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Population pharmacokinetics of quinidine

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1 Population pharmacokinetic parameters of quinidine were determined based on 260 serum drug concentration measurements in 60 patients treated for arrhythmias with quinidine sulphate or quinidine bisulphate (Kinidin duriles®) orally.

2 Quinidine kinetics were best described by a two compartment model with zero order absorption from the gastrointestinal tract. The pharmacokinetics are influenced by severe heart or liver failure and renal function impairment. No effect was found for mild or moderate heart failure, for age, for body weight or for coadministration of nifedipine.

3 Population pharmacokinetic parameters of quinidine (assuming 100% bioavailability of oral quinidine sulphate) were: nonrenal clearance for patients without severe heart and liver failure 12.6 l h^{-1}, reduction in patients with severe heart or liver failure to 6.8 l h^{-1}, renal clearance (l h^{-1}) related to creatinine clearance (ml min^{-1}), proportionality constant 0.0566, volume of distribution of the central compartment 161 l, maximum serum drug concentration 1.4 h after administration of quinidine sulphate and 6.0 h after administration of quinidine bisulphate.

4 The results were validated by predicting the serum drug concentration in a separate group of 30 patients. The model reliably predicted both the population average and the variability of the serum concentration of quinidine.

5 Using Monte Carlo computer simulations, an *a priori* dosing regimen was derived that should maximize the proportion of patients having quinidine serum concentrations within the recommended range (2–5 mg l^{-1}): initial dose of 600 mg quinidine sulphate in all patients, 3 h later first maintenance dose of quinidine bisulphate. For patients without severe heart and liver failure and with a creatinine clearance > 50 ml min^{-1} 500 mg should be administered three times daily. If the creatinine clearance is below 50 ml min^{-1} we recommend 500 mg twice daily. In case of severe heart or liver failure the dosage should be reduced to 250 mg three times daily.

Keywords quinidine population pharmacokinetics NONMEM

Introduction

Quinidine is one of the oldest but still frequently used antiarrhythmic agents. Like other antiarrhythmics, it has a narrow therapeutic range (Follath *et al.*, 1983). This fact and the large variability in the dose-concentration relationship makes it difficult to make reliable dosage recommendations.

In spite of its clinical use there are only few pharmacokinetic data on quinidine that have been derived from patients treated for arrhythmias. Conrad *et al.* (1977) measured the serum concentration at steady-state in 21 patients with heart failure and found that for these patients the same dosage regimen results in higher mean quinidine concentrations and in higher variability than for those without heart failure. Drayer *et al.* (1978) investigated quinidine kinetics in patients with renal failure and found higher dose-normalized concentrations in haemodialysis patients and in azotemic patients. Ochs *et al.* (1978) studied the effect of age on the pharmacokinetics of quinidine and found that elderly volunteers have a lower quinidine clearance and a longer terminal elimination half-life than younger ones.

The aim of this study was to estimate the pharmacokinetic parameters of quinidine in patients treated for arrhythmias, to determine the influence of various patient characteristics and to design an *'a priori'* dosing regimen that maximizes the number of patients having serum

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concentrations within the recommended range. We used the population pharmacokinetic approach to analyze serum drug concentration data obtained in patients on quinidine therapy, mostly during routine therapeutic drug monitoring.

Methods

Study population

Data from 60 patients with a total number of 260 measured concentrations were collected for the population analysis. There were 46 male and 14 female patients in the study sample. Their median age was 65.5 years (range 28 to 82 years) and their median body weight was 70.5 kg (range 45 to 105 kg (Figure 1)).

The patients received quinidine sulphate (Chinidin sulfuricum, Siegfried) and slow release quinidine bisulphate (Kinidin duriles®, Astra) or both orally for the treatment of supraventricular or ventricular arrhythmias. Most of the measurements were obtained as a part of clinically requested drug level monitoring. Additional measurements were taken in 11 patients during the 24 h after cessation of treatment. Fifty-six samples were obtained under steady-state conditions (i.e. unchanged dosage for at least 96 h) and 204 not under steady-state (i.e. at the beginning of therapy, after changing dosage or after stopping therapy) (Figure 2). The median number of measurements for each patient was 4 (range 1–10) and the measured concentrations lay between 0.1 and 8.84 mg l^{-1} (Figure 3). In more than 20% of patients at least one sample was obtained between 0.5 and 3 h after the dose to allow estimation of the absorption characteristics.

