原 著

Prediction of Cibenzoline Dose from that of Digoxin

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Abstract

In clinical use, digoxin and cibenzoline are prescribed together for the treatment of cardiac arrhythmias. They are mainly excreted unchanged in urine, and their rates of excretion are similar. It has therefore been suggested that the pharmacokinetics of digoxin can predict that of cibenzoline. The aim of this study was to examine the possibility of prediction of cibenzoline dose from that of digoxin. We retrospectively examined 141 Japanese inpatients who received treatment for atrial fibrillation after cardiac surgery in the National Cardiovascular Center from April 2000 to December 2002. We found that CIBCL/F increased in proportion to DxCL/F. We obtained and evaluated a formula to predict cibenzoline dose from that of digoxin. If the dosage predicted from the formula was administered, about 70% patients could be maintained within the therapeutic range. The formula obtained in this study, which can predict cibenzoline dose from that of digoxin, should thus be very valuable in clinical practice.

Key words; cibenzoline, digoxin, dose, prediction, formula

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Introduction

Digoxin is one of the most frequently used cardiac glycosides in the treatment of congestive heart failure and atrial flutter or fibrillation[1]. It is mainly eliminated by the kidney (50～70%)[2], and is transported by P-glycoprotein[3～5]. Individual variation in the pharmacokinetics of digoxin is large[6] and the therapeutic range of digoxin is narrow[7～10]. Therapeutic drug monitoring (TDM) should be performed to control the pharmacokinetics of digoxin. Because serum digoxin concentration can easily be measured using assay kits, digoxin TDM is performed in many hospitals.

Cibenzoline succinate is a class I antiarrhythmic agent, and is mainly eliminated by the kidney (60～70%)[11～14] and partly metabolized by CYP2D6 and CYP3A4[15,16]. The antiarrhythmic effect of cibenzoline is proportional to its serum concentration[17,18], but the therapeutic range of cibenzoline is narrow. The major side effects of cibenzoline include hypoglycemia and proarrhythmia, especially at high serum concentration[19～21]. TDM should therefore be performed to control the pharmacokinetics of cibenzoline. Since no assay kit has been developed for cibenzoline, cibenzoline serum concentration should be determined by high performance liquid chromatography (HPLC). In many hospitals, serum cibenzoline concentration cannot be measured, making rapid adjustment of the cibenzoline dose difficult.

In the treatment of cardiac arrhythmias, digoxin is frequently used for rate control, while antiarrhythmic

Table 1 Characteristics of subjects

Parameters	Male	Female	Total
Number of subjects	106	35	141
Age (year)	67.0±11.7	62.9±10.6	66.0±11.6
Body weight (kg)	61.2±9.6	49.8±9.3	58.4±10.7
Dose of digoxin (mg/day)	0.178±0.067	0.162±0.061	0.174±0.066
Dose of cibenzoline (mg/day)	210±72.8	192±64.3	205±71.0
Serum creatinine (mg/dl)	0.97±0.49	0.66±0.22	0.89±0.45
Creatinine clearance (ml/min)	74.0±32.6	68.6±21.5	72.7±30.2
Digoxin concentration (ng/ml)	0.85±0.37	0.86±0.45	0.85±0.39
Cibenzoline concentration (ng/ml)	293±248	248±117	282±223

Data are given as mean±SD.

agents are used for rhythm control[22]. In clinical use, digoxin and cibenzoline are prescribed together for the treatment of cardiac arrhythmias. They are mainly excreted unchanged in urine[2,11~14], and their rates of excretion are similar. It has therefore been suggested that the pharmacokinetics of digoxin can predict that of cibenzoline.

The aim of this study was to examine the possibility of prediction of cibenzoline dose from that of digoxin.

Subjects and Methods

Data were retrospectively collected from 141 Japanese inpatients (106 males and 35 females, age 66.0± 11.6 years, weight 58.4 ± 10.7kg) who received treatment for atrial fibrillation after cardiac surgery in the National Cardiovascular Center from April 2000 to December 2002 (**Table 1**). They received digoxin orally once daily at 7:00 for more than 7 days, and cibenzoline succinate was coadministerd orally two or three times daily (7:00, 12:00 and 18:00) for more than 4 days. Blood samples were obtained at 6:00 from an arm vein, and serum was obtained by centrifugation (3,000rpm, 10min). Written informed consent was obtained from all subjects before these studies. Creatinine clearance (Ccr, ml/min) was calculated by the Cockcroft-Gault formula[23], which was developed to predict Ccr from serum creatinine.

