ORIGINAL ARTICLE

The role of a regulatory factor for the determination of dosage of digoxin and other drugs in patients with renal dysfunction

Efstratopoulos A, Ioakimidis N, Marougas N, Dimou D, Gialernios Th, Karbouniaris N

3rd Medical Dept. and Hypertension Unit of General Hospital of Athens "G. Gennimatas"

Background: In cases of chronic renal dysfunction, the dose of drugs that are excreted mainly from the kidneys should be adjusted according to the level of renal function. In such cases, the use of a regulatory factor (RegF) is of clinical importance. In the present work a RegF was calculated from the glomerular filtration rate (GFR) of the patient (Gault –Cockroft method), in relation to normal GFR (120ml/min/1,73m^2 of body surface area), taking into account the body weight, age, sex of the patient and the renal (%) excretion of the drug. The dose based on calculation of Reg F was estimated by either the division of the daily dosage or the multiplication of the interval of administration. In our study we used the RegF to estimate the proper dose of digoxin in patients with heart failure or atrial fibrillation, in order to achieve therapeutic plasma levels.
Patients and Methods. A total of 29 patients (14 M/15F, 52-92 years-old) with either heart failure or atrial fibrillation, were included in the study. In every patient, digoxin plasma levels were measured initially (following the initial dosage of the drug) and later, after dosing adjustment based on RegF. In every patient, serum creatinine, body weight, GFR and blood pressure were determined. One-way analysis of variance (ANOVA) was used to compare responses following dosing modification due to regulatory factor.
Results: The initial plasma digoxin levels (i.e. plasma levels obtained from the initial dosage) ranged from 0.56 to 3.88 ng/mL (1,63 ±0,18 ng/mL, M±SE), while, the normal plasma levels ranged from 0.7 to 2.0 ng/mL. Plasma digoxin levels after dosage adjustment according to calculation of the regulatory factor ranged from 0.75 to 2.0 ng/mL (1,17±0,076), (in relation to the initial plasma levels, P=0.02). Following the initial dosage, 7 patients had toxic digoxin plasma levels, 3.06±0.24, (range 2.14-3.88), whereas, after dosage modification, nobody from this study group had toxic plasma levels (i.e.>2.0 ng/mL) (p<0.001).
Conclusions. We conclude that the use of RegF to determine the appropriate dosage of digoxin leads to the proper therapeutic plasma levels of digoxin, avoiding the unwanted higher plasma levels of digoxin in patients with heart failure or atrial fibrillation.
Hippokratia 2004, 8 (2): 73-77

Over the past decade, digoxin has received renewed attention because of the recognition of it's neurohormonal effect and the successful use of lower dosages. The goal of digoxin therapy in patiens with congestive heart failure is to improve quality of life by reducing symptoms and preventing hospitalizations[1]. Digoxin is also used for control of supraventricular arrhythmias, mainly control of ventricular rate during atrial fibrillation. Digoxin is largely excreted by the kidneys unchanged with a clearance rate proportional to the GFR, which results in the excretion of the approximately one-third of body stores daily[2,3]. Patients with heart failure usually have a reduced volume of distribution and reduced renal function. Although nomograms on digoxin dosing have been published, these nomograms should not be used in patients with heart failure because of the narrow therapeutic index and the unpredictability of the numerous factors that can alter digoxin pharmacokinetics. One of the main reasons that digoxin use has decreased is the narrow window between therapeutic and toxic concentrations[4]. The purpose of the present study was to formulate a simple equation for determining the daily dose requirements of digoxin by inclusion of creatinine clearance calculated by Gault-Cockroft equation as an explanatory variable taking into account age, weight, sex and the fractional excretion by the kidneys. The clinical application of the proposed model called *regulatory factor* will allow for the accurate and rapid determination of the initial maintenance dosage regimen of digoxin level without actual measurement of its serum concentration.

Methods

The study population consisted of 29 hospitalized patiens (age 77±8.14 males/15females) with a wide range of blood pressure and GFR [mean SBP 129±19 mmHg (range:100-180 mmHg, mean diastolic –BP: 75±10 (range: 60-100 mmHg), mean GFR 59±4.59 (range: 27 - 129 ml/min/1.73m^2)]; 13 patients had impaired left ventricular systolic function, detected by echocardiography, II and III NYHA class[5,6] with sinus rhythm, 10 patients had heart failure with atrial fribrillation, in whom ventricular response slowing is required and 6 patients with chronic atrial fibrillation to control the ventricular

rate. Patients with hypertrophic cardiomyopathy, LV diastolic dysfunction, recent myocardial infraction, heart failure- IV NYHA class, atrial fibrillation in Wolf-Parkinson-White syndrome and severe degree of A-V block, end stage renal failure and electrolyte abnormalities were excluded prior to entry into study.

