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Short Communication

Serum Digoxin Concentrations: A Retrospective Analysis

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Abstract

The use of digoxin is limited by its narrow therapeutic index. American and European guidelines for the management of heart failure and atrial fibrillation recommend targeting a serum digoxin concentration (SDC) between 0.5 and 0.9ng/ml. The aim of the study was to retrospectively analyse SDCs and to assess compliance to the SDC target range recommended in the guidelines.

SDCs recorded at the hospital Pathology laboratory between January 2008 and December 2017 were analysed according to gender, age, origin of request, specialty of referring physician and reason for request, and were compared to the SDC target range. Serum potassium (K^+) levels and estimated glomerular filtration rate (eGFR) were analysed for SDCs recorded in 2017.

A total of 19,065 SDCs from 6,107 patients (65% female, mean age 78 ± 11 years) were analysed. Mean SDC was 1.31 ± 1.01ng/ml (range <0.1-20.0ng/ml). Variations from the recommended SDC target range (0.5-0.9ng/ml) were: 32% within, 11% below and 57% above target range. Mean serum K^+ level was significantly higher ($p=0.020$) in patients with SDC ≥ 2.0ng/ml (4.66 ± 0.66) compared to patients with SDC ≤ 0.9ng/ml (4.54 ± 0.73mEq/L). Mean eGFR was significantly lower ($p<0.001$) in patients with SDC >0.9ng/ml (66.76 ± 36.43) and ≥ 2.0ng/ml (64.39 ± 34.23) compared to patients with SDC ≤ 0.9ng/ml (73.84 ± 35.21mL/min/1.73m²).

The mean SDC observed was higher than the upper limit of the recommended target SDC range. Further investigation to establish the clinical significance of the observed SDC findings on patient outcomes is warranted.

ABBREVIATIONS

ACCF: American College of Cardiology Foundation; AHA: American Heart Association; DIG: Digitalis Investigation Group; eGFR: estimated Glomerular Filtration Rate; ESC: European Society of Cardiology; HFSA: Heart Failure Society of America; SD: Standard Deviation; SDC: Serum Digoxin Concentration

INTRODUCTION

Digoxin is one of the oldest drugs still in use in cardiology for the management of heart failure and atrial fibrillation [1,2]. The Heart Failure Society of America (HFSA), the American College of Cardiology Foundation/American Heart Association (ACCF/AHA), and the European Society of Cardiology (ESC) guidelines recommend digoxin to be considered in patients with heart failure with reduced ejection fraction in sinus rhythm and who remain symptomatic despite treatment with first and second line options, with the goal to reduce the risk of hospitalisation [3-5]. The ACCF/AHA assigns use of digoxin a Class IIa, level of evidence B recommendation [4], and the ESC guideline includes digoxin use under 'Other treatments with less-certain benefits', with a Class IIb, level of evidence B recommendation [5]. In atrial fibrillation, both the ACCF/AHA guideline and the ESC guideline endorse digoxin use as an adjunct to beta-blocker therapy for heart rate control, as a Class IIa, level of evidence B, anda Class I, level of evidence B recommendation, respectively [6,7].

Digoxin is a high-alert drug owing to its complex pharmacokinetic profile, narrow therapeutic window and multiple drug interactions, hence serum digoxin concentration (SDC) determinations are taken to monitor forsigns of toxicity and sub-therapeutic levels [8-10]. The upper limit of the traditional SDC range was established as 2.0ng/ml [10]. Although patients do not commonly manifest toxic effects if SDC is maintained below 2.0ng/ml, digoxin toxicity may still occur, especially in the presence of electrolyte imbalance and in patients with renal impairment including frail elderly patients likely to have reduced renal function [10-12]. Hypokalaemia and hyperkalaemia are associated with digoxin toxicity [12,13], and serum potassium (K^+) monitoring is important in patients taking digoxin since SDC determinations considered in the absence of corresponding serum K^+ levelsdo not provide sufficient information for clinical

auctioning [14]. As regards renal function, reduced digoxin elimination may result in SDC exceeding the recommended therapeutic range which necessitates adjustment in digoxin dosing regimens [8,10,13].

Various studies have demonstrated that heart failure patients dosed to lower SDCs below an upper limit of 0.9-1.0ng/ml experienced improved symptom control, fewer hospitalisations, a decrease in all-cause mortality and less safety concerns compared to patients with higher SDCs [10,15-22]. In light of this evidence, the HFSA and ACCF/AHA guidelines for heart failure and the ESC guideline for atrial fibrillation presently recommend maintaining SDC between 0.5 and 0.9 ng/ml [3,4,7].