Assay

A. Digoxin

Serum digoxin concentrations were determined by fluorescence polarization immunoassay (TDx, Abbott Japan). The minimum detectable concentration of digoxin was 0.2ng/ml, and the inter- and intra-day coefficients of variation were less than 10%.

B. Cibenzoline

Serum concentrations of cibenzoline were measured by HPLC using the method of Ueno et al.[24] with 4-methylmexiletine as an internal standard. In brief, cibenzoline was extracted with diethyl ether, followed by evaporation. The residue was reconstituted with a mobile phase. The ODS-column (250mm×46mm, Shinwa Chemical Industries, LTD., Kyoto, Japan) was used, and the absorbance of effluent from the column was measured at 210nm. The mobile phase consisted of acetonitrile-44mM phosphate solution (pH2.6, 0.5% trietylamine) (75:25, vol/vol). Using this method, the minimum detectable concentration of cibenzoline was 50ng/ml, and the inter- and intra-day coefficients of variation were less than 5%.

Calculation of clearance

Digoxin clearance was calculated by Dx2[25] (Otsuka Pharmaceutical Co. Ltd., Tokyo Japan), and cibenzoline clearance by CIBTDM20[26] (Astellas Pharma Inc., Tokyo, Japan). Dx2 and CIBTDM20 are software, which calculate individual parameters by a least squires method termed MULTI2 (BAYES) by Yamaoka[27].

Developing and evaluating a formula for prediction of cibenzoline dose from that of digoxin

Cibenzoline dosage was calculated using a formula

for prediction of cibenzoline dose from that of digoxin. Since the tablets of cibenzoline marketed in Japan are 50mg or 100mg, fractions of calculated dosage were omitted as follows: 100～124mg→100mg, 125～174mg→150mg, and 175～199mg→200mg. The cibenzoline concentration for administration of the predicted dosage was calculated by CIBTDM20[26].

Statistical analysis

Results are expressed as mean±standard deviation. Statistical analysis was performed by regression analysis.

Results

Fig. 1 shows the correlation between Ccr and digoxin clearance (DxCL/F). DxCL/F increased in proportion to Ccr ($p<0.05$). **Fig. 2** shows the correlation between Ccr and cibenzoline clearance (CIBCL/F). CIBCL/F also increased in proportion to Ccr ($p<0.05$). **Fig. 3** shows the correlation between DxCL/F and CIBCL/F. CIBCL/F was found of increase in proportion to DxCL ($p<0.05$). In order to evaluate the effect of Ccr on the correlation between DxCL/F and CIBCL/F, the subjects were divided into three groups by Ccr: (i) 0 to 49, (ii) 50 to 119, and (iii) above 120ml/min, and the results are shown in **Fig. 4**. CIBCL/F increased in proportion to DxCL for Ccr values ranging from 0 to 49 ($p<0.05$). We obtained the following formula for prediction of the cibenzoline dose from that of digoxin:

$$CIBCL/F = DxCL/F \times \alpha + \beta$$

$$CL/F = Dose/(Css)^{mean} \times \tau$$

$$CIB\ Dose = [Dx\ Dose/\{(Dx\ Css)^{mean} \times \tau\} \times \alpha + \beta] \times \{(CIB\ Css)^{mean} \times \tau\}$$

α: slope of the regression line

β: intercept of the regression line

CIB Dose: cibenzoline dose

Dx Dose: digoxin dose

τ: interval of administration

$CIB(Css)^{mean}$: serum cibenzoline concentration at steady-state

$Dx(Css)^{mean}$: serum digoxin concentration at steady-state

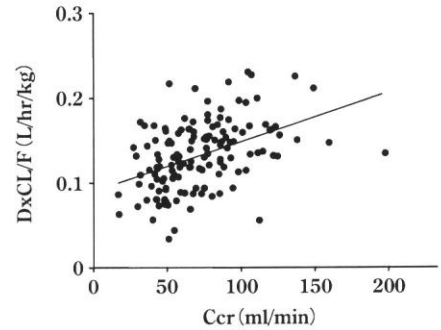

Figure 1 Relationship between digoxin clearance (DxCL/F) and creatinine clearance (Ccr) in 141 patients

The regression equation determined by least-squares method was
$y=0.0006x+0.0906$, $r=0.435$, $p<0.05$. F, bioavailability.

