Preliminary Study of Low Serum Digoxin Concentration on Heart Failure in Thai Pediatric Patients with Congenital Heart Disease

Yupaporn Preechagoon[1*], Peeraya Somsaard[1] and Setthasiri Petcharattana[2]

[1]Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002, Thailand

[2]Department of Medicine, Queen Sirikit Heart Center of the Northeast, Khon Kaen University, Khon Kaen 40002, Thailand

** Corresponding author. E-mail: yuppre@kku.ac.th*

ABSTRACT

The objective of this study was to present the controllable low serum digoxin concentrations (SDCs) on heart failure in Thai pediatric patients with congenital heart disease (CHD). The total of 32 patients (5 boys and 27 girls) with 37 SDCs at Queen Sirikit Heart Center of the Northeast, Thailand, were studied. All patients had not been considered for surgery and received digoxin for CHD at least 1 week. Clinical symptoms and grading of the severity of heart failure were assessed by pediatric cardiologist, using modified Ross score. Most of patients (59.5%) had subtherapeutic SDCs. The concentrations of controllable patients were in therapeutic level (0.8-2.0 µg/L), subtherapeutic level (0.2-0.8 µg/L) and unreliable level (<0.2 µg/L) of 50%, 72.7% and 80%, respectively. From SDC subgroups; low level (<0.8 µg/L), middle level (0.8-1.2 µg/L), and high level (>1.2 µg/L), there were patients whose heart failure could be controlled in low level group more than in middle level group (74.1% and 44.4%, respectively). According to grading of the severity of congestive heart failure (CHF), patients with no CHF were 71.4% and 75% in subtherapeutic level and therapeutic level groups, respectively. It was surprising that 75% of patients in unreliable level group had no CHF. Similar to the low level group and middle level group, percentages of patients without CHF were 77.2 and 66.7, respectively. This preliminary study shows that low SDCs expressed a trend toward controllable signs and symptoms of heart failure in such patients. The use of digoxin doses to achieve low serum concentrations of ≤0.8 µg/L had favorable clinical effect as well as in high level and may also reduce digoxin toxicity.

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

INTRODUCTION

In pediatrics, incidence of congenital heart disease (CHD) is approximately 0.8% (Kay et al.,2001). Prevalence of heart failure in such patients is as high as

20%. 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). Problems of digoxin use include narrow therapeutic range, large interpatient variability in its pharmacokinetics and pharmacodynamics, serious toxic effect may occur even when drug is used in recommended dose. Many laboratories recommend a therapeutic range in adults between 0.5 and 2 μg/L. In pediatrics, high serum levels of digoxin are better tolerated by infants than by older children or adults. However, some studies found that serum levels more than 2 μg/L are often associated with toxicity and are not demonstrably necessary for adequate inotropic response. Recent studies suggest that lower serum levels of digoxin are as effective as high levels for controlling CHF in children. Therefore, most common 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, therapeutic range, both of upper and lower reference values, 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). Recently, the Digitalis Investigation Group (DIG) trial findings demonstrate that serum digoxin concentrations (SDCs) of 1.2 μg/L and higher may be harmful whereas 0.5-0.8 μg/L likely constitutes the optimal therapeutic range for men with stable heart failure and left ventricular dysfunction (Rathore et al., 2003). Similar to previous study, Adam et al. (2002) reported that there was no difference of developing worsening heart failure during the 12-week follow-up period among subgroups with low (≤0.9 μg/L), middle (0.9 to 1.2 μg/L) or high (>1.2 μg/L) SDCs. Therefore, lower SDC levels may associate with reduced toxicity as well as favorable clinical effects (Adam et al., 2002; Veldhuisen, 2002). From this new finding in adult, there is the need of more detail in pediatrics. However, there has been no study of low SDC for the treatment of CHF in these patients. This preliminary study was therefore undertaken to report the controllable lower SDCs on heart failure in pediatric outpatients with CHD.

MATERIALS AND METHODS

Data sources

The clinical and blood sampling data were collected from 32 pediatric outpatients (5 boys and 27 girls) and 37 SDCs at Queen Sirikit Heart Center of the Northeast, Thailand, between November 2004 to August 2005. These patients had not been considered for surgery of the defect and received digoxin for CHD. All patients had taken recommended doses of digoxin for at least 1 week with good compliance, such that all concentrations were considered to be on steady state. Blood samples were drawn after taking digoxin at least 6 hours.

The study was approved by the Ethic Committee on Human Research, Faculty of Medicine, Khon Kaen University. Informed consent was obtained from their parent or caregiver to participate in the study.

The data collected were 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.