The aim of the study was to analyse SDCs recorded in a Pathology laboratory affiliated with an acute public hospital and to assess compliance to the SDC target range recommended in the guidelines.

MATERIALS AND METHODS

Study setting

Data for this retrospective study was collected from the Pathology Laboratory of the Department of Pathology at Mater Dei Hospital in Malta.

Ethical approval

The research protocol was approved by the University of Malta Research Ethics Committee.

Analysis of serum digoxin concentrations

SDCs recorded at the Pathology Laboratory over a ten-year period (1 January 2008 to 31 December 2017) were retrieved and analysed according to gender, age, origin of SDC request, specialty of requesting physician and reason for SDC request. The origin of SDC request within the hospital was classified into five categories namely; Accident and Emergency Department, cardiology inpatients and outpatients, and inpatients and outpatients from specialties other than cardiology. The reason for SDC request was classified into four categories namely routine testing, suspicion of digoxin toxicity (including cardiac, central nervous system and gastro-intestinal symptoms), electrolyte imbalance and reason not recorded.The SDC levels were compared to the SDC target range recommended in the HFSA, ACCF/AHA and ESC guidelines [3,4,7], and were classified as below the lower limit of the target range (<0.5ng/ml), within range (0.5-0.9 ng/ml), or above the upper limit of the target range (>0.9ng/ml).

For SDCs recorded over the one-year period of 1 January to 31 December 2017, serum potassium level (K^+) levels and estimated glomerular filtration rate (eGFR) results were analysed and the relationship with SDC levels was assessed.

Statistical analysis was performed using the JASP graphical program. Descriptive statistics were generated for the SDC results and patient variables were analysed. Mean, median, mode, standard deviation and range were calculated. Given that the patient variables had a fairly normal distribution, comparison of means was carried out using two parametric tests. The One-sample t-test was used to compare mean SDC with the upper limit of the guideline-recommended target range (0.9ng/ml) and the Independent Samples t-test was used to compare mean SDC between two independent groups, such as between male and female gender and between age groups. For both tests a 0.05 level of significance was adopted.

RESULTS AND DISCUSSION

A total of 19,065 SDC levels from 6,107 patients were analysed. Sixty-three percent (n=3,970) of the patients were female and 35% (n=2137) were male. Forty-eight percent (n=2,931) of the patients were over 80 years of age. The mean age of the patients was 78 ± 11 years (median 80, mode 81, range 1-117 years).

The largest number of SDCs were processed in 2012 (12%, n=2,256). The mean number of SDC requests per year was 1,907 ± 182, with a mean of 980 ± 80 individual patients tested annually. The mean SDC was 1.31 ± 1.01 ng/ml (range <0.1-20.0, median 1.1, mode 0.8ng/ml). The highest mean SDC was observed in 2011 (1.48 ± 1.25, range <0.10-20.0ng/ml) and the lowest mean SDC was observed in 2009 (1.18 ± 0.90, range <0.10-8.7ng/ml). The mean SDC significantly exceeded the upper limit of the target SDC range (0.9 ng/ml) in each year ($p<0.001$) (Table 1). The percentage distribution of SDCs by origin of request within the hospital was: Accident and Emergency department (42%), in patients from specialties other than cardiology (33%), cardiology inpatients (16%), outpatients from specialties other than cardiology (9%) and cardiology outpatients (0.1%).

Compared to the HFSA, ACCF/AHA and ESC guidelines [3,4,7], 32% (n=6,101) of the SDCs were found to be within the target range (0.5-0.9 ng/ml) and 68% (n=12,964) of the SDCs were either below the lower limit (11%, n=2,097) or above the upper limit (57%, n=10,867) of the target range. Seventeen percent (n=3,241) of the SDCs were ≥ 2.0ng/ml (Figure 1). The mean SDC (1.31ng/ml) was significantly higher than the upper limit of the target range (0.9ng/ml) ($p<0.001$). The impact of elevated SDC levels on patient outcomes was not assessed.

