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Full Length Research Paper

Appropriateness of digoxin level monitoring in a children's hospital

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To evaluate the proportion of inappropriate digoxin level determinations in children at Children's Hospital of Fudan University. A retrospective analysis of 291 digoxin level determinations in 210 inpatients was performed. Appropriateness criteria were based on existing criteria that were revised using local expert opinion. The main outcome measure was the proportion of digoxin levels assessed as inappropriate by these criteria. Of the 291 digoxin levels, 126 (43.3%) were considered inappropriate and the remaining 165 (56.7%), appropriate. For the majority of the inappropriate determinations timing of blood sampling was incorrect (74.6%); the remaining determinations were done without proper indication. Almost half the digoxin blood level monitoring was assessed as inappropriate, mainly because of incorrect timing of sampling. Interventions to ensure that appropriate indications and procedures for serum digoxin determination in children at the Children's Hospital of Fudan University are urgently needed, moreover, special criteria need to be made for children in digoxin blood level monitoring.

Key words: Digoxin, therapeutic drug monitoring, children, appropriateness.

INTRODUCTION

For drug therapy to be optimal for children it is important that they are not treated as miniature adults. The pharmacokinetics of drugs in children can differ widely from adults due to physiological differences, including immaturity of enzyme systems and clearance mechanisms. Pharmacokinetics also differs among children of different ages because many physiologic systems are immature in the first months after birth and change rapidly throughout childhood. These considerations mean that children are likely to benefit from therapeutic drug monitoring (TDM) for some drugs. TDM enables the clinician to adjust drug dosage according to the characteristics of the individual patient and this makes it an important tool to monitor safety and optimize therapy (Egberts et al., 2011; Johannessen et al., 2003; Kearns et al., 2003).

Digoxin is widely used for congestive heart failure and atrial fibrillation. Because of its narrow therapeutic index and large interindividual pharmacokinetic variability, it is important to know digoxin blood levels. However, studies have shown that procedures for digoxin serum concentration monitoring are frequently not within accepted guidelines (Clague et al., 1983; Copeland et al., 1992; Canas et al., 1999; Mordasini et al., 2002; Haim et al., 2002; Sidwell et al., 2003; Puche et al., 2004; Lippi et al., 2007; Orrico et al., 2011). Digoxin level monitoring performed without proper indication or with incorrect timing may not only significantly limit its benefits but also result in toxicity and unnecessary costs. The present retrospective study was performed to assess the proportion of digoxin level determinations in hospitalized children not fulfilling accepted criteria for appropriate digoxin level monitoring and to identify reasons for these inappropriate measurements.

MATERIALS AND METHODS

This study was conducted at the Children's Hospital of Fudan University, a tertiary care teaching hospital with 600 beds and approximately 16,000 admissions per year. Staff physicians are the

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Table 1. Appropriateness of digoxin level monitoring (Clague et al., 1983; Mordasini et al., 2002; Canas et al., 1999; Copeland et al., 1992).

Main element	Detail element	Detail element
(A) Adequate indication	1. Suspected digoxin toxicity	(i) Appearance of arrhythmias suspected to be associated with digoxin therapy (for example, supraventricular tachycardia, atrioventricular conduction defects, multifocal premature ventricular contractions)
		(ii) Noncardiac signs of digoxin toxicity (that is, loss of appetite, nausea, vomiting, diarrhoea, abdominal pain, visual disturbances, confusion, headache)
	2. High risk patient	(i) Newborn
		(ii) Unstable or declining renal function
		(iii) Surgical patient
		(iv) Hypo- or hyperthyroidism
		(v) Other (ICU patient, low weight, electrolyte abnormalities, hypoxia)
	3. sub-therapeutic response	(i) No improvement or worsening of congestive heart failure, atrial fibrillation or flutter
		(ii) Suspected noncompliance
		(iii) suspected malabsorption
		(iv) Concomitant use of an interacting drug (for example, verapamil, erythromycin, spironolactone, furosemide, nifedipine, amiodarone)
	4. Initiation of digoxin therapy or dosage adjustment	
	5. Admission level for inpatients without digoxin determination within previous 9 months	
	6. Suspected digoxin abuse	
(B) Appropriate timing	1. The blood sample was taken at least 6 h after the last digoxin dose and, if therapy was started or dose changed, at least 6 days before the digoxin determination (in patients with normal renal function).	
	2. If toxicity is suspected, digoxin TDM can be performed before steady state is reached; sampling should occur at least 6 hours after the last dose.	

primary prescribers of tests. Clinical pharmacists provide routine pharmacokinetic consultations for the neonatal and the intensive care units.