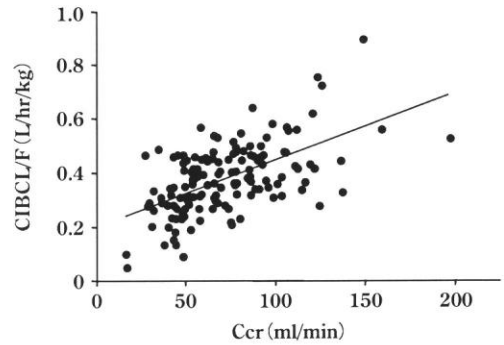

Figure 2 Relationship between cibenzoline clearance (CIBCL/F) and Ccr in 141 patients

The regression equation determined by least-squares method was
$y=0.0025x+0.1964$, $r=0.577$, $p<0.05$.

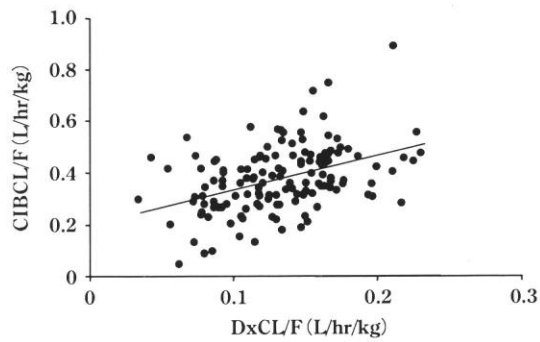

Figure 3 Relationship between CIBCL/F and DxCL/F in 141 patients

The regression equation determined by least-squares method was
$y=1.33x+0.202$, $r=0.406$, $p<0.05$.

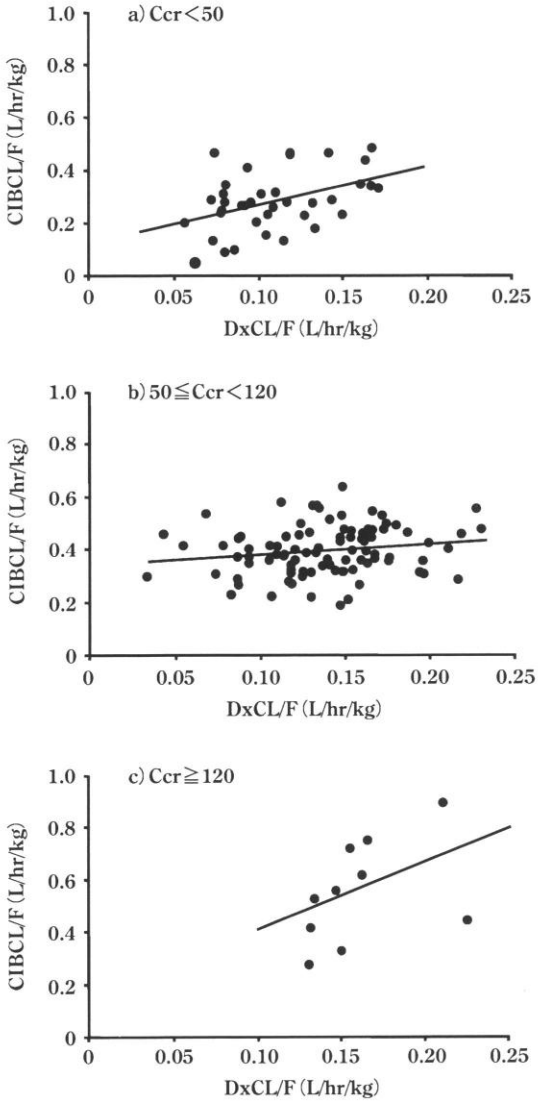

Figure 4 Relationship between CIBCL/F and DxCL/F classified by Ccr

The regression equations determined by least-squares method were
a) $y=1.50x+0.116$, $r=0.437$, $p<0.05$,
b) $y=0.417x+0.337$, $r=0.177$, $p=0.18$, and
c) $y=2.62x+0.145$, $r=0.418$, $p=0.20$. F, bioavailability.