Following the large-scale Digitalis Investigation Group (DIG) trial in 1997 [23],various studies have provided evidence that SDC levels higher than 0.9-1.2ng/ml may be harmful to the digoxin-treated patient and advocated that maintaining SDC below an upper limit of 0.9ng/mL, specifically between 0.5 and 0.9ng/mL, optimises digoxin effectiveness and decreases hospitalisation, morbidity and mortality [15-19,24,25]. In a 2016 editorial

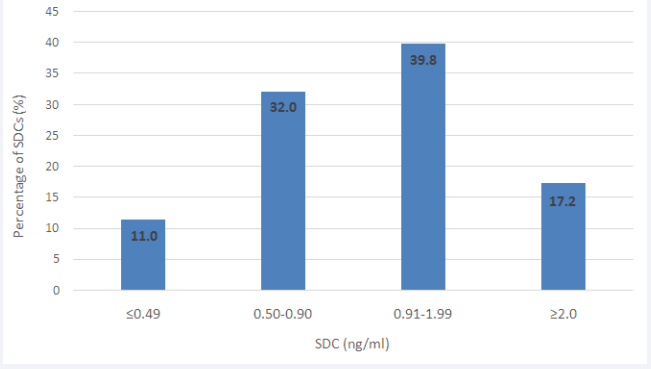

Figure 1 Classification of SDC determinations according to target range (0.5-0.9ng/ml) specified in guidelines [3,4,7] (N=19,065).

Table 1: Descriptive statistics of SDC determinations by year (N=19,065).

Year	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Numberof SDCs	1,936	1,793	1,986	2,149	2,256	1,892	1,740	1,836	1,800	1,677
Mean ± SD(ng/ml)	1.23 ± 0.97	1.18 ± 0.90	1.28 ± 0.97	1.48 ± 1.25	1.40 ± 1.1	1.24 ± 0.91	1.30 ± 0.85	1.29 ± 0.85	1.29 ± 0.93	1.39 ± 1.19
Median (ng/ml)	1.0	1.0	1.1	1.2	1.1	1.0	1.1	1.1	1.0	1.1
Mode (ng/ml)	0.9	0.5	0.8	0.8	0.8	0.8	0.8	0.9	0.7	0.7
Minimum-Maximum (ng/ml)	<0.10-11	<0.10-8.7	<0.10-8.8	<0.10-20.0	<0.11- 2.7	<0.11-5.1	<0.18-4.0	<0.11-0.2	<0.11-0.5	<0.11-5.9

SDC: Serum Digoxin Concentration; SD: Standard Deviation

Table 2: Mean SDC by age group (N=19,065).

Age group *in years*	**Percentage of patients**	**Number of SDCs**	**Mean SDC (±SD)** *in ng/ml*
1-50	1	257	1.06 (±1.22)
51-60	4	770	1.26 (±0.96)
61-70	13	2,533	1.29 (±1.00)
71-80	34	6,372	1.31 (±1.04)
>80	48	9,133	1.33 (±1.07)

comment in the European Journal of Heart Failure, Ambrosy and Gheorghiade were skeptical regarding the feasibility and clinical value of dosing digoxin according to this target SDC and suggested additional prospective studies to establish the optimal dosing of digoxin and the role of ongoing SDC monitoring in routine clinical practice [26].

In the present study, the mean SDC in females (1.36 ±1.02 ng/ml) was significantly higher than the mean SDC in males (1.22 ± 0.98ng/ml) (p<0.001). However, the digoxin treatment-gender interaction with respect to patient outcomes was not evaluated. In a post hoc analysis of DIG trial data in 2002, Rathore et al., concluded that the effect of digoxin therapy differs between men and women and a 5.8% absolute increase in the all-cause death rate among females on digoxin compared to their male counterparts was reported [27]. This finding was not replicated in other studies which found no evidence that women treated with digoxin fared worse than their male counterparts, particularly in terms of an increased mortality risk [16,17,28,29].

The highest mean SDC (1.33 ± 1.07ng/ml) in the present study was observed in patients older than 80 years. Mean SDC was >0.9ng/ml in all age groups and mean SDC was significantly higher (p=0.001) in patients >60 years (1.31 ± 1.05ng/ml) than in patients ≤ 60 years (1.20 ± 1.08ng/ml) (Table 2). In another post hoc analysis of the DIG trial data in 2007 [18], a higher number of patients ≥ 65 years compared to patients younger than 65 years were observed to have a SDC ≥ 1.0ng/ml, however this finding was not significant. As regards the importance of maintaining SDC determinations within the recommended SDC range in the elderly, the post hoc analysis showed that chronic heart failure geriatric patients with SDC between 0.5 and 0.9ng/ml had significantly reduced all-cause mortality and heart failure hospitalisation and a lower percentage of patients with SDC between 0.5 and 0.9ng/ml compared to SDC ≥ 1.0ng/ml were hospitalised for suspected digoxin toxicity (1.3%/2.2%). The post hoc analysis identified low-dose digoxin (≤ 0.125mg/day) as the strongest independent predictor of low SDC [18]. The digoxin dose was not available to be correlated to the SDC determinations in the present study.

