SUMMARY

Pharmacokinetic approach was used in establishing predictive models to estimate individual dosage regimen. Study was performed on β-Methyldigoxin, used with the aim of oral rapid digitalisation and maintenance dose.

The principle for estabilishing a dosage regimen was to achieve a desired plasma concentration within concentration limits. The concept is to take the individual patient as his/her own reference standard.

The study consists of two parts : First on healthy volunteers, and second on preselected hospitalized cardiac patients with a strong indication for Digitalis.

Studies on healthy volunteers (3 substudies) were aimed to find the characteristic profiles of β-Methyldigoxin with measured pharmacokinetic parameters :

(1) The pharmacokinetics of oral absorption of β-Methyldigoxin (β-MD) and Digoxin (DG) were observed in 16 male subjects. Equal dose of 0.500 mg β-MD and DG were given in a cross-over manner, with a wash-out periode of 2 weeks. Better rate (T_{max}, C_{max}) and extent of absorption (AUC) were found with β-Methyldigoxin in comparison to Digoxin, respectively : T_{max} (0.625 and 1.156) hr; C_{max} (4.55 and 3.12) ng/ml; AUC_0^{∞} (26.67 and 23.77) ng hr/ml.

(2) Absorption of multiple doses of β-MD were observed in 9 healthy volunteers (3 females + 6 males). Initial dose was started with 2 x 0.200 mg β-MD/day for 3 days, followed by 0.200 mg/day for the next 7 days. The steady state concentration was obtained on day -4, there was no significant diference of serum glycoside concentration (SGC) day-by-day after day-4. An intial dose twice the amount of

the maintenance dose resulted in achieving more rapid steady state concentration.

(3) The effect of Furosemide was studied on 10 healthy male volunteers. In a two way cross-over study the drugs were given as follows : β-MD 0.400 mg as single drug and β-MD + Furosemide (0.400 mg β-MD + 40 mg F) after 6 hrs followed by 40 mg Furosemide as second dose. The pharmacokinetic parameters (T_{max}, C_{max}, AUC, $t_{1/2}$ elimination) of β-MD were not significantly changed before and after using Furosemide in combination with β-MD.

Studies on preselected cardiac patients(3 sub studies):
(1) The serum concentration after a maintenance dose of Digoxin were observed in 28 patients (10 females + 18 males), aged 14-68 yrs, body weight 32-65 kg. The drug was administered 2 hrs before breakfast. Serum samples were drawn from the cubital vein at 6-8 hrs after drug ingestion on 2-3 conscecutive days at steady state. Multiple regression analysis indicated that identifiable independent factors as body weight and dose/day, were found to contribute on steady state concentrations of the drug (SGC), as found with the following equation :

$$SGC = 0.28131 + 0.22601\ DOS/BW/DAY$$

(SGC= ng/ml; DOS/BW/DAY = mcg/kg/day)

$R_{square} = 0.44470$; $R_{multiple} = 0.66686$

F = 21.62210; Sign F = 0.0001

(2) A loading dose for oral rapid digitalisation with β-MD were observed on 40 patients (22 females + 18 males), aged 15-80 yrs, body weight 28-80 kg. The total loading dose, given in 24-30 hrs as divided dose, with an interval of 6 hrs. Serum samples were drawn from the cubital vein before

the dose and 6-8 hrs after the last dose. In all forty patients upon admitance to the hospital, SGC of pre-dose were found inadequate (therapeutic level <0.8 ng/ml). Multiple regression analysis indicated that between the SGC after-dose was related to following individual factors : body weight, and creatinine serum, as found with this following equation (Formula A) :

SGC= 0.2400 + 0.18001 CREAT SER + 0.06455 DOS/BW/DAY

(SGC= ng/ml; CREAT SER= mg%; DOS/BW/DAY= mcg/kg/day)

$R_{multiple}$ = 0.65484; R_{square} = 0.429881; DF = 2:38

F = 14.2632; Sign F = 0.0001

(3) Serum Glycoside Concentration (SGC) of a maintenance dose with β-MD were observed on 74 patients (39 females + 35 males), aged 18-83 yrs, body weight 35-80 kg. The drug was administered daily 2 hrs before breakfast. Serum samples were drawn from the cubital vein at 6-8 hrs after the dose, and on 2-3 consecutive days when steady state was reached. Multiple regression analysis indicated the SGC appreared to be related to the dose administered and influenced by individual factors : sex, age, body weight and creatinine serum, as found with this following equation (Formula B) :

SGC = 0.05630 + 0.00466 AGE + 0.15562 CREAT SER + 0.21584 DOS/BW/DAY

(SGC= ng/ml; AGE = yr; CREAT SER = mg%;

DOS/BW/DAY = mcg/kg/day)

$R_{multiple}$ = 0.68582; R_{square} = 0.47035;

F = 15.31897; DF = 4;69 Sign F = 0.0001

Correction factors for male and female :

SGC (male) = 0.80 SGC (female)

or

DOS (female) = 0.80 DOS (male)

Predictive models of calculation of individual dosage regimen can be established by means of : (1) Knowing the

pharmacokinetic profile and pharmacokinetic characteristics of the drug used. (2) Recognizing and identifying the pharmacokinetic parameters which are relevant to individual characteristics. (3) Collecting empiric data from patients treated with the drugs as given in accordance with therapy and pharmacokinetic behaviour of the drug. (4) Analyzing the relationship of the dose and serum levels of the drug and related individual factors. (5) Verifying the validity of the predictive model for dose estimation.