

## Evaluation of Digoxin Dosing in Two Egyptian Hospitals A Pilot Study

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**Abstract:** Introduction: Digoxin is one of the digitalis cardiac glycosides indicated in heart failure and atrial fibrillation. Due to individual variability in digoxin pharmacokinetics, digoxin doses need to be calculated based on patient's weight, renal function and indication. Furthermore, therapeutic drug monitoring of digoxin is highly recommended. However, it is common practice among cardiologists in Egypt to prescribe one and the same dose and dosing regimen to all patients for both heart failure and atrial fibrillation. Objective: The objective of this study is to predict digoxin plasma concentrations at digoxin steady state to assess the appropriateness of digoxin dosing. Methods: Digoxin plasma concentrations were calculated for 14 patients using prescribed digoxin doses and patient specific data and compared to target digoxin concentrations. Results: Patients had generally digoxin levels within the recommended therapeutic levels not taking into consideration the interrupted dosing schedule followed in Egyptian hospitals which might lead to sub-therapeutic levels. However, patients with reduced renal function had predicted levels higher than the recommended dosing range. Conclusion: Prescribing policy for digoxin in Egypt needs to be re-evaluated. Correct doses can easily be calculated using simple pharmacokinetic equations or computer programs to achieve therapeutic digoxin levels for different indications. The role of therapeutic drug monitoring should also be emphasized to ensure optimum therapeutic outcome and safety.

**Key words:**

### INTRODUCTION

Digoxin is one of the digitalis cardiac glycosides indicated in heart failure and atrial fibrillation. The recommended therapeutic range is 0.8 to 2 µg/L. However, patients with atrial fibrillation might require a concentration greater than 2 µg/L (Winter 2004). Due to individual variability in digoxin pharmacokinetics, the narrow therapeutic index and toxicity, digoxin doses need to be calculated based on patient's weight, renal function and indication. Furthermore, therapeutic drug monitoring of digoxin is highly recommended in monitoring toxicity, assessing patient compliance and in cases of therapeutic failure. However, it is common practice among cardiologists in Egypt to prescribe one and the same dose and dosing regimen to all patients for both heart failure and atrial fibrillation. In addition, a digoxin "holiday" is given where the patient is given the dose only five days a week to minimize digoxin toxicity due to the lack of therapeutic drug monitoring. Although this might be beneficial in patients with renal failure to reduce toxicity, it is not clear whether this "holiday" is justified in all cases since the digoxin plasma level might decrease to below therapeutic levels.

The aim of this pilot study is to evaluate this dosing regimen by predicting the expected steady state concentration from the given dose based on patient specific parameters.

### MATERIALS AND METHODS

The research was performed according to the ethical principles of the Declaration of Helsinki (Rickham 1964). Patients less than 16 years were excluded from this monitoring process. Fourteen in-patients on digoxin tablets in Kasr Al Aini (educational) hospital and Al Salam (private) hospital were studied. The data collected was: gender, age, weight, height, serum creatinine, medical condition and other drugs the patient is taking. All patients were prescribed a dose of 0.25 mg oral digoxin tablets daily except Thursday and Friday when no dose was given (digoxin "holiday").

To be able to calculate the expected digoxin steady-state concentration ( $C_{ss}$ ) from the given dose total digoxin clearance was calculated from the following equation (Winter 2004):

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$$\text{Total } Cl_{\text{digoxin}} \text{ (mL/min)} = [(0.33 \text{ mL/kg/min)} \times (\text{weight in kg})] + 0.9 \times Cl_{\text{cr}} \text{ in mL/min}$$

where  $Cl_{\text{digoxin}}$  is the total digoxin clearance and  $Cl_{\text{cr}}$  is the creatinine clearance. The above equation is used provided that the patient is suffering from congestive heart failure.

$Cl_{\text{cr}}$  was calculated from Cockcroft- Gault equation(Cockcroft and Gault 1976) :

$$Cl_{\text{cr}} \text{ for males (mL/min)} = \frac{(140 - \text{Age}) \times (\text{Weight})}{72 \times SCr_{\text{ss}}}$$

$$Cl_{\text{cr}} \text{ for females (mL/min)} = \frac{0.85 \times (140 - \text{Age}) \times (\text{Weight})}{72 \times SCr_{\text{ss}}}$$

where weight is the ideal body weight in kg calculated for male or female if patient is not obese. In case of obesity (defined as an increase in weight exceeding 20 % of ideal body weight), an adjusted body weight is used. Adjusted body weight is the ideal body weight plus 40% of difference between actual body weight and ideal body weight.