Clinical symptoms of heart failure

All patients were evaluated and monitored for clinical symptoms of heart failure by pediatric cardiologist. Signs and symptoms of heart failure were recorded on monitoring sings and symptoms of heart failure form. Grading of the severity was assessed, following clinical score modified from Ross, Reithmann and Laer for infants and children or modified Ross score (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 (Table 1), respectively.

Table 1. Classification of congestive heart failure score in infants and children.

Total Score	
0-2	No CHF
3-6	Mild CHF
7-9	Moderate CHF
10-12	Severe CHF

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

Routinely-therapeutic range of digoxin in pediatrics is 0.8-2.0 µg/L. Therefore, patients were divided into 4 groups of therapeutic range at each visit; unreliable level (<0.2 µg/L), subtherapeutic level (0.2-0.8 µg/L), therapeutic level (0.8-2.0 µg/L) and toxic level (>2.0 µg/L). In addition, patients 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).

Data analysis

Patient characteristics were presented in terms of mean ± SD and percentage. Percentage of patients with CHF and in each grading severity (no, mild, moderate and severe CHF) of each SDC subgroups were assessed.

Table 2. Summary of characteristic data.

Characteristics	Pediatric patients
Number of patients (N)	32
Number of SDCs (N)	37
Age (years, mean±SD)	5.42±4.74
Weight (kg, mean±SD)	15.85±12.0
Gender (N, %)	
Boy	5 (16%)
Girl	27 (84%)
Underlying disease (N, %)	
VSD	6 (19.0%)
VSD+PS	1 (3.0%)
VSD+AS	1 (3.0%)
VSD+PHT	3 (9.0%)
VSD+PDA+PHT	4 (13.0%)
VSD+ASD	1 (3.0%)
VSD+ASD+PDA	1 (3.0%)
ASD+PHT	2 (6.0%)
ASD+PDA+PHT	2 (6.0%)
PDA+PHT	1 (3.0%)
RHD	5 (16.0%)
AV canal defect	3 (9.0%)
CAF	1 (3.0%)
TGA	1 (3.0%)

AS, aortic stenosis; ASD, atrial septal defect; AV canal defect, atrioventricular canal defect; CAF, coronary artery fistula; PDA, patent ductus arteriosus; PHT, pulmonary hypertension; PS, pulmonary stenosis; RHD, rheumatic heart disease; TGA, transposition of the great arteries; VSD, ventricular septal defect

Table 3. Percentage of signs and symptoms of heart failure based on therapeutic range.

Serum Digoxin Concentration	Number (%)	Signs & Symptoms of heart failure	
		No (%)	Yeas (%)
Subtherapeutic level (0.2-0.8 µg/L)	22 (59.5%)	16 (72.7%)	6 (27.3%)
Therapeutic level (0.8-2.0 µg/L)	10 (27.0%)	5 (50%)	5 (50%)
Toxic level (>2.0 µg/L)	-	-	-
Unreliable level (<0.2 µg/L)	5 (13.5%)	4 (80%)	1 (20%)

RESULTS

The characteristics of patients are given in Table 2. Thirty-seven SDCs from 32 pediatric patients aged 0.4 to 14.6 years were assessed. Digoxin was orally administered 3.6 to 11.4 µg/kg/day.

As shown in Table 3, 27.0 % of SDCs (n=10) reached therapeutic level (0.8-2.0 µg/L), 59.5 % of SDCs (n = 22) were less than therapeutic level (0.2-0.8 µg/L), 13.5% (n=5) were unreliable level (<0.2 µg/L) and there was no toxic level. SDCs in patients who had no signs and symptoms of heart failure were in therapeutic level, subtherapeutic level and unreliable level of 50%, 72.7% and 80%, respectively.

When we categorized SDCs into 3 subgroups, there were 27 SDCs of low level (<0.8 µg/L), 9 SDCs of middle level (0.8-1.2 µg/L) and 1 of high level (>1.2 µg/L) (Table 4). Patients in low level, middle level and high level groups had no CHF of 74.1%, 44.4% and 100%, respectively.

Only 22 patients were assessed for clinical symptoms and grading the severity of heart failure by clinical score modified from Ross, Reithmann and Laer. Patients who had no CHF in subtherapeutic level, therapeutic level and unreliable level group were 71.4%, 75% and 75%, respectively. Patients who had signs and symptoms of heart failure and were evaluated into mild CHF grading in subtherapeutic level group and therapeutic level group were 21.4% and 25%, respectively (Table 5). Patients with moderate CHF grading were in subtherapeutic level (1 patient) and unreliable level (1 patient). When the controllable patients were divided into SDC subgroups, there were 72.2%, 66.7% and 100% in low level, middle level and high level, respectively (Table 6). Patients with mild CHF grading were 16.7% and 33.3% in low level and middle level group, respectively. There were 2 patients in low level who had moderate CHF grading.