Regulatory factor

Whether the drug dosage needs to be modified in patients with renal dysfunction depends on whether the drug is primarily excreted through the kidneys. This is especially true for drugs with long half-lives and narrow therapeutic indexes(e.g. digoxin)[7]. The goal of any dosage adjustment is to modify the dosing schedule so that the drug's plasma concentration-time profile is similar to the desired one as possible, and that the steady state is reached in about the same time as in patient with normal renal function. In these cases the estimation of the regulatory factor is of first clinical importance. Thus, we formulated an equation for determing daily dose of digoxin by inclusion of creatinine clearance estimated by Cockroft - Gault equation in relation to normal GFR(120ml/min/1,73), taking into account the age, body weight , sex and the fractional excretion of the drug by the kidneys. As can be seen from the following formula:

$$\mathrm{RegF} = \frac{1}{\mathrm{f\%}(\mathrm{Ka}-1)+1}$$

where RegF=regulatory factor, f%=fractional excretion of the drug by the kidney (90%for digoxin) (2) and

$$Ka = \frac{GFR(estimated\_by\_Cockroft\_\&Gault\_equation)}{normal\_GFR(120ml/\min/\mathrm{m}^2)}$$

According to Gault-Cockroft equation:

$$GFR = \frac{(140-age)*weight(kg)}{72*Pcr(mg/dL)}(mL/\min)$$

where Pcr=serum creatinine level, *=times

For women, the estimate by the above equation should be multiplied by 0,85 to reflect their smaller muscle mass.

To obtain the desired profile based on regulatory factor, a modification will be made by descreasing the dose while maintaining the dosage interval or keeping the dose the same but increasing the dosing interval, as we can see in the following two formulas(8):

$$Regular\_Dosage = \frac{Common\_Dosage}{Regulatory\_Factor}$$

$$New\_Interval = regular\,interval * \mathrm{Re}g.\,factor$$

*=times

Study design

Digoxin plasma levels were measured two times. Firstly, after the initial dosage (empirical, either acute loading doses or daily maintenance doses) and secondly after dosing adjustment according to calculation of regulatory factor for each patient(at least 3 days after dosing modification). Blood samples for measurement of serum digoxin levels were taken at least 6 to 8 hours following the last digoxin dose[7]. Digoxin concentration in serum were measured by fluorecence polarisation immunoassay. The therapeutic range for serum digoxin concentrations is frequently cited as 0.8 to 2.0 ng/mL. We also measured serum creatinine, potassium, calcium and magnesium. Moreover, daily ECG was taken for early detection of disturbances in cardiac impulse, formation, or both which are hallmarks of digitalis toxicity. Patients with substantial overlap in serum levels were questioned for the earliest signs of digitalis intoxication. The study protocol was approved by the institutional ethical committee and written informed consent was obtained from each patient.

Statistical Analysis

Statistical analysis was performed using Statistica -6 statistical package. Data are expressed as means ±SE. P values less than 0,05 were considered statistically significant. One-way analysis of variance (ANOVA) was used to compare responses following dosing modification due to regulatory factor We also assessed in 12 of the 29 patients, taking 0,125 mg of the drug after dosing modification according to calculation of regulatory factor, how much digoxin plasma levels changed on the average- as age, weight, serum creatinine, GFR and regulatory factor change- with a regression line for each of the 5 variables and quantified the strength of the association with a correlation coefficient (Pearson product –moment correlation coefficient).

Results

Table 1 summarizes the baseline characteristics of the study population and change in serum digoxin concentration for each patient after dosing adjustment based on estimation of regulatory factor.

The initial average daily dose of digoxin was 0,21 ± 0,015 and range 0,125 to 0,50mg/day which was associated with

Table 1. *Clinical and laboratory data* (n=29)

	M ± SE	Range	
Age(years)	77±7,7	52	92
Weight(Kgr)	68,4±10,3	52	94
Pcr(mg/100ml)	1,05±0,08	0,6	2,2
SBP(mmHg)	129±19	100	180
DBP(mmHg)	75±10	60	100
GFR(ml/min/1,73m^2)	59,78±24,6	27	129
RegF	2,02±0,12	0,93	3,30
Dose Baseline(mg/d)	0,210±0,015	0,125	0,500
Dosage after RegF(mg/d)	0,175±0,012	0,0625	0,25
Pdig1(ng/mL)	1,63±0,18	0,56	3,88
Pdig2(ng/mL)	1,17±0,075	0,7	2,0

