Analysis of the predictive ability of different methods in dosage adjustment of digoxin

J.M. Fraga[1]; M.J.P. Rocha[1]; A. Almeida[2]

[1] Pharmacy Department, Hospital and University Centre of Coimbra – Director – J. Feio

[2] Pharmacology Department, Faculty of Pharmacy, Coimbra University, Coimbra, Portugal

BACKGROUND

Given the individual variability and the degree of physiological and pathological aging of each one is pertinent adaptation of the drug and dosage regimen for each patient, according to its particular characteristics. The methodology used to compare the predicted and observed concentrations in clinical practice was developed by Sheiner and Beal (1981).

OBJECTIVES

The aim of the present work was to evaluate predictive performance of four different methods, selected according to literature and that represent four sets of digoxin pharmacokinetic parameters.

METHODS

The calculation of the expected concentrations of digoxin was obtained using the equations of the method Jelliffe, Sheiner, Koup/Jusko and Konishi, using the trough value observed at steady state.

Table 1 – Equations for the determination of serum digoxin expected concentrations.

Author	Parameter	Equation
Jelliffe	**C_{ss}digo** (ng/mL)	- 0.416+(0.185x[(D daily /[14+(CL_{Cr}/5)]/100)/IBW]
Sheiner	**C_{ss}digo** (ng/mL)	(D daily x F)/CL_{digo} Sheiner with or without HF
Koup	**C_{ss}digo** (ng/mL)	(D daily x F)/CL_{digo} Koup with or without HF
Konishi	**C_{ss}digo** (ng/mL)	D daily (μg/day)/[2.22xCL_{Cr} (mL/min)+25.7]

The absolute and relative predictive performances were evaluated by applying the prediction errors of analysis as suggested by Sheiner & Beal, using the comparison between the values of the predicted concentrations (calculated by methods) and observed (measured).

RESULTS AND DISCUSSION

This study involves 26 inpatients with an average age of 78.6±11.0 years, a total of 78 observed concentrations. We determined the serum concentrations of digoxin using the equations shown in Table 1. The results obtained by different methods are shown in Table 3.

Table 2 – Data relating to patients with concentrations obtained at steady state in 2013.

Gender, n(%)	
Male	20 (76.9%)
Female	6 (23.1%)
Diagnosis, n(%)	
Heart failure	14 (53.9%)
Heart failure + Atrial Fibrillation	12 (46.1%)
Weight, Kg – Mean ± SD	64.09 ± 14.58
Minimum	40
Maximum	95
Ideal body weight, Kg - Mean ± SD	52.97 ± 6.82
Minimum	38.80
Maximum	65.03
Height, m – Mean ± SD	1.59 ± 0.06
Minimum	1.45
Maximum	1.69

Table 3 – Serum concentrations of digoxin predicted by the 4 methods and observed.

C_{ss} (ng/mL)	Mean ± SD	CV (%)	Min	Máx
C_{ss} observed	1.19 ± 0.66	55.46	0.30	3.60
C_{ss} Jelliffe	1.66 ± 0.91	54.82	0.60	4.40
C_{ss} Sheiner	1.25 ± 0.70	56.00	0.30	3.60
C_{ss} Koup	1.06 ± 0.62	58.49	0.30	3.10
C_{ss} Konishi	1.15 ± 0.65	56.52	0.02	3.70

The worst precision and accuracy were obtained by Jelliffe method, with the best to be obtained by Koup/Jusko and Konishi, followed by Sheiner practically the same value.

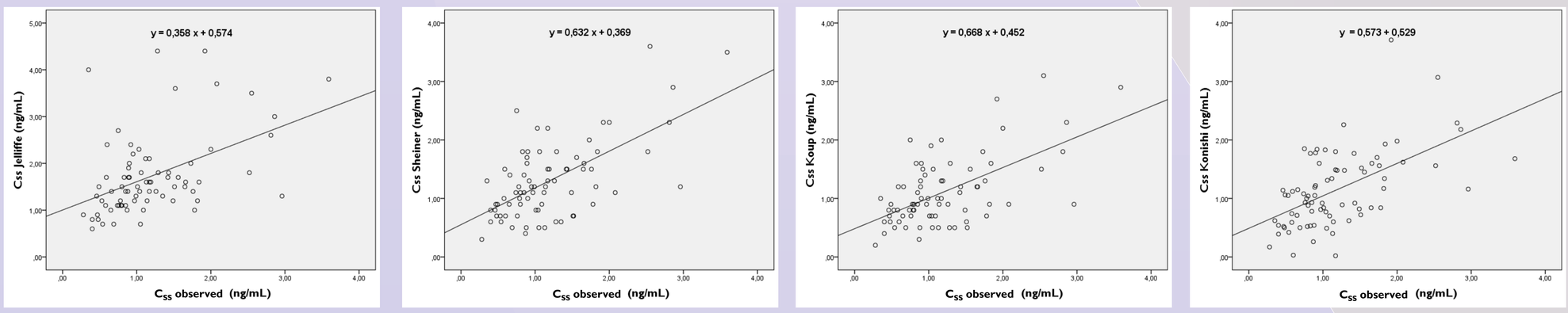

Figure 1 – Correlation between the expected serum concentrations (Cprev) and observed serum concentrations (Cobs) for Jelliffe methods (r = 0.47) , Sheiner (r = 0.63), Koup (r = 0.59) and Konishi (r = 0.56), p <0.01.