The present study identified general medicine (25%), nephrology (11%) and cardiology (9%) as the top three specialties requesting SDC levels. This is an expected finding since general medicine and cardiology are the specialties primarily involved in prescribing drugs for heart failure and atrial fibrillation, and patients with renal disease under the care of nephrologists require SDC monitoring for patient safety with digoxin use. Most SDCs in the present study were requested as routine monitoring (35%) or due tosuspicion of digoxin toxicity due to cardiac, central nervous system and gastro-intestinal symptoms (34%). These findings are similar to a study by Orrico et al., in 2011[14], which showed that SDCs were commonly measured as part of routine monitoring and to confirm signs and symptoms of toxicity. The authors stated that routine monitoring is considered to be an inappropriate indication for SDC testing which does not lead to treatment modifications, particularly when not accompanied by higher quality markers for digoxin toxicity, such as serum potassium levels and renal function parameters [14].

In the present study, the number of SDCs with concurrent serum K^+ levels extracted was 1,406 out of the total 1,677 SDCs in 2017. The mean serum K+ level was 4.53 ± 0.69mEq/L (median 4.52, mode 4.17, range 2.75-9.32mEq/L) and the corresponding mean SDC was 1.41 ± 1.19ng/ml (median 1.1, mode 0.9, range <0.01-15.9ng/ml). There was no statistically significant difference (p=0.103) in mean serum K^+ level between patients with SDC ≤ 0.9ng/ml (4.54 ± 0.73mEq/L) and patients with SDC >0.9 but <2.0ng/ml (4.53 ± 0.67mEq/L). Mean serum K^+ level was significantly higher (p=0.020) in patients with SDC ≥ 2.0 ng/ml (4.66 ± 0.66mEq/L) compared to patients with SDC ≤ 0.9ng/ml (4.54 ± 0.73mEq/L).

As regards renal function, the number of SDCs with

corresponding eGFR results extracted was 1,439 out of the total 1,677 SDCs in 2017. The mean eGFR was 69.6 ± 36.1mL/min/1/73m^2 (median 67, mode 60, range 5-358mL/min/1/73m^2) and the corresponding mean SDC was 1.41 ± 1.19ng/ml (median 1.1, mode 0.9 ng/ml, range <0.01-15.9). Mean eGFR was significantly lower ($p<0.001$) in patients with SDC >0.9ng/ml (66.76 ± 36.43) and in patients with SDC ≥ 2.0ng/ml (64.39 ± 34.23) compared to patients with SDC ≤ 0.9 ng/ml (73.84 ± 35.21mL/min/1.73m^2). Similarly, in the study by Ahmed in 2007, patients with SDC ≥ 1.0ng/ml had lower eGFR compared to patients with SDC between 0.5 and 0.9ng/ml [18]. It is reported that quality initiatives related to the yearly therapeutic drug monitoring parameters for digoxin require the routine measurement of renal function and serum potassium level with SDC measurement to provide clinically actionable information [14], such as intermittent digoxin dosing in patients with renal impairment [22].

Healthcare professionals involved in digoxin use monitoring need to be aware of chronic digoxin toxicity irrespective of whether SDCs fall within the endorsed target range. Serum level monitoring is suggested at the start of therapy, during times of changes in physiological parameters and when adding, adjusting or eliminating medicines which may potentially interact with digoxin. Personalisation of digoxin dosing in accordance with various patient-specific considerations, including age, renal function, frailty, electrolyte levels, comorbidities and concomitant medications, is recommended [13,30].

LIMITATIONS

The authors acknowledge the following limitations of this retrospective study namely, unavailability of the timing of sample collection for SDC determination vis-à-vis digoxin dose administration, the lack of clinical data regarding indication for digoxin, dose and patient outcomes, and no information on whether SDC results were acted upon when outside the target range.

CONCLUSIONS

The mean SDC over the ten-year period studied was significantly higher than the upper limit of the target SDC range recommended in the guidelines for heart failure and atrial fibrillation. This finding is discordant with clinical evidence which demonstrates that digoxin at a low serum concentration is effective in reducing hospitalisations and mortality, and that maintaining low serum concentrations is important for the safety of continued digoxin use in all populations, including the elderly. Further prospective investigation to establish the clinical significance of the observed signals on patient outcomes is warranted.

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AUTHOR CONTRIBUTIONS

The study aims were elaborated by all the authors. Mr John Vella carried out the study under the supervision and guidance of Professor Anthony Serracino-Inglott and Dr. Francesca Wirth. Mr Vella and Dr. Wirth drafted the manuscript and Professor Serracino-Inglott and Professor Lilian M. Azzopardi critically reviewed the manuscript.

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