The steady-state concentration was then calculated as follows:

$$C_{\text{ss}} = \frac{F \times \text{Dose} / \tau}{\text{Total } Cl_{\text{digoxin}}}$$

where F is the bioavailability of the tablets (f = 0.8) and  $\tau$  is the dosing interval (1 day). The  $C_{\text{ss}}$  was then compared to the therapeutic range.

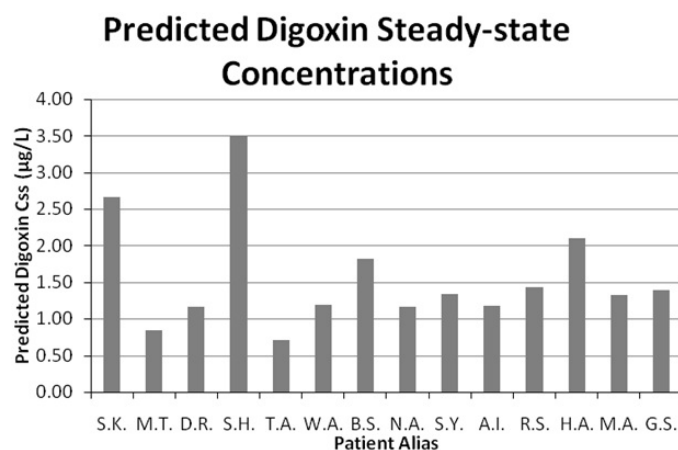
### RESULTS AND DISCUSSION

Eight female and 6 male patients were studied. They all suffered from congestive heart failure. Twelve of the fourteen patients were suffered from and were treated for atrial fibrillation as well. One patient suffered from renal failure. The demographics for the patients are shown in Table 1. Predicted  $C_{\text{ss}}$  are shown in Figure 1.

The predicted steady-state concentrations ranged from 0.7 to 3.5 $\mu\text{g/L}$ . One patient treated for atrial fibrillation had predicted  $C_{\text{ss}}$  of less than 0.8  $\mu\text{g/L}$ . Ten patients had a predicted  $C_{\text{ss}}$  between 1 and 2 $\mu\text{g/L}$  with only one patient exceeding 1.5 $\mu\text{g/L}$ . One patient with reduced renal function (calculated Creatinine clearance of 37 mL/min) showed a predicted  $C_{\text{ss}}$  of 2.66 $\mu\text{g/L}$ . The patient who had renal failure had diminished clearance and hence a higher predicted  $C_{\text{ss}}$  of 3.5 $\mu\text{g/L}$ .

**Table 1:** Patient demographics (gender, age, weight, height and conditions other than congestive heart failure), serum creatinine levels (mg/dL), predicted digoxin clearance (mL/min) and predicted steady state concentration

Patient Alias	Gender	Age (years)	Weight (kg)	Height (cm)	Serum Creatinine (mg/dL)	Conditions	Predicted Digoxin Clearance (mL/min)	Predicted Digoxin Steady State Concentration ( $\mu\text{g/L}$ )
S.K.	f	63	55	160	1.3	Chest infection, diarrhea, hypertension	52	2.66
M.T.	f	39	55	160	0.4	Mitral stenosis, atrial fibrillation, chest infection	164	0.85
D.R.	f	35	57	160	0.6	Mitral stenosis, atrial fibrillation, chest infection	120	1.16
S.H.	f	60	70	157	2.2	Renal failure, atrial fibrillation, chest infection	40	3.50
T.A.	f	50	65	160	0.3	Atrial fibrillation	194	0.72
W.A.	f	32	78	155	0.7	Atrial fibrillation, mitral stenosis, rheumatic heart disease	116	1.19
B.S.	f	70	68	172	0.9	Atrial fibrillation	76	1.82
N.A.	f	17	55	160	0.7	Atrial fibrillation, mitral valve replacement	119	1.16
S.Y.	m	45	70	170	1	Ischemic heart disease	104	1.33
A.I.	m	42	75	170	0.9	Mitral valve replacement, atrial fibrillation, chest disease	118	1.18



**Fig. 1:** Predicted steady-state concentrations for fourteen patients in Egyptian hospitals. The concentrations are calculated as discussed in the methods section. The x-axis depicts the patient aliases and the y-axis is the predicted steady-state concentration in microgram per liter.