The usual dosing regimen in most patients was as follows: the first dose was 400 mg or 600 mg quinidine sulphate orally followed 3 h later by 500 mg quinidine bisulphate twice daily or three times daily. Quinidine sulphate and quinidine bisulphate do not contain the same amount of quinidine base. Therefore, the doses

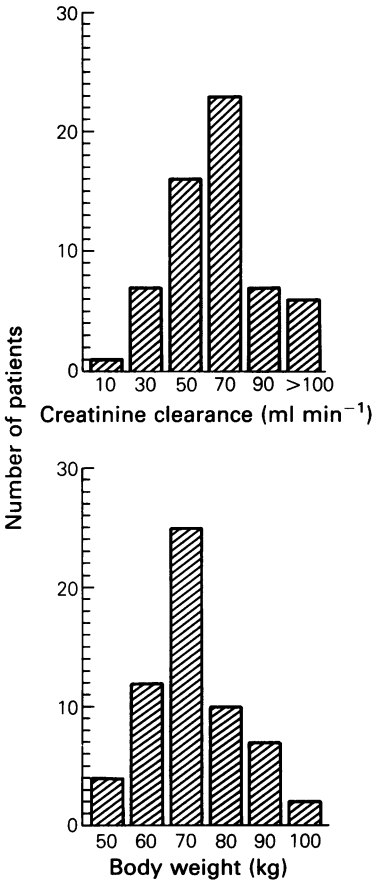

Figure 1 Distribution of body weight and creatinine clearance in the study population. Creatinine clearance was calculated from a steady-state value of the serum creatinine.

were corrected for quinidine base using the following factors: 0.663 for quinidine bisulphate and 0.829 for quinidine sulphate (Windholz *et al.*, 1983). The following data were collected in each patient in addition to drug concentration measurement: complete drug dosing history (dosage, preparation, time of administration), time of blood sampling, patient characteristics (age, weight, sex), presence of liver disease, heart disease and renal failure, coadministration and dosage of nifedipine.

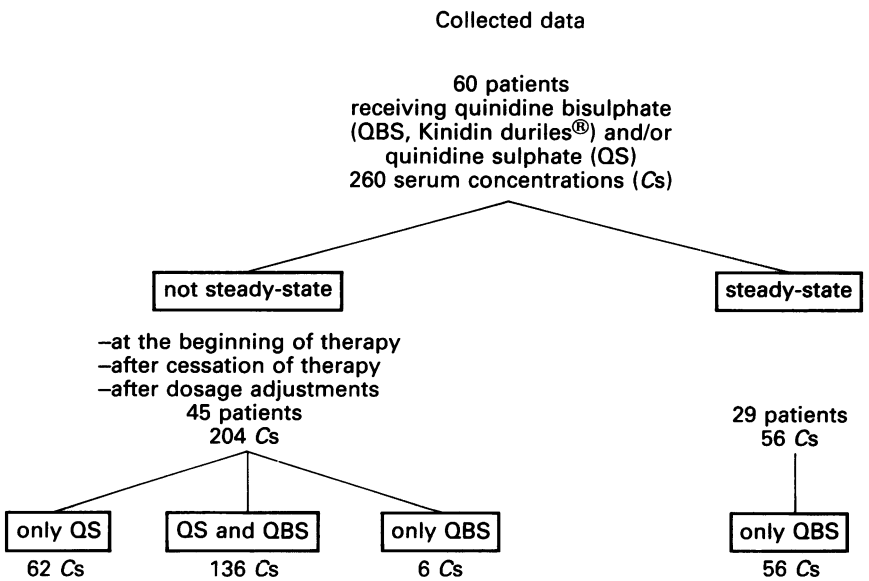

Figure 2 Description of the serum drug concentration data.

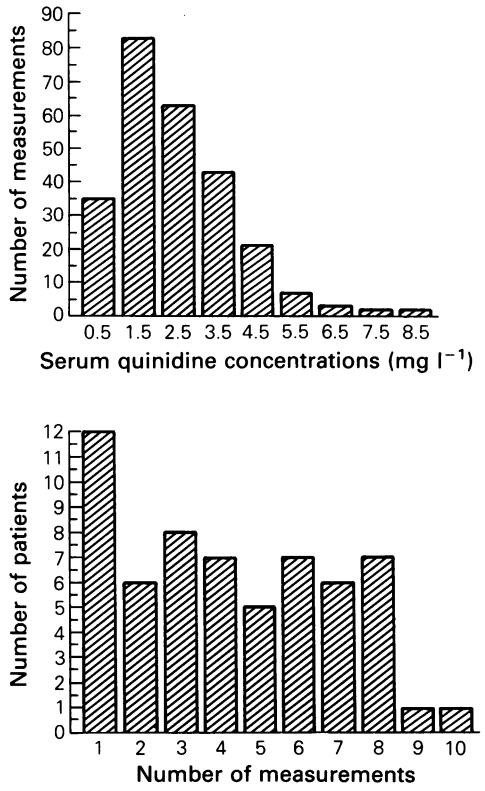

Figure 3 a) Histogram of the measured serum drug concentration values. b) Histogram of the number of serum drug concentration measurements per patient.