Methods of Konishi and Koup/Jusko show a tendency to underestimate, while the other two methods (Jelliffe and Sheiner) are marked by an over-estimation.

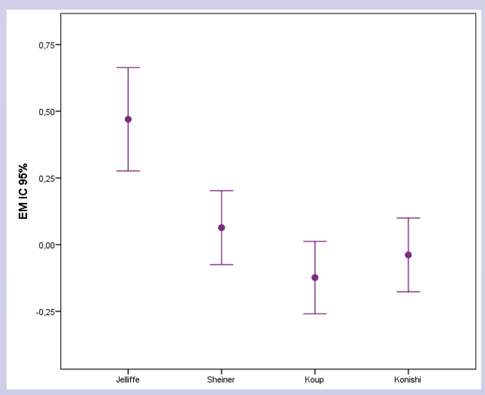

Figure 2 – Predictive capacity (accuracy) evaluated by average predictor error. In all cases, p <0.05 compared with zero (*t* student) .

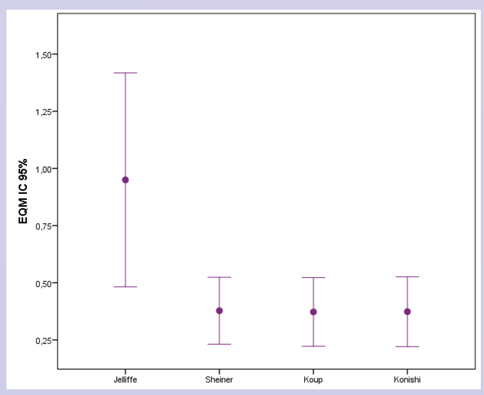

Figure 3 – Predictive capacity (precision) evaluated by average square error prediction. In all cases, p <0.05 compared with zero (*t* student) .

The choice of a method for optimization of a dosage regimen must take into account the maximum acceptable error from the clinical point of view, in the case of digoxin must have amplitude of 0.375 ng/ml, to trough of 0.5-2 ng/ml. Thus, the method Konishi (53.9%) is one that has a better clinical acceptability profile, followed by Sheiner and Koup, with 50% each.

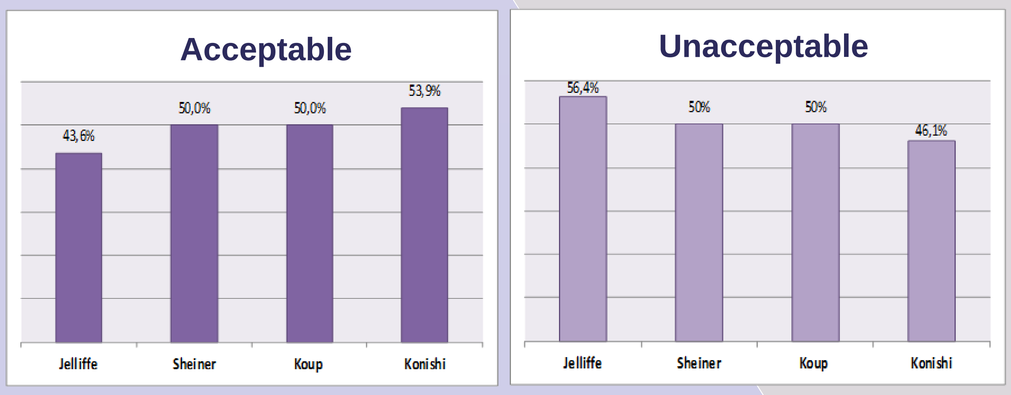

Figure 4 – Percentage of acceptable and unacceptable errors for each of the methods studied.

CONCLUSIONS

Comparison of serum digoxin highlights clearly the over-estimation of the concentrations provided by the methods of Jelliffe, Sheiner, Koup and Konishi in relation to the observed concentrations. It concludes that the Jelliffe method is the least accurate and precise, and then lower clinical acceptability. Konishi was the best method, although we are talking about a unacceptability of error of almost 50%. This study shows that are needed more studies of this drug in the elderly.

REFERENCES

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