a mean serum digoxin concentration of 1.63±0.18ng/mL and range 0.56 to 3.88ng/mL,whereas the therapeutic range is frequently cited as 0.8 to 2.0 ng/mL. The final mean dose according to calculation of regulatory factor was 0.17±0.012 and range 0.063 to 0.25mg/day which was associated with a mean digoxin plasma levels of 1.17±0.076 (range: 0.75 to 2.0) (in relation with the initial plasma levels p=0.02). In 7 of the 29 patients, (Table 2) serum concentrations with empirical dose were greater than 2.0ng/mL. These patients neither had ECG abnormalities nor clinical evidence of intoxication. In this study population, doses based on calculation of regulatory factor were associated with plasma levels <2.0ng/mL (1.66±0.14 means±SE and range 0.92 - 2.0)(p<0.001) (figure 1).

Table 2. *Characteristics of patients* (n=7) *with toxic initial plasma levels*

	M ± SE	Range	
GFR(ml/min/1,73m^2)	40,45±4	29,36	55,49
RegF	2,06±0,21	1,94	3,31
Dose Baseline(mg/d)	0,196±0,025	0,125	0,25
Dosage after RegF(mg/d)	0,098±0,012	0,0625	0,125
Pdig1(ng/mL)	3,06±0,24	2,14	3,88
Pdig2(ng/mL)	1,66±0,14	0,92	2,0

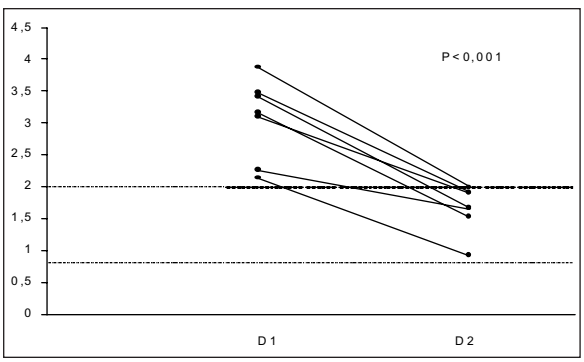

Figure 1. *Changes in serum plasma concentrations in patients with toxic initial levels based on calculation of regulatory factor (D1: initial dose, D2: dose adjusted to individual regulatory factor)*

Interestingly, in 5 of the 29 patients, the initial dose did not corresponded to that estimated by regulatory factor. With this doses, the initial serum concentration ranged between 1.67-1.88 (mean 1.8±0.4 which were close to upper therapeutic levels. According to regulatory factor digoxin serum concentration in this study group reduced to a range between 0.82 to 1.22 (1.06±0.7) (p=0.01). Correlations between digoxin plasma levels and age, weight, serum creatinine, GFR and regulatory factor in 12 of the 29 patients taking 0.125 mg after dosing adjustment are shown in table 3. Importantly GFR and regulatory factor where significantly correlated with plasma digoxin levels (figure 2), (figure 3). The strength of the association was similar for these two variables.

Table 3. *Correlation coefficients of digoxin plasma levels in 12 of the 29 patients taking 0.125 mg, after dosing modification according to calculation of regulatory factor (Reg F) with other variables in this study group*

DIGOXIN PLASMA LEVELS		
Variables	**(r)**	**(p)**
Age	**-0,25**	**NS**
Weight	**0,42**	**<0,001**
Pl.Creatinine	**0,52**	**<0,001**
GFR	**-0,65**	**<0.001**
Reg F	**0,60**	**<0,001**

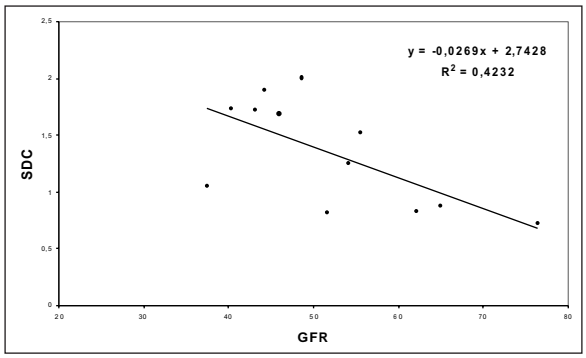

Figure 2. *Correlation between digoxin plasma levels and glomerular filtration rate (GFR) (r=-0.65, P<0.001)*