The creatinine clearance (CL_{Cr}, ml min^{-1}) was estimated from the serum creatinine (C_{Cr}, μmol l^{-1}) using a modified version of the equation of Cockcroft & Gault (1976):

$$CL_{Cr} = \frac{(150 - \text{age}) \cdot \text{Body weight}}{C_{Cr}}$$

For males 10% was added and for females 10% was subtracted from the calculated value of CL_{Cr} (Dettli, 1983). The median creatinine clearance in our study sample was 62.5 ml min^{-1} (range 17 to over 100 ml min^{-1}, Figure 1).

Liver function was evaluated by measurement of serum bilirubin, prothrombin time, expressed in % of normal (Quick), and hepatic enzymes. If serum bilirubin was more than 30 μmol l^{-1} and prothrombin time less than 60%, the patient was considered to have severe liver disease ($n = 3$). Patients who had values outside the normal range but did not meet the above criteria, were classified as having moderate liver dysfunction ($n = 22$). Concerning the presence of congestive heart failure the following four clinical signs were recorded: elevated jugular pressure, third heart sound, basal pulmonary rales and radiologic evidence of pulmonary congestion. Patients who showed one of these signs were considered to suffer from mild heart failure ($n = 19$) whereas moderate heart failure was assumed if two or more signs were positive ($n = 20$). If the patient showed low output or had pulmonary oedema he was classified as having severe heart failure ($n = 2$). Nine of our patients also received nifedipine, five of them 30–40 mg nifedipine day^{-1} and four of them 60 mg nifedipine day^{-1}. Other medication was not recorded.

Assay of quinidine

Serum quinidine concentrations were measured by high performance liquid chromatography (h.p.l.c.) (Leroyer *et al.*, 1982). This method is specific for quinidine, without interference from its metabolites. The coefficients of variation for within run and between run assays, measured at concentrations between 0.5 and 7 mg l^{-1}, were 1.5% and 4.2%, respectively.

Population pharmacokinetic data analysis

The analysis was performed with the computer program NONMEM which had been developed by Beal & Sheiner (1986). This method has been described in detail previously (Sheiner *et al.*, 1977). It uses a mixed (fixed and random) effects regression model to estimate the population mean and the variance of the pharmacokinetic parameters and to search for factors that may influence them. A stepwise procedure was used to find the model that fitted the data best. The procedure implemented was similar to that described previously (Aarons *et al.*, 1989; Maitre *et al.*, 1987). First we compared 1- and 2-compartment models with first or zero order absorption of the drug from the gastrointestinal tract. The influence of the recorded patient characteristics was tested with both pharmacokinetic models. At the end of the analysis all patient characteristics showing evidence for influence on the pharmacokinetic parameters were re-evaluated by comparing the full model (with all factors included) with a regression model from which one of the factors was deleted. A log-additive error distribution was assumed for description of the interindividual variability of the pharmacokinetic parameters and of the intra-individual variability. The difference in the minimum value of the objective function was used to compare two models. This difference corresponds to the log-likelihood ratio and is thus asymptotically χ^2 distributed. In addition, the following goodness of fit parameters were considered when choosing between two models: Residual plots, standard error and the correlation matrix of the parameter estimates, size of the interindividual variance of the pharmacokinetic parameters, size of the residual error.

Validation

In a separate group of 30 consecutive patients treated with quinidine a sample for serum drug concentration measurement was obtained. Knowing the drug dosing history, the time of sampling and the patient characteristics which were found to influence the pharmacokinetics of quinidine, predictions of the serum concentration and of the standard deviation were made and compared with the measured concentrations. Using a t-test we determined if the mean of the residuals (i.e. the difference between observed and predicted concentration) was significantly different from zero. To test the prediction of the variability the fraction of measurements within the 90% prediction interval, calculated with the parameter estimates, was used. We also calculated the standard deviation of the weighted residuals (i.e. the residual divided by the predicted standard deviation). If the model and the estimates of the variability are correct,

the standard deviation of the weighted residuals should be equal to one (Vozeh *et al.*, 1988).

Design of dosing regimen

Assuming that our parameter estimates adequately describe the dose-serum drug concentration relationship and its variability, we calculated, using Monte Carlo simulations, the concentration-time profile (average and variability) that one would expect in patient populations with different characteristics. Comparing the simulated profiles with the recommended therapeutic range of 2–5 mg l^{-1} (Follath *et al.*, 1983) dosage recommendations were derived that should maximize the proportion of patients having serum drug concentrations within the therapeutic range.