#### Discussion:

Digoxin has been used as a treatment of heart failure for the past 200 years (Demers, McKelvie *et al.* 1999). The therapeutic range of digoxin in plasma is 0.5 to 2 µg/L. Patients treated for heart failure are usually adjusted on the lower side of the range (0.5 to 1 µg/L) (Terra, Washam *et al.* 1999) and those treated for atrial fibrillation usually closer to 2 µg/L (Chamberlain, White *et al.* 1970).

With this narrow therapeutic range, a long half-life of about 48 hours in patients with normal renal function (Winter 2004), and toxicity occurring during treatment, digoxin dosing is usually tailored to patients according to their medical status and kidney function. Patients are monitored for digoxin toxicity symptoms and in many cases the blood levels are measured. However, in Egyptian hospitals the policy is to give one dose for all the patients (0.25 mg orally) and the dose is given daily except for Thursdays and Fridays to minimize patient toxicity by preventing the plasma levels from exceeding the therapeutic range.

In this study, we predicted digoxin steady-state concentrations in 14 patients in two Egyptian hospitals based on patient information. For most of the patients the predicted C<sub>ss</sub> was within 1-2 µg/L. However, a C<sub>ss</sub> of 2.66 and 3.5 µg/L were predicted for two patients. The first patient was only treated for CHF, not warranting such high digoxin level. The high level was probably due to renal impairment since this patient had a calculated creatinine clearance of 37 mL/min. A lower digoxin dose might still be beneficial and less prone to inducing toxicity (Rathore, Curtis *et al.* 2003). The patient with predicted C<sub>ss</sub> of 3.5 µg/L suffered from renal failure which was not taken into account when dosing. Since a large fraction of digoxin is cleared renally, patients with renal dysfunction need to have a reduced dose.

Two patients had a predicted C<sub>ss</sub> of less than 1 µg/L, one of which was treated for atrial fibrillation. AF patients usually need therapeutic concentrations close to 2 µg/L (Chamberlain, White *et al.* 1970).

It has to be noted that the predicted C<sub>ss</sub> levels are dependent on the fact that patients with congestive heart failure have reduced clearance of digoxin. Patients without congestive heart failure would have had lower predicted C<sub>ss</sub>, which in addition to the drug "holiday" might result in sub-therapeutic levels.

It is not clear whether the digoxin "holiday" is effective in reducing toxicity of digoxin in patients with normal renal function. The digoxin plasma levels might not be maintained within the therapeutic range due to interrupted dosing. This would be even more pronounced in patients with atrial fibrillation who need higher therapeutic levels. The digoxin "holiday" has been previously studied in the literature (Sadray, Namazi *et al.* 2003). Although the authors recommended further studies on interrupted dosing, it was concluded that continuous dosing is recommended rather than interrupted dosing since around 27% of studied patients on 0.25 mg oral digoxin 5 days a week had sub-therapeutic digoxin levels.

The therapeutic range has been established more to limit toxicity than to define efficacy (Terra, Washam *et al.* 1999) hence, clinical monitoring is indispensable. The need for therapeutic drug monitoring arises in the following cases: confirmation of toxicity, assessing factors altering pharmacokinetics, therapeutic failure and medication compliance (Barclay and Begg 2003).

These results need to be confirmed with a larger study involving a wider sample of patients and measurement of plasma digoxin levels pre- and post-holiday. Our recommendations to the Egyptian hospitals

regarding digoxin dosing are: 1- Caution needs to be exercised when dealing with patients having reduced renal function or renal failure where digoxin holiday might not be enough to avoid toxicity and a reduced dose might be needed as well, 2- Digoxin level monitoring in Egyptian hospitals needs to be adopted especially for this patient population, 3-The interrupted dosing schedule has to be re-evaluated to ensure therapeutic levels.

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