Relationship Between Serum Digoxin Concentrations and Clinical Symptoms of Heart Failure in Pediatric Patients with Heart Disease

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ABSTRACT

The objective of this study was to evaluate relationship between 3 SDC (serum digoxin concentration) subgroups (low, middle and high level) and clinical symptoms of HF (heart failure) in pediatric patients with heart disease. This study was carried out in 175 Thai pediatric patients who were treated with digoxin in routine care. SDCs on steady state were divided into 3 subgroups; low level: <0.8, middle level: 0.8 to 1.2 and high level: >1.2 µg/L. Clinical symptoms of CHF (congestive heart failure) were assessed and categorized by pediatric cardiologist, by using modified Ross score; 0-2: no CHF, 3-6: mild CHF, 7-9: moderate CHF, and 10-12: severe CHF. The outcome of this study was graded no CHF (total score 0-2). The association between 3 SDC subgroups and clinical symptoms of HF were evaluated by multiple logistic regression analysis. Graded no CHF patients in the group of low, middle and high level were 94(72.3%), 14(48.3%), and 9(56.3%), respectively. Multivariable analysis by binary logistic regression indicated that patients in middle and high level groups were approximately 2.00 and 1.32 times, respectively, as likely to be graded CHF as a similar patient in low level group (odds ratio [OR]: 2.00, 95% CI: 0.79-5.00, p=0.14 and OR: 1.32, 95% CI: 0.37-4.67, p=0.67, respectively). However, there was no statistically significant relationship. The other significant factors for clinical symptoms of HF included age (OR: 0.91, 95% CI: 0.83-0.98, p=0.017), surgical treatment (OR: 0.44, 95% CI: 0.21-0.92, p=0.029) and respiratory tract infection (OR: 5.56, 95% CI: 1.72-16.67, p=0.004). This finding showed the absence of significant relationship between SDC subgroups and clinical symptoms of HF. Increasing of age and surgical treatment for removing the defect significantly increased the success of heart failure control whereas codisease, especially respiratory tract infection, precipitated the clinical symptoms of heart failure. Hopefully, the use of digoxin doses to achieve low concentration of ≤0.8 µg/L will associated with favorable clinical effects and may also reduce toxicity.

Key words: Digoxin, Pediatrics, Heart failure, Low serum digoxin concentration

INTRODUCTION

Digoxin, a cardiac glycoside, is most commonly used in the treatment of heart failure and cardiac rhythm disturbance in neonates, infants and children (Latifi et al., 2000). The yearly incidence of heart failure (HF) is as high as 20% of patients with congenital heart disease (Talner et al., 2000). Usually, laboratories recommend a therapeutic range between 0.5 and 2 μg/L in adults (Mutnick, 1995). Digitalis Investigation Group (DIG) trial revealed that serum digoxin concentrations (SDCs) of 0.5-0.8 μg/L likely constitutes the optimal therapeutic range for men with stable heart failure (Rathore et al., 2003). In addition, there was no difference in developing worsening heart failure among subgroups of low (≤0.9 μg/L), middle (0.9 to 1.2 μg/L) and high (>1.2 μg/L) level (Adam et al., 2002). In pediatrics, although high serum levels of digoxin are better tolerated than in adults, some studies found that serum levels higher than 2 μg/L were often associated with toxicity and did not demonstrate the adequate inotropic response. Routinely therapeutic range of digoxin in pediatrics is 0.8-2.0 μg/L (Tange et al., 1994; McEvoy, 2002; Soldin and Soldin, 2002). However, both upper and lower values of therapeutic range used in pediatrics are usually derived from adult studies despite the fact that drug effects in infants and children may differ from those in adults (Tange et al, 1994). According to new findings in adult, the need for more detail in pediatrics is necessary. Unfortunately, there are no data of low SDC for the treatment of CHF in these patients. Therefore, this study was undertaken to evaluate relationship between 3 SDC subgroups (low, middle and high level) and clinical symptoms of HF in pediatric patients with heart disease by using clinical routine data.

MATERIALS AND METHODS

Patients and Ethics

The clinical and blood sampling data were collected from 175 pediatric patients (70 boys and 105 girls) in Queen Sirikit Heart Center of the Northeast, Khon Kaen University, Thailand, during 2004 to 2006. All patients had taken recommended doses of digoxin for at least 1 week with good compliance for heart disease, such that all concentrations were considered to be on steady state. Blood samples were drawn after taking the last digoxin dose at least 6 hours. The study was approved by the Ethic Committee of Human Research, Faculty of Medicine, Khon Kaen University. Informed consent was obtained from their parent(s) or caregiver(s) to participate in the study. Age, gender, body weight, height, underlying diseases, vital sign, laboratory data, dosage regimen of digoxin, date and time of digoxin administration, concomitant drugs, last date and last time of digoxin administration before blood sampling, date and time of blood sampling, SDC and clinical symptoms of heart failure were collected from each patient.