Results

Results of the regression analysis

A two compartment model with zero order absorption from the gastrointestinal tract was found to describe the data better than a one compartment model. The difference in the objective function was 19.7, which corresponds to a P value < 0.0005 if the χ^2 distribution is assumed. The rate of absorption was, as expected, different for quinidine sulphate and quinidine bisulphate (which is used as a slow release preparation). The time to peak concentration was 1.37 h for quinidine sulphate and 6.0 h for quinidine bisulphate (difference in the objective function 56.9, $P < 0.0005$). The bioavailability of the two preparations was also different—the introduction of an additional parameter describing the relative bioavailability quinidine bisulphate *vs* quinidine sulphate resulted clearly in a better fit (the difference in the objective function was 12.2, $P < 0.0005$). The value of the relative bioavailability of quinidine bisulphate compared with quinidine sulphate was 1.36.

Interindividual variability was assigned to the following parameters: clearance, volume of distribution of the central compartment and duration of absorption (time to peak concentration) for quinidine sulphate. No improvement of the fit was obtained by allowing for interindividual variability in the following parameters: duration of the absorption for quinidine bisulphate, relative bioavailability of quinidine bisulphate relative to quinidine sulphate, intercompartmental clearance and volume of distribution of the peripheral compartment.

The values of the population parameters for the final regression model are given in Table 1. Among the tested patient characteristics only creatinine clearance and severe heart or liver failure showed an influence on the pharmacokinetics of quinidine. Mild to moderate heart or liver dysfunction had no influence. As the effect of severe heart and liver dysfunction were of similar magnitude, and as we had only few patients in these groups, we pooled these patients into one group. The nonrenal clearance was reduced in these patients by almost 50%, see Table 1 (difference in the objective function 10.8, $P < 0.005$). Adjusting renal clearance for the estimated creatinine clearance also improved the fit (difference in the objective function 5.04, $P < 0.025$). We estimated the value for the parameter CL_R—i.e. proportionality constant relating creatinine clearance to drug renal clearance (Table 1). No influence on the pharmacokinetics of quinidine was found for the following parameters: body weight, sex, nifedipine cotherapy and age.

For a patient without kidney disease and without severe heart and liver failure, the two half-lives associated with the two compartment model were 2.22 h and 10.1 h and the average oral clearance was 18.1 l h^{-1}. The fraction of the total clearance due to renal elimination (for a creatinine clearance of 100 ml min^{-1}) was estimated as 31%.

Table 1 Population pharmacokinetic parameters of oral quinidine—2 compartment model

Parameter	*Population mean* Estimate	*s.e.*	*Interindividual variability* Estimate[a]	*s.e.*[b]
CL_{renal}[c]	0.0566	0.0242		
$CL_{nonrenal}$ (l h^{-1})				
for patients without severe HF[d] and LF[d]	12.6	1.8	40.2%	55%
for patients with severe HF or LF	6.8	1.8		
V_1 (l)	161	14	75.6%	53%
Q (l h^{-1})[e]	12.6	5.8		
V_2 (l)	66.7	16.4		
$t_{max,\,QS}$[f] (h)	1.37	0.04	49.4%	65%
$t_{max,\,QBS}$[f] (h)	6.00	0.25		
F	1.36	0.12		
σ[g]	22%	39%[b]		

a Estimates of variability expressed as coefficient of variation

b s.e. of variance components (var(CL), var (V_1), var($t_{max,QS}$), σ) taken as $\sqrt{\text{s.e.(estimate)/estimate}}$ expressed as percentage

c proportionality constant relating creatinine clearance (ml min^{-1}) to apparent drug renal clearance (l h^{-1}) i.e. renal clearance divided by bioavailability of quinidine sulphate

d HF: heart failure, LF: liver failure

e Q: intercompartmental clearance

f QS: quinidine sulphate, QBS: quinidine bisulphate

g residual intraindividual variability of the serum concentration, expressed as coefficient of variation

Validation

The 30 patients of our control group had a median creatinine clearance of 48.7 ml min^{-1} (range 19.5 to over 100 ml min^{-1}). In no case was severe heart or liver failure present. Figure 4 shows measured and predicted concentrations ± 1.64 standard deviation (90% confidence interval under the assumption of normal distribution) of these 30 patients. Twenty-eight measured values (93%) lay within the predicted serum drug concentration ± 1.64 standard deviation—this is very close to the expected 90%. A large difference between measured and predicted concentration can be seen in Figure 4 for patient No. 25. Reviewing his medical history we found that he had probably suffered from severe heart failure—he showed a fall in blood pressure during the episode of atrial flutter followed by an increase in serum creatinine. Since this was a retrospective finding, we did not reclassify the patient but evaluated our data with and without this outlier. In both cases, the mean of the residuals was not significantly different from zero (0.38 with and 0.18 without patient No. 25, $P > 0.1$) and the standard deviation of the weighted residuals was close to 1 (1.47 with and 0.97 without patient No. 25).