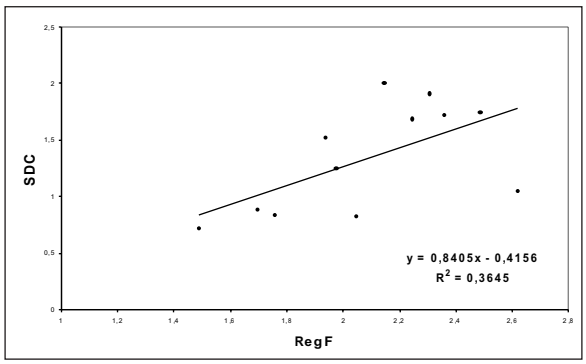

Figure 3. *Correlation between digoxin plasma levels and regulatory factor (Reg F) (r=0.60, p<0.001)*

Discussion

The present study has important clinical implications. The newly developed formula involving the creatinine clearance values estimated by Cockroft-Gault equation, in relation to normal GFR and fractional excretion by the kidneys, provided good predicted performance of serum digoxin concentration. Digoxin is eliminated primarily by renal mechanisms, both glomerular filtration and tubular excretion. Digoxin has an extremely low therapeutic index and its use should be carefully monitored by serum blood levels. In clinical practice

today most decisions involving dosing modification in patients with renal failure, use published tables of recommended dosage reduction or dosing interval lengthening based on the level of renal function indicated by creatinine clearance[9]. Such modifications are, however, rigorously based on pharmacokinetic principles and are best used when resulting plasma concentration data and clinical observation are used as necessary to further optimize therapy for the individual patients. Taking simplicity in practical use into account, the clinical application of the proposed formula will allow the accurate and rapid determination of the initial maintenance dosing regimen of digoxin, based on the individual creatinine clearance value, without actual measurement of its serum concentration. The much higher correlation between digoxin plasma levels and regulatory factor demonstrates the value of the proposed equation. Furthermore, dosing adjustment was just an approximate of dose calculated in this formula. The latter stresses the importance of this method.

The majority of the study population were elderly individuals with reduced muscle mass. The principle body reservoir is skeletal muscles. Although many individuals preserve good renal function into old age, elderly patients as a group have and increased likelihood of impaired renal excretion of drugs[10]. Even in the absence of kidney disease, renal clearance is generally reduced by about 35 to 50% in elderly patients[11]. The decrease in lean body mass, causes a decrease in distribution volume of digoxin. In this regard it is important to recognize that the reduced muscle mass of older individuals results in a reduced rate of creatinine production, meaning that a normal serum creatinine concentration can be present even though creatinine clearance is impaired[12]. Moreover hypochlorydria which is common in elderly patients reduces gastric metabolism and no renal clearance of the drugs[13]. In the proposed formula of regulatory factor, age affects not only creatinine clearance calculated by Gault-Cockroft equation, but also fractional excretion of the drug by the kidneys.

Multiple drugs interact with digoxin at multiple levels, including reduced renal tubular excretion by drugs inhibiting P-glycoprotein renal tubular transport, induction of gut P-glycoprotein , alternations in gut flora by antibiotics causing less gut metabolism of digoxin before absorption, displacement from plasma protein binding sites ,or reduction in renal function[21,22].

Patients with heart failure usually have a reduced volume of distribution and reduced renal function and both may be influenced by other treatments. Whereas the therapeutic range for serum digoxin concentration is frequently cited as 0.8-2 ng/mL, recent studies suggest an upper limit of 1.0 ng/mL for treating heart failure[14] The serum digoxin concentration required for optimal clinical efficacy and acceptance toxicity remains controversial[15]. One of the most important findings to emerge from the DIG trial was that mortality was directly related to the digoxin serum levels[16]. Studies using non invasive indices of ventricular function suggest a nonlinear relationship between the serum digoxin concentration and observed inotropic or neurohormonal antagonism, with the majority of the increase in contractility or neurohormonal effects, occurring by the time that steady state levels around 1.4ng/mL are reached[17]. This information plus DIG trial mortality data, indicates that the optimal trough digoxin serum levels is 0.5 to 1.0ng/mL[15,18].This concentration range is also the one that should be used to control the ventricular rate response to atrial fibrillation in heart failure patients, particularly since digoxin is not a very effective agent in this regard in the setting of high amount of adrenergic activity[19]. However in a multivariable Cox analysis from two randomized, double blind, placebo- controlled, digoxin withdrawal trials (PROVED –RADIANCE) the risk of worsening heart failure was significantly less (all $P<0.02$) for patients in any category of serum digoxin concentration who continued digoxin, as compared with patients withdrawn from digoxin. The beneficial effects of digoxin on common clinical end- points in patients with heart failure were similar, regardless of serum digoxin concentration[20].

