concentration and turnover of tritiated digoxin in dogs. Am. J. Cardiol., 17 (1966) 47–52.

Dungan, W.T., Doherty, J.E., Harvey, C., Char, F. and Dalrymple, G.V., Tritiated digoxin XVIII: studies in infants and children. Circulation, 46 (1972) 983–988.

Ewy, G.A., Kapadia, G.G., Yao, L., Lullin, M. and Marcus, F.I., Digoxin metabolism in the elderly. Circulation, 39 (1969) 449–453.

Gault, H.M., Jeffrey, J.R., Chirito, E. and Ward, L., Studies of digoxin dosage, kinetics, and serum concentrations in renal failure and review of the literature. Nephron, 17 (1976) 161–187.

Gibson, T.P. and Nelson, H.A., Digoxin alters quinidine and quinidine alters digoxin pharmacokinetics in dogs. J. Lab. Clin. Med., 95 (1981) 417–428.

Guentert, T.W., Upton, R.A., Holford, N.H.G. and Riegelman, S., Divergence in pharmacokinetic parameters of quinidine obtained by specific and nonspecific assay methods. J. Pharmacokin. Biopharm., 7 (1979) 303–311.

Hager, W.D., Fenster, P., Mayersohn, M., Perrier, D., Graves, P., Marcus, F.I. and Goldman, S., Digoxin–quinidine interaction: pharmacokinetic interaction. N. Engl. J. Med., 300 (1979) 1238–1241.

Harrison, L.I. and Gibaldi, M., Pharmacokinetics of digoxin in the rat. Drug Metab. Dispos., 4 (1976) 88–93.

Hooymans, P.M. and Merkus, F.W.H.M., Effect of quinidine on plasma concentration of digoxin. Br. Med. J., 2 (1978) 1022.

Kim, D.-H., Akera, T. and Brody, T.M., Interactions between quinidine and cardiac glycosides involving mutual binding sites in the guinea pig. J. Pharmacol. Exp. Ther., 218 (1981) 108–114.

Koup, J.R., Greenblatt, D.J., Jusko, W.J., Smith, T.W. and Koch-Weser, J., Pharmacokinetics of digoxin in normal subjects after intravenous bolus and infusion doses. J. Pharmacokin. Biopharm., 3 (1975) 181–192.

Kramer, W.G., Kolibash, R.P., Lewis, M.S., Bathala, J.A., Visconti, J.A. and Reuning, R.H., Pharmacokinetics of digoxin: relationship between response intensity and predicted compartmental drug levels in man. J. Pharmacokin. Biopharm., 7 (1979) 47–61.

Leahey, E.B., Reiffel, J.A., Drusin, R.E., Heissenbuttel, R.H., Lovejoy, W.P. and Bigger, J.T., Interaction between quinidine and digoxin. J. Am. Med. Ass., 240 (1978) 533–534.

Leahey, E.B., Reiffel, J.A., Heissenbuttel, R.H., Drusin, R.E., Lovejoy, W.P. and Bigger, J.T., Enhanced cardiac effect of digoxin during quinidine treatment. Arch. Intern. Med., 139 (1979) 519–521.

Leahey, E.B., Digoxin–quinidine interaction: current status. Ann. Intern. Med., 93 (1980) 775–776.

Leahey, E.B., Scaffidi, L.E., O'Connell, G.C., Bigger, J.T. and Butler, V.P., Effect of quinidine on the pharmacokinetics of digoxin in normal volunteers. Clin. Res., 28 (1980) 475A.

Lloyd, B.L., Greenblatt, D.J., Allen, M.D., Harmatz, J.S. and Smith, T.W., Pharmacokinetics and bioavailability of digoxin capsules, solution and tablets after single and multiple doses. Am. J. Cardiol., 42 (1978) 129–135.

Morselli, P.L., Assael, B.M., Gomeni, R., Mandelli, M., Marini, A., Reali, E., Visconti, U. and Sereni, F., Basic and Therapeutic Aspects of Perinatal Pharmacology, Raven Press, New York, 1975, pp. 377–392.

Nyberg, L., Anderson, K.E. and Bertler, A., Bioavailability of digoxin from tablets. II Radioimmunoassay and disposition pharmacokinetics of digoxin after intravenous administration. Acta Pharmacol. Suec., 11 (1974) 459–470.

Ochs, H.R. and Greenblatt, D.J., Impairment of digoxin clearance by coadmistration of quinidine. J. Clin. Pharmacol., 21 (1981) 396–400.

Ochs, H.R., Greenblatt, D.S., Bodem, G. and Harmatz, J.S., Dose-independent pharmacokinetics of digoxin in humans. Am. Heart J., 96 (1979) 507–511.

Park, E., Einzig, S., Staley, N.A. and Noren, G.R., Pharmacokinetics of digoxin in the turkey and comparison with other species. J. Pharmacokin. Biopharm., 9 (1981) 357–366.

Rabkin, S.W. and Grupp, G., A two compartment open model for digoxin pharmacokinetics in patients receiving a wide range of digoxin doses. Acta Cardiol., 30 (1975) 343–351.

Reuning, R.H., Sams, R.A. and Notari, R.E., Role of pharmacokinetics in drug dosage adjustment. I. Pharmacologic effect kinetics and apparent volume of distribution of digoxin. Clin. Pharmacol. New Drugs, 4 (1973) 127–141.

Turner, J., Dobbs, S.M., Nicholson, P.W., McGill, A.P.J. and Rodgers, E.M., Influence of diet on digoxin dose requirements. Br. J. Clin. Pharmacol., 4 (1977) 489–491.

Schenk-Gustafsson, K. and Dahlgvist, R., Pharmacokinetics of digoxin in patients subjected to the quinidine-digoxin interaction. Br. J. Clin. Pharmacol., 11 (1981) 181–186.

Sperber, I., Investigations on the circulatory system of the avian kidney. Zool. Bidrag (Uppsala), 27 (1948) 429–448.

Straub, K.D., Kane, J.J., Bissett, J.K. and Doherty, J.E., Alteration of digitalis binding by quinidine: a mechanism of digitalis–quinidine interaction. Circulation, 58 (1978) II-58 (Abstr.)

Weidler, D.J., Jallad, N.S., Movahhed, H.S., Sakmar, E. and Wagner, J.G., Pharmacokinetics of digoxin in the cat and comparisons with man and dog. Res. Comm. Chem. Pathol. Pharmacol., 19 (1978) 57–66.

Wettrell, G., Distribution and elimination of digoxin in infants. Eur. J. Clin. Pharmacol., 11 (1977) 329–335.

Wilkerson, R.D., Mockridge, P.B. and Massing, G.K., Effects of selected drugs on serum digoxin concentration in dogs. Am. J. Cardiol., 45 (1980) 1201–1210.