Discussion

In this study we used the population pharmacokinetic approach to estimate the dose-concentration relationship in patients treated with oral quinidine. In spite of the difference in methods our results correspond well to the data estimated from studies in volunteers and the few available data on quinidine kinetics in patients. We determined a value of 18.3 l h^{-1} for total quinidine clearance after oral dosing of quinidine sulphate in patients whose creatinine clearance is larger than 100 ml min^{-1}. Correcting for the absolute bioavailability of quinidine sulphate of 70% (Guentert *et al.*, 1979), our clearance value is comparable with the value of 13.2 l h^{-1} found by Ochs *et al.* (1978) for elderly volunteers. Our estimate, corrected for bioavailability, is about 35% lower than the values reported for young healthy subjects after a single i.v. dose (Conrad *et al.*, 1977; Guentert *et al.*, 1979; Rakhit *et al.*, 1984). This difference is not surprising, considering the difference in the study population.

The inclusion of patients with different renal function enabled us to estimate the renal and nonrenal components of clearance. Our estimate of the nonrenal fraction was 0.69. This corresponds well to the reported values of 0.63 to 0.79 (Conrad *et al.*, 1977; Ochs *et al.*, 1978; Rakhit *et al.*, 1984). We were able to estimate this value without the need of either extensive pharmacokinetic studies in patients with renal failure or urinary data. This shows one of the advantages of the population approach. It should be emphasized, however, that in our study sample there were only patients with a creatinine clearance greater than 15 ml min^{-1}. The results should therefore be used with caution in patients with more severely impaired kidney function.

Conrad *et al.* (1977) reported that the same dosage regimen results in higher quinidine serum concentrations in patients with congestive heart failure than in those without. In our study severe heart or liver failure was found to cause a considerable reduction of nonrenal clearance by almost 50%. It is therefore important to use lower doses in such patients. This applies, however, only for cases with severe heart failure—i.e. low output or pulmonary oedema—or with severe liver failure—i.e. advanced cirrhosis. A mild to moderate impairment of heart or liver function does not seem to influence the kinetics of quinidine. Since there was a large number of study patients in these latter groups, we are confident that in such cases no dosage adjustment is needed. We found a possible influence of severe heart or liver failure also on the volume of distribution of the central compartment. But considering that the improvement of our model was only minor ($0.01 < P < 0.025$) and that there were only five patients in that group, we did not include

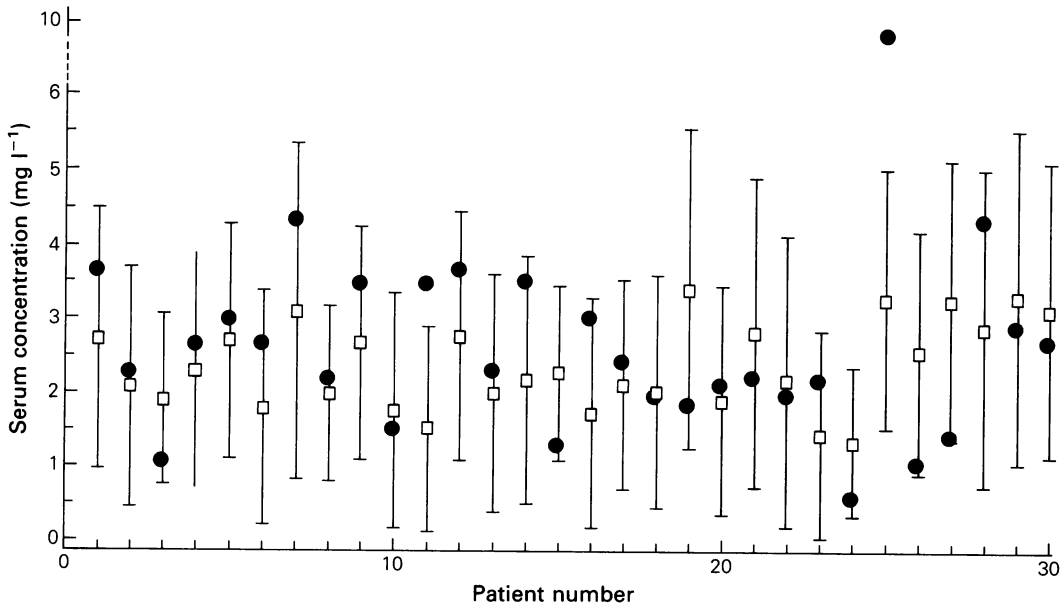

Figure 4 Validation of the results. Measured (•) and predicted (□) serum drug concentrations in another group of 30 patients. Note that 28 of the 30 values (93%) lie within ± 1.64 s.d. (90% C.I.).

this parameter in the regression model. Further studies would be needed to clarify this issue.