In conclusion, the newly formulated equation provided good performance of serum digoxin concentration. The clinical application of the proposed equation will allow for accurate and rapid determination of the initial maintenance dosing regimen of digoxin according to individual creatinine clearance value and excretion by the kidneys . Moreover, reducing the upper limit of the therapeutic range to 1.0 ng/mL on computerized and paper laboratory report forms may guide clinicians to avoid unnecessarily high digoxin plasma levels,thus minimizing risk of digoxin toxicity without sacrifying therapeutic benefit for heart failure.

References:

1. Haji SA, Mohaved A: Update on digoxin therapy in congestive heart failure.*Am.Fam. Physician* 2000; 62: 409-416
2. Smitz TW:Pharmacokinetics,bioavailability and serum levels of cardiac glycosides *J.Am.Coll.Cardiol.* 1985; Suppl A: 43A-50A
3. Reuning RH,Geraets DR: Digoxin in Applied pharmacokinetics principles of therapeutic drug monitoring *Vancouver WA: Applied Therapeutic Inc,* 1986: 570-623
4. Cauffield JS,Gums JG, Grauer K:The serum digoxin concentration:Ten questions to ask. *Am Fam Physician* 1997; 56: 495-503
5. Uretzky BF, Young JB,Shahid F, et all:Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure:Results of the Proved trial PROVED Investigative Group. *J Am Coll Cardiol* 1993*,* 22:955-962
6. Parker M, Gheordiade M, Young JB, et all:Withdrawal of digoxin from patients with chronic heart failure traited with ACE. RADIANCE Study. *N Engl J Med.* 1993, 329:1-7
7. Reynolds DJ, Aronson JK: ABCs of monitoring drug therapy.Making the most of plasma drug concentration measurements. *BMJ* 1993, 306:48
8. Benet Z et all: Design and optimization of dosage regimens: Pharmacokinetics data, in Goodman and Gilmans.The Pharmacological Basis of therapeutics 9th ed, JG Hardman et

all(eds) New York, Mc Graw Hill, 1995, Appendix II p. 1707
9. Aronson JK; Clinical pharmacokinetics of cardiac glycosides in patients with renal dysfunction. *Clin Pharmacokin* 1983;8 155-78
10. Dall JL: Maintenance digoxin in elderly patients, *BMJ* 1970; 2 705-06
11. Sonnenblink M, Abraham AS: Digoxin treatment and control in elderly; *Isr J Med Sci:* 1985;21 276-8
12. Van der Aa GC: Pharmacokinetics of digoxin in the aged: *Tidjskr Gerontol Geriatr*. 1984; 15: 67-71
13. Hui J, Gereates DR, Chandraskaram A, et all: Digoxin disposition in elderly humans with hypochlorydria: *J Clin Pharmacol:* 1994 34;734
14. Zuccala G, Pedone C, Carosella L, Carbonin P, Berhabei R: Optimum dose of digoxin: *Lancet* 1997; 349: 1845
15. Rathore SS, Curtis JP, Wang W, Bristow MR, Krumholz HM:Association of serum digoxin concentration and outcomes in patients with heart failure: *JAMA 2002* 289: 871-888
16. Rekha G, Gorlin R, Smith T,et all:The effect of digoxin on mortality and morbidity in patients with heart failure: *N Engl J Med* 1997; 335: 525-33
17. Slatton ML, Irani WN, Hall SA, et all: Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm; *J Am Coll Cardiol 1997: 29;1206-1213*
18. Sameri RM, Soberman JE, Finch CK, Self TH:Lower serum digoxin concentrations in heart failure and reassessment of laboratory report forms: *Am J Phycisian:1999;* 32: 15-23
19. Goldman S, Probst P, Sclzer A,Cohn K:Efficacy of therapeutic serum levels of digoxin in controlling the ventricular rate in atrial fibrillation: *Am J Cardiol 1975, 35; 651-65*
20. Adams KF, Georghiade M, Uretzky BF, Patterson JH, Scwartz TA, Young JB:Clinical benefits of low serum digoxin concentration in heart failure: *J Am Coll Cardiol: 2002 Mar 20, 39(6) 954-6*
21. Nakamura T, Kakunoto M, Yamashita K, Takara K, Tanigawra Y, Sakaeda T, Okumura K:Factors influencing the prediction of steady state concentration of digoxin . *Biol Pharm Bull* 2001; 24: 403-8
22. Fomm MF, Kim RB, Stein SM, et all: Inhibition of P-glycoprotein mediated drug transport: A unifying mechanism to explain the interaction between digoxin and quinidine: *Circulation* 1989, 99:552-557

Corresponding author: Efstratopoulos A.D, 20, Vas. Irakliou str., Athens-10608 - Tel & Fax: 210-8226488
e-mail: arlemio@hol.gr