Clinical outcome

Clinical symptoms of heart failure of all patients were evaluated and monitored by pediatric cardiologist, using monitoring signs and symptoms of heart failure form. Grading the severity was assessed by clinical score modified from Ross, Reithmann et al. and Laer et al. for infants and children (Laer et al., 2002; Mir et al., 2002). Variables included diaphoresis, tachypnea, breathing with abdominal retractions, respiratory rate, heart rate and hepatomegaly. Total score of grading severity of 0-2, 3-6, 7-9 and 9-12 referred to no CHF, mild CHF, moderate CHF and severe CHF, respectively.

Digoxin assay

SDCs were determined by the fluorescence polarization immunoassay (FPIA) technology, using TDx analyzer from Abbot Laboratories (TDx digoxin-II), Abbot Park, IL, U.S.A. located at Academic Research Tool, Faculty of Pharmaceutical Sciences, Khon Kaen University. Sensitivity is defined as the lowest measurable level which can be distinguished from zero with 95% confidence, it is determined to be 0.2 μg/L. The typical yield coefficient of variation (CV) was less than 8%.

Serum digoxin concentrations subgroups

SDCs on steady state were divided into 3 subgroups: low level (<0.8 μg/L), middle level (0.8-1.2 μg/L) and high level (>1.2 μg/L).

Statistical analysis

Patient characteristics were described as mean?SD and percentage. A multivariable analysis by multinomial logistic regression model was evaluated to determine the association between 3 SDC subgroups (low, middle and high level group) and clinical symptoms of HF (no CHF, mild CHF, moderate CHF and severe CHF). The following variables were considered as potential predictors for clinical symptoms of HF: age, gender, surgical treatment, patient status (outpatient or inpatient), type of heart disease (simple or complex), receiving spironolactone, thaizide diuretics, loop diuretics, angiotensin- converting enzyme inhibitors (ACEIs) and codisease (respiratory tract infection or other infections).

RESULTS

The patient characteristics are presented in Table 1. One-hundred-and-seventy-five Thai pediatric patients with mean age±SD of 6.3±4.7 years and mean weight±SD of 18.3±12.5 kg were assessed. One-hundred-and-forty-eight SDCs and 27 SDCs were collected from admission and outpatient clinic, respectively. There were 66.3% of simple heart defect patients and 33.7% of complex heart defect patients. There were 50.9% of patients considered for surgery of a heart defect. The percentage of patients who took spironolactone, thiazide diuretics, loop diuretics and ACEIs were 2.3%, 50.9%, 19.4% and 39.4%, respectively. There were 11.4% and 2.9% of patients who had respiratory tract infection and other infections, respectively, during SDC and clinical symptoms of HF assessment. According to

SDC subgroups dividing, SDCs in low, middle and high level were 130(74.3%), 29(16.6%) and 16(9.1%), respectively. The numbers of patients in moderate and severe CHF groups were small. None of patient was categorized into severe CHF group (total score 10-12) and there were only 3 patients in moderate CHF group (total score 7-9), therefore, clinical symptoms of heart failure were categorized into 2 groups: no CHF (total score 0-2) and CHF group (total score >2). Graded no CHF patients in each group, low, middle and high level, were 72.3%, 48.3% and 56.3%, respectively.

Multivariable analysis by binary logistic regression demonstrated that there was poor relationship between SDC subgroups and clinical symptoms of HF. The patients in middle level group was approximately 2.00 times as likely to be graded CHF as a similar patient in low level group (odds ratio [OR]: 2.00, 95%CI: 0.79-5.00, p=0.14). The patients in high level group was approximately 1.32 times as

Table 1. Patient characteristics.