Since it has been reported that the concentration of cibenzoline yielding clinically useful antiarrhythmic effects is about 300ng/ml[28], we considered CIB $(Css)^{mean}$ to be 300ng/ml. Since it has also been reported that the therapeutic range of digoxin in Japanese is 0.5～1.5ng/ml[29], we considered Dx $(Css)^{mean}$ to be 0.8ng/ml. Thus,

CIB Dose (mg/kg) = Dx Dose (mg/kg) × 723 + 2.11.

Because 66.7% patients can be controlled within the therapeutic range, which is 100～350ng/ml (trough concentration) and below 800ng/ml (peak concentration), it appears that this formula can predict cibenzoline dose well.

In order to evaluate effects of Ccr, the subjects were divided into three groups by Ccr: (i) 0 to 49, (ii) 50 to 119, and (iii) above 120ml/min, and corresponding formulas were obtained to predict cibenzoline dose from that of digoxin.

i) Ccr < 50ml/min

CIB Dose (mg/kg) = Dx Dose (mg/kg) × 827 + 1.39

ii) 50ml/min ≦ Ccr < 120ml/min

CIB Dose (mg/kg) = Dx Dose (mg/kg) × 290 + 3.48

iii) Ccr ≧ 120ml/min

CIB Dose (mg/kg) = Dx Dose (mg/kg) × 1450 + 1.57

These formulas can predict cibenzoline dose, since 68.8% patients can be controlled within the therapeutic range. These results suggest that the formula does not differ markedly whether subjects are divided by Ccr or not.

Discussion

DxCL/F was found to increase in proportion to Ccr ($p<0.05$, **Fig. 1**). This finding corresponds to those of the previous studies[2,30]. Since digoxin is mainly eliminated by the kidney (50～70%)[2], its pharmacokinetics depends on renal function. CIBCL/F also increased in proportion to Ccr ($p<0.05$, **Fig. 2**), and this finding again corresponds to those of previous studies[28,31～33]. It has been reported that cibenzoline is mainly eliminated by the kidney (60～70%)[11～14] and is partly metabolized by CYP2D6 and CYP 3A4[15,16].

These findings showed that digoxin and cibenzoline pharmacokinetics are regulated by renal function. Since it has been suggested that the pharmacokinetics of both digoxin and cibenzoline are much in common, we investigated the relationship between DxCL/F and CIBCL/F, and found that CIBCL/F was increased in proportion to DxCL/F ($p<0.05$, **Fig. 3**). We obtained and evaluated a formula to predict ciben-

zoline dose from that of digoxin. Clinical efficacy was obtained with cibenzoline trough concentration in the range from 100 to 200ng/ml[34], and trough concentrations of cibenzoline in the range of 200 to 400ng/ml reduced ventricular premature contractions[35]. It has also been reported that, to prevent cibenzoline-induced hypoglycemia, cibenzoline trough concentration should be maintained below 400ng/ml[36]. On the other hand, it was reported that cibenzoline peak concentrations over 800ng/ml increased side effects[37]. We therefore considered the therapeutic range of cibenzoline to be from a trough concentration of 100 ~350ng/ml to a peak concentration below 800ng/ml, and evaluated the formula. If the dosage predicted from the formula was administered, about 70% patients could be maintained within the therapeutic range, with no difference in the formula whether or not subjects were divided by Ccr.

Serum digoxin concentration can easily be measured using assay kits, making possible rapid adjustment of its dose. However, since no assay kit for cibenzoline has been developed, cibenzoline serum concentration should be determined by HPLC. In many hospitals, serum cibenzoline concentration cannot be measured, making rapid adjustment of cibenzoline dose difficult. The formula obtained in this study, which can predict cibenzoline dose from that of digoxin, should thus be very valuable in clinical practice.

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