Ochs *et al.* (1978) found an influence of age on quinidine kinetics in healthy volunteers. We could not find any correlation between age and the pharmacokinetic parameters. This discrepancy could be partly due to the fact that most of our patients were older than 40 years whereas Ochs *et al.* (1978) compared volunteers of 23 to 34 years to those of 60 to 69 years.

Our population analysis showed that a correction of the pharmacokinetic parameters for body weight did not improve the model. This in spite of exploring different relationships (simple proportionality, power model) between body weight and both clearance and volume of distribution. Thus a correction of clearance or volume of distribution for body weight—often found in the literature—does not seem appropriate for patients between 50 and 100 kg (the range of body weight values in our study).

For the relative bioavailability of quinidine bisulphate *vs* quinidine sulphate we estimated a value of 1.36. Comparing reports on the absolute bioavailability of these two substances (Amelie *et al.*, 1979; Guentert *et al.*, 1979) a relative bioavailability of 1.24 is calculated. This corresponds well to our results.

Guengerich *et al.* (1986) reported that quinidine is metabolized in part by the same enzyme as nifedipine. In two patients Farringer *et al.* (1984) found an influence of nifedipine on quinidine kinetics. In our study no effect of nifedipine therapy on the kinetics of quinidine could be detected. This is in accordance with the work of Munger *et al.* (1989) who found no changes in quinidine pharmacokinetics during coadministration of nifedipine, and he suggested that this interaction may be limited to a few subjects.

Prospective evaluation

A population pharmacokinetic analysis is often performed in an exploratory way and is based on data

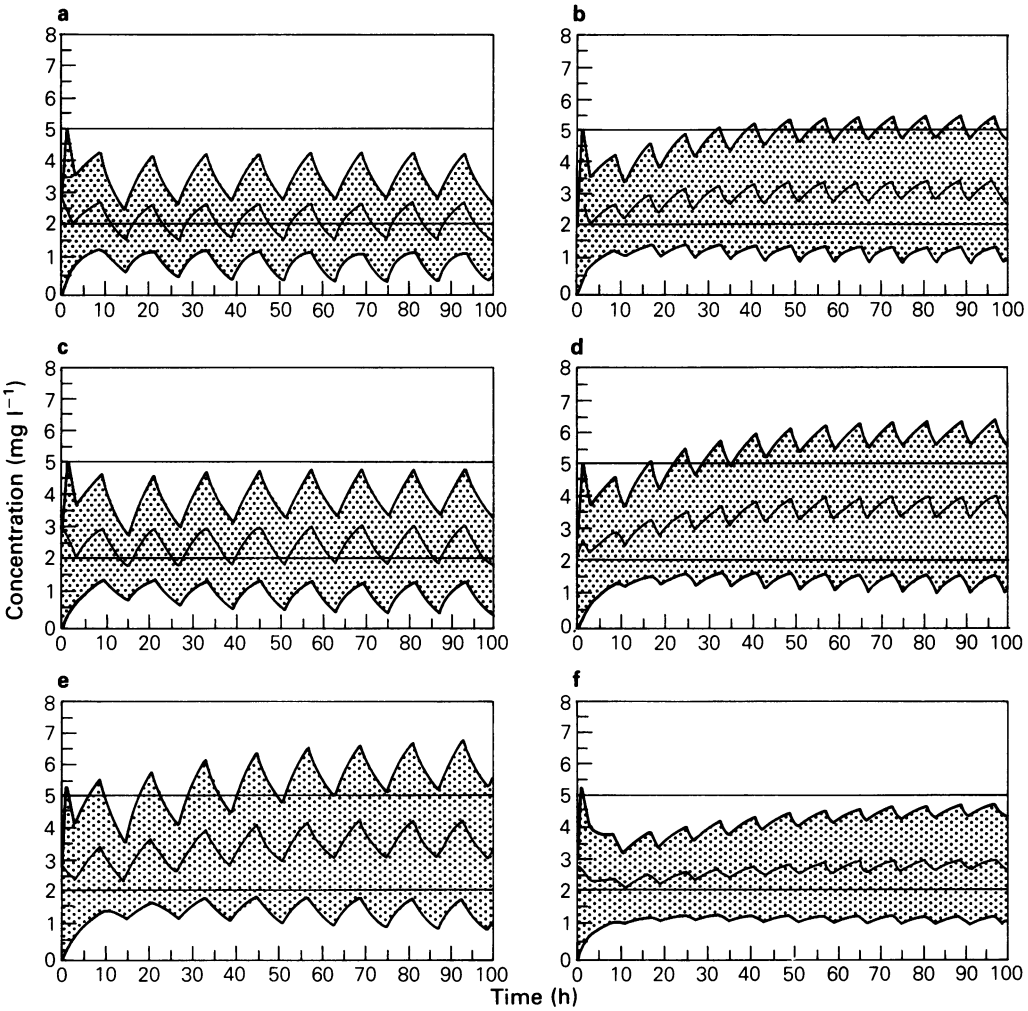

Figure 5 Monte Carlo computer simulations of the serum drug's concentration-time profile under different dosing schemes: solid line, population average; shaded area, 90% confidence interval.