Characteristics	Patients N (%)			
	Low level (<0.8 µg/L)	Middle level (0.8-1.2 µg/L)	High level (>1.2 µg/L)	Total
Number of patient	130 (74.3)	29 (16.6)	16 (9.1)	175
Age (year±SD)	7.1±4.6	4.0±4.2	4.4±4.6	6.3±4.7
Weight (kg±SD)	19.9±12.2	12.4±11.8	15.5±13.5	18.3±12.5
Patient status				
Outpatient	117 (90)	21 (72.4)	10 (62.5)	148 (84.6)
Inpatient	13 (10)	8 (27.6)	6 (37.5)	27 (15.4)
Gender				
Boy	50 (38.5)	12 (41.4)	8 (50)	70 (40)
Girl	80 (61.5)	17 (58.6)	8 (50)	105 (60)
Type of heart defect				
Simple	91 (70)	16 (55.2)	9 (56.3)	116 (66.3)
Complex	39 (30)	13 (44.8)	7 (43.8)	59 (33.7)
Surgical treatment				
No	62 (47.7)	16 (55.2)	8 (50)	86 (49.1)
Yes	68 (52.3)	13 (44.8)	8 (50)	89 (50.9)
Concomitant drugs				
Spironolactone	1 (0.8)	1 (3.4)	2 (12.5)	4 (2.3)
Thiazides	69 (53.1)	14 (48.3)	6 (37.5)	89 (50.9)
Loop diuretics	15 (11.5)	12 (41.4)	7 (43.8)	34 (19.4)
ACEIs	45 (34.6)	17 (58.6)	7 (43.8)	69 (39.4)
Codisease				
None	114 (87.7)	22 (75.9)	14 (87.5)	150 (85.7)
Respirotory tract infection	14 (10.8)	4 (13.8)	32 (12.5)	20 (11.4)
Other infections	2 (1.5)	3 (10.3)	0	5 (2.9)
Clinical symptoms of CHF				
No CHF	94 (80.3)	14 (12.0)	9 (7.7)	117
(Modified Score 0-2)	(72.3)	(48.3)	(56.3)	(66.9)
CHF	36 (62.0)	15 (25.9)	7 (12.1)	58
(Modified Score >2)	(27.7)	(51.7)	(43.7)	(33.1)

likely to be graded CHF as a similar patient in low level group (OR: 1.32, 95%CI: 0.37-4.76, p=0.67). However, there was no significant relationship. Patient status, gender, type of heart defect and concomitant drugs; thaizide diuretics, loop diuretics and ACEIs were also poorly related with clinical symptoms of HF (Table 2). In addition, spironolactone variable was dropped from the analysis because only 4 patients used it. Specifically, other variables including age, surgical treatment and respiratory tract infections significantly influenced clinical symptoms of HF. For a year of age increasing, the graded CHF patients significantly decreased 0.91 times (OR: 0.91, 95% CI: 0.83-0.98, p=0.017). The patients with surgical treatment was 0.44 times significantly more likely to be graded CHF than a similar patient without surgical treatment (OR: 0.44, 95%CI: 0.21-0.92, p=0.029). In contrast, the patients with respiratory tract infection was 5.56 times as likely to be graded CHF as a similar patient without the infection (OR: 5.56, 95%CI: 1.72-16.67, p=0.004) (Table 3).

Table 2. Initial logistic regression model for controlling signs and symptoms of heart failure in pediatric patients.

Variables	Odds ratio[a]	Coefficients	p-vale	95% CI
Patient status	0.33	-1.090	0.110	0.09-1.28
Age	1.11	0.103	0.024	1.01-1.21
Gender	1.63	0.491	0.225	0.74-3.61
Types of heart defect	0.82	-0.198	0.681	0.32-2.11
Surgical treatment	2.64	0.973	0.039	1.05-6.66
Concomitant drugs				
Thaizide diuretics	0.63	-0.460	0.307	0.26-1.53
Loop diuretics	1.02	0.021	0.976	0.26-3.94
ACEIs	0.81	-0.209	0.618	0.36-1.85
Codisease				
None	1			
Respirator tract infection	0.19	-1.651	0.008	0.06-0.65
Other infections	1.32	0.254	0.819	0.12-14.3
SDC subgroups				
Low level group	1			
Middle level group	0.56	-0.536	0.299	0.21-1.61
High level group	0.95	-0.051	0.942	0.24-3.70

[a]Odd ratios for graded no CHF patient

Table 3. Final logistic regression model for signs and symptoms of heart failure in pediatric patients.

Variables	Value	Odds ratio	95% CI
Age (year)	-	0.91	0.83-0.98
Surgical treatment	No	1	
	Yes	0.44	0.21-0.92
Respiratory tract infection	No	1	
	Yes	5.56	1.72-16.67
SDC subgroup	Low level	1	
	Middle level	2.00	0.79-5.00
	High level	1.32	0.34-4.76