Table 4. Percentage of signs and symptoms of heart failure based on SDC subgroups.

SDC subgroups	Number (%)	Signs & Symptoms of heart failure	
		No (%)	Yeas (%)
Low level (<0.8 µg/L)	27 (73.0%)	20 (74.1%)	7 (25.9%)
Middle level (0.8-1.2 µg/L)	9 (24.3%)	4 (44.4%)	5 (55.6%)
High level (>1.2 µg/L)	1 (2.7%)	1 (100%)	-

DISCUSSION AND CONCLUSION

The previous study, DIG trial, suggested that low SDC of 0.5-0.8 µg/L likely constitutes the optimal therapeutic range. SDC of 0.5-0.8 µg/L had lower rate of all-cause mortality (hazard ration [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). Similar to Adamís study, re-analyzed study from two digoxin withdrawal 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), patient treated with low SDC (≤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). This present study revealed that the most of SDC were in subtherapeutic level (59.5%). Patients in subtherapeutic level (0.2-0.8 µg/L) and unreliable level (<0.2 µg/L) had no signs and symptoms of heart failure more than therapeutic level (0.8-2.0 µg/L), 72.7%, 80% and 50%, respectively. When we categorized patients into SDC subgroups, patients in low level group (74.1%) could be controlled heart failure more than in middle level group (44.4%) and was similar to patient in subtherapeutic level group (72.7%). When grading severity of heart failure was assessed, 71.4% and 75.0% of patients had no signs and symptoms of heart failure in subtherapeutic level and therapeutic level, respectively. Similar to low level group and middle level group, percentages of patients who had no signs and symptoms of heart failure were 72.2 and 66.7, respectively. Surprising that 75% of patient in unreliable level group had no CHF. However, most of patients who had mild and moderate CHF had digoxin level less than 0.8 µg/L. It is possible that since only 1 patient was categorized into high level, therefore, 100% of patient in high level group did not present signs and symptoms of heart failure. Although this study could not clearly present clinical benefit of low level as well as high level, the low level showed a trend towards controllable signs and symptoms of heart failure. Clinical benefit of low level is consistent with the hypothesis that digoxin provides a neurohormonal benefit. Previous study showed that low dose may attenuate the neurohormonal activation without improving the hemodynamics, whereas a higher dose improves hemodynamics without having a modulating effect on neurohormonal. Therefore, neurohormonal modulation is believed to contribute to digoxinís symptomatic benefits in patients with stable heart failure at lower SDCs (Gheorghiade et al., 1995; Veldhuisen, 2002,). These benefits are achieved at low level of 0.7-0.8 µg/L and do not need to increase to higher SDCs (Slatton et al., 1997; Rathore et al., 2003,). It has been found that there are few limitations of this study such as small sample size and unequal numbers in each subgroup. However, the used data collected from real situation on clinical practice would reflect reasonable outcome in such patients. Moreover, some factors such as simple or complex CHD, receiving ACEI, K-sparing diuretics and/or other diuretics may influence signs and symptoms of heart failure in the patients. A further study on larger sample size with multivariate analysis for adjustment of the confounding factors will be necessary to definitely establish the SDCs on heart failure in pediatric patients.

Table 5. Grading severity of signs and symptoms of heart failure based on therapeutic range.

Serum Digoxin Concentration	Number (%)	Grading of severity (%)		
		No CHF* (0-2)	Mild CHF* (3-6)	Moderate CHF* (7-9)
Subtherapeutic level (0.2-0.8 µg/L)	14 (63.6%)	10 (71.4%)	3 (21.4%)	1 (7.1%)
Therapeutic level (0.8-2.0 µg/L)	4 (18.2%)	3 (75.0%)	1 (25.0%)	-
Toxic level (>2.0 µg/L)	-	-	-	-
Unreliable level (<0.2 µg/L)	4 (18.2%)	3 (75%)	-	1 (25%)

*CHF, congestive heart failure

Table 6. Grading severity of signs and symptoms of heart failure based on SDC subgroups.

SDC subgroups	Number (%)	Grading of severity (%)		
		No CHF* (0-2)	Mild CHF* (3-6)	Moderate CHF* (7-9)
Low level (<0.8 µg/L)	18 (81.8%)	13 (72.2%)	3 (16.7%)	2 (11.1%)
Middle level (0.8-1.2 µg/L)	3 (13.6%)	2 (66.7%)	1 (33.3%)	-
High level (>1.2 µg/L)	1 (4.5%)	1 (100%)	-	-

*CHF, congestive heart failure

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