a and b: patients with creatinine clearance over 100 ml min^{-1}, without severe heart and liver failure. a) Quinidine sulphate 600 mg followed 3 h later by 500 mg quinidine bisulphate twice daily. b) Quinidine sulphate 600 mg followed 3 h later by 500 mg quinidine bisulphate three times daily.

c and d: patients with creatinine clearance of 50 ml min^{-1} without severe heart and liver failure. c) Quinidine sulphate 600 mg followed 3 h later by 500 mg quinidine bisulphate twice daily. d) Quinidine sulphate 600 mg followed 3 h later by 500 mg quinidine bisulphate three times daily.

e and f: patients with a creatinine clearance of 60 ml min^{-1} and with severe heart or liver failure. e) Quinidine sulphate 600 mg followed 3 h later by 500 mg quinidine bisulphate twice daily. f) Quinidine sulphate 600 mg followed 3 h later by 250 mg quinidine bisulphate three times daily.

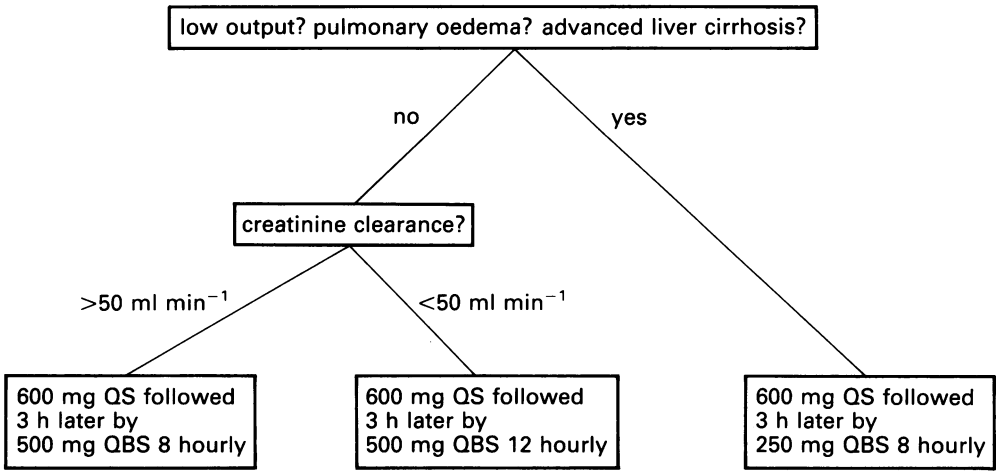

Figure 6 Dosage recommendations. QS: quinidine sulphate, QBS: quinidine bisulphate (Kinidin duriles®).

obtained in patients on routine treatment rather than in controlled randomized studies. Such an approach has, on the one hand, the important advantage of yielding results which are representative of the patient population in which the drug is actually used. On the other hand, the exploratory nature of the study requires in our opinion a prospective evaluation of the parameter estimates that describe the average dose-concentration relationship and its variability before clinical application of the results. This prospective evaluation in another group of 30 patients revealed that the fraction of patients having serum drug concentrations within a certain range could be predicted reliably by our model.

Derivation of 'a priori' *dosage regimens*

The estimation of interindividual variability of the pharmacokinetic parameters and of the intraindividual variability is helpful for the development of dosage recommendations, because it enables calculation of the proportion of patients at risk for toxic or ineffective concentrations. Based on our results we performed Monte Carlo computer simulations of the concentration-time profile for different patient groups and dosing regimens. Figure 5a and b show the concentration-time profile for a group of patients with creatinine clearance greater than 100 ml min^{-1} and no severe heart or liver failure. The simulations indicate that for these patients the higher maintenance dose, 500 mg quinidine bisulphate three times daily, leads to therapeutic concentration in a larger proportion of patients without a high risk of toxic concentrations. Figure 5c and d show the concentration-time profile under the same dosing regimens as in Figure 5a and b for patients with a creatinine clearance of 50 ml min^{-1}. Here the higher maintenance dose results in a relatively large proportion of patients having serum drug concentrations above 5 mg l^{-1}. Figure 5e shows that for patients with severe heart or liver failure even the lower maintenance dose (500 mg quinidine bisulphate twice daily) leads to potentially toxic concentrations in some patients. In Figure 6 our dosage recommendations based on the results of this study and the recommended concentration window for quinidine are summarized. Although they represent the best initial guess, the large interindividual variability shown in Figure 5 clearly indicates the need for individual dose adjustments based on drug concentration measurements, if serum drug concentrations within the desired range are to be achieved in most patients. This applies in particular to patients with renal function impairment and severe heart or liver failure. Making these recommendations we should like to point out again the limitations of our study. No patients with end stage renal disease were studied and the number of patients with severe heart or liver failure was small. In addition, the results in the latter group could not be validated, because only one of the 30 patients could be classified as having severe heart or liver failure. In these patients careful individual dose adjustment based on close monitoring is therefore recommended.