DISCUSSION

In 2003, *post hoc* analysis of the Digitalis Investigation Group (DIG) trial revealed that SDC of 0.5-0.8 μg/L had lower rate of all-cause mortality (hazard ratio [HR], 0.8; 95%CI, 0.68-0.94) and mortality due to worsening of heart failure (HR, 0.66; 95%CI, 0.49-0.89) among men with stable heart failure (Rathore et al., 2003). Early study of Adam et al. which re-analyzed two digoxin studies: the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED) and the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE), demonstrated patients in low level group (≤0.9 μg/L) as well as in clinical efficacy (developing of worsening heart failure) with medium SDC (0.9-1.2 μg/L) and higher SDC (>1.2 μg/L) in adults (Adam et al., 2002). Clinical benefit of low level is consistent with the hypothesis that digoxin provides a neurohormonal benefit which is believed to contribute to digoxin's symptomatic benefits in stable heart failure patients. Low dose of digoxin may attenuate the neurohormonal activation without improving the hemodynamics. On the other hand, a higher dose improves hemodynamics without having a neurohormonal modulation (Gheorghiade et al., 1995; Slatton et al., 1997; Veldhuisen, 2002). However, the drug effects in pediatrics may vary from adults. Furthermore, the common etiology of HF in adults is secondary to ischemic heart disease or chronic hypertension, leading to myocardial dysfunction whereas in pediatrics, it is primarily due to the hemodynamic consequence of anatomic defect in the heart or great vessels, congenital or acquired, and results in abnormal loading condition (Dreyer and Fisher, 1998; Latifi et al., 2000). This present study is the first time of the investigation of SDC subgroups and clinical symptoms of heart failure in pediatric patients. Multivariable analysis revealed that there was an absence of significant relation adjusted with covariates between SDC subgroups and control of heart failure in pediatrics. The patients in middle level group (0.8-1.2 μg/L) and high level group (>1.2 μg/L) were estimated to be 2 and 1.32 times, respectively, as likely to be graded CHF as patients in low level group (<0.8 μg/L). However, there was no statistically significant relationship. It seems non-significant to increase the clinical effect of SDC to >0.8 μg/L on such patients. Apart from digoxin treatment, according to pathophysiology and management of CHD, there are various factors in the success of CHD treatment and heart failure control. Increasing of age, surgical treatment and codisease significantly influenced on controlling of heart failure. Increasing of age and surgical treatment for removing the defect significantly increased the success of heart failure control whereas codisease, especially respiratory tract infection, precipitated the clinical symptoms of heart failure. In the pediatric population, Ross et al. determined historical variables and examination findings, including feeding history, respiratory rate, heart rate, respiratory pattern, peripheral perfusion, diastolic rumble and hepatomegaly which most accurately define CHF in infant in 1992 (Ross et al., 1992). The modified scoring system which was described first by Ross for infant was further modified by Reithmann et al. and Laer et al. (this would be called modified Ross Score). Both Ross score and modified Ross Score were used to be the reference in many studies of CHF in children (Mir et al., 2001, 2002; Buchhorn et al., 2002; Laer et al., 2002). Several pa-

rameters such as plasma norepinephrine level, the pulmonic-to-systemic flow ratio (Qp/Qs) and degree of pulmonary arterial hypertension correlate well with severity of CHF symptoms (Ross et al., 1987) but norepinephrine level is not available for clinical practice. Pulmonary artery pressures and Qp/Qs ratio were invasive methods and not routinely measured or calculated in all patients. In this study, modified Ross score was considered for assessing symptoms of heart failure because of possibility and appropriateness for using data in real clinical practice. However, there were some limitations of this study. Firstly, this study was performed by using clinical routine data which need to be adjusted the confounding factors by binary logistic regression analysis. Secondly, there were small numbers of patient in the high level group. And thirdly, there was the lack of control group or clinical data before digoxin treatment. Therefore, patients who were classified as having no CHF does not mean that digoxin treatment has been effective or these patients were actually not in need for digoxin treatment. The benefit of low SDC from this method may not be definitely concluded. The only study to definitively establish whether lower level of digoxin is as effective as or better than higher level is to conduct a prospective, randomized controlled trial with sufficient power or assessment of CHF symptoms at before and after treating with digoxin. Randomized controlled trial may have some obstacles such as ethical barrier and sample size, however, the further study of SDC subgroups (low, middle and high) and toxicity relationship may support the benefit of low SDC in pediatrics. Although the results could not clearly explain the clinical benefit of low level on the hypothesis of neurohormonal modulation as in adults, it was likely that this study could express a trend towards controlling signs and symptoms of heart failure in pediatrics.

CONCLUSION

The use of digoxin doses to achieve low concentrations of ≤0.8 μg/L may associate with favorable clinical effects and may also reduce toxicity. This finding shows a probable new trend on controlling signs and symptoms of HF with digoxin in pediatrics with heart disease. The target at low SDCs should be considered and supported by further study.

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