References

Aarons, L., Vozeh, S., Wenk, M., Weiss, Ph. & Follath, F. (1989). Population pharmacokinetics of tobramycin. *Br. J. clin. Pharmac.*, **28**, 305–314.

Amlie, J. P., Storstein, L., Olsson, B., Fremstad, D. & Jacobsen, S. (1979). Absolute bioavailability of quinidine in two sustained release preparations. *Eur. J. clin. Pharmac.*, **16**, 45–48.

Beal, S. L. & Sheiner, L. B. (1986). *NONMEM users guide—Part I, II, V and VI.* University of California, San Francisco 1980, 1985 and 1986.

Cockcroft, D. W. & Gault, M. H. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**, 31–41.

Conrad, K. A., Molk, B. L. & Chidsey, C. A. (1977). Pharmacokinetic studies of quinidine in patients with arrhythmias. *Circulation*, **55**, 1–7.

Dettli, L. (1983). Pharmacokinetische Grundlagen der Arzneimitteldosierung. In *Arzneimittelkompendium der Schweiz*, Vol. 2, Documed, Basel 1983; 1520.

Drayer, D. E., Lowenthal, D. T., Restivo, K. M., Schwartz,

A., Cook, C. E. & Reidenberg, M. M. (1978). Steady-state serum levels of quinidine and active metabolites in cardiac patients with varying degrees of renal function. *Clin. Pharmac. Ther.*, **24**, 31–39.

Farringer, J. A., Green, J. A., O'Rourke, R. A., Linn, W. A. & Clementi, W. A. (1984). Nifedipine-induced alterations in serum quinidine concentrations. *Am. Heart J.*, **108**, 1570–1572.

Follath, F., Ganzinger, U. & Schuetz, E. (1983). Reliability of antiarrhythmic drug plasma concentration monitoring. *Clin. Pharmacokin.*, **8**, 63–82.

Guengerich, F. P., Mueller-Enoch, D. & Blair, I. A. (1986). Oxidation of quinidine by human liver cytochrome P-450. *Mol. Pharmac.*, **30**, 287–295.

Guentert, Th. W., Holford, N. H. G., Coates, P. E., Upton, R. A. & Riegelman, S. (1979). Quinidine pharmacokinetics in man: Choice of a disposition model and absolute bioavailability studies. *J. Pharmacokin. Biopharm.*, **7**, 315–330.

Leroyer, R., Jarreau, C. & Pays, M. (1982). Specific determination of quinidine and metabolites in biological fluids by reversed-phase high-performance liquid chromatography. *J. Chromatogr.*, **228**, 366–371.

Maitre, P. O., Vozeh, S., Heykants, J., Thomson, D. A. & Stanski, D. R. (1987). Population pharmacokinetics of alfentanil: The average dose-plasma concentration relationship and interindividual variability in patients. *Anesthesiology*, **66**, 3–12.

Munger, M. A., Jarvis, R. C., Nair, R., Kasmer, R. J., Nara, A. R., Urbancic, A. & Green, J. A. (1989). Elucidation of the nifedipine-quinidine interaction. *Clin. Pharmac. Ther.*, **45**, 411–416.

Ochs, H. R., Greenblatt, D. J., Woo, E. & Smith, T. W. (1978). Reduced quinidine clearance in elderly persons. *Am. J. Cardiol.*, **42**, 481–485.

Rakhit, A., Holford, N. H. G., Guentert, Th. W., Maloney, K. & Riegelman, S. (1984). Pharmacokinetics of quinidine and three of its metabolites in man. *J. Pharmacokin. Biopharm.*, **12**, 1–21.

Sheiner, L. B., Rosenberg, B. & Marathe, V. V. (1977). Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *J. Pharmacokin. Biopharm.*, **5**, 445–479.

Vozeh, S., Uematsu, T., Aarons, L., Maitre, P., Landolt, H. & Gratzl, O. (1988). Intravenous phenytoin loading in patients after neurosurgery and in status epilepticus, a population pharmacokinetic study. *Clin. Pharmacokin.*, **14**, 122–128.

Windholz, M., Budavari, S., Blumetti, R. F. & Otterbein, E. S. (1983). *The MERCK index*, 10th edition, p. 7963. Rahway, N.J.: Merck & Co. Inc.

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