Development of appropriateness criteria

The appropriateness criteria used in this study were based on published criteria (Clague et al., 1983; Mordasini et al., 2002; Canas et al., 1999; Copeland et al., 1992) which were reviewed and revised by two expert pharmacists. Digoxin level monitoring was considered appropriate if the following two criteria were met (Table 1): (1) there was an adequate indication for monitoring: adequate indication for monitoring: suspected digoxin toxicity; high risk patient; sub-therapeutic response; initiation of digoxin therapy or dosage adjustment; admission level for inpatients without digoxin determination within previous 9 months; suspected digoxin abuse, and (2) the blood sample was drawn at least six hours after digoxin administration. Correct timing was important to ensure that the distribution phase was terminated and that steady state conditions had been achieved (defined as 4 half-lives after digoxin initiation or dose adjustment).

Measurement of digoxin serum levels

Digoxin serum levels were measured by the hospital clinical medicine laboratory using the AxSYM® Digoxin II assay (a polarization fluorescence immunoassay). The therapeutic range for our department is 0.8 to 2.0 ng/mL.

Blood sampling and data collection

A total of 291 digoxin serum levels for 210 inpatients determined

Table 2. Characteristics of 210 in patients for whom digoxin levels were determined.

Parameter	N (%)
Age	
<1 month	35 (16.7)
1 month to 1 year	136 (64.8)
>1 year	39(18.6)
Sex	
Male	135 (64.3)
Source of digoxin test order	
(i) Cardiology	113 (53.8)
(ii) Cardiac surgery	33 (15.7)
(iii) Newborn room	16 (7.6)
(iv) ICU	41 (19.5)
(v) Other	7 (3.3)
Duration of hospitalization, mean days (range)	29.5 (3-114)
Indication for digoxin	
(i) Congenital heart disease	173 (82.4)
(ii) Dilated cardiomyopathy	17 (8.1)
(iii) Arrhythmia with/without above diseases	20 (9.5)
Measurements/patient*	
1	158 (75.2)
2	40 (19.1)
>2	12 (5.7)

*During the same hospitalization.

during a two year period, January, 2009 to December, 2010, were selected for analysis. TDM request forms and patient charts were reviewed to obtain the following information: age, sex, weight, patient status, digoxin dose and dosing interval, indication for digoxin level determination, use of concomitant drugs potentially interacting with digoxin (for example, amiodarone, quinidine, propafenone, verapamil), serum creatinine concentration and potassium level. The sample was sent to our department immediately after it has been collected, hence if the sampling time cannot be obtained in TDM request forms and patient charts, we view it as the sample was collected in 1 h ago when we received it. On the basis of this information digoxin level measurements were determined to be appropriate or inappropriate in terms of indication for the request and timing of sampling as judged by the criteria established.

Data analysis

Data are presented as ratios and percentages of cases and analyzed using the SPSS 13.0 statistical program.

RESULTS

The characteristics of the 210 patients selected for assessment are shown in Table 2. The median age of patients was 1.07 years and 64.3% were male. About half (53.8%) of the tests were ordered by the cardiology department, 19.5% by the intensive care unit and 15.7% by cardiac surgery, with the remaining coming from the neonatal unit and other sources. The majority of digoxin serum determinations (82.4%) were ordered for patients with congenital heart disease. Almost a quarter of patients (24.8%) had more than one digoxin measurement ordered during their hospital stay.

The mean serum level observed in children aged less than one month was higher than in older children (1.29 ± 0.58) (Table 3), there was statistically significant differences in mean serum digoxin among less than 1 month group and other age groups ($P < 0.01$), moreover the proportion of digoxin serum concentrations >2.0 ng/mL (17.7%) was significantly higher ($p < 0.05$) in patients less than one month of age and in patients being cared for in the ICU, cardiac surgery, newborn room than cardiology and other units (12.5, 10 and 18.2% vs. 1.8 and 0%; $p < 0.01$; Table 4). Of the 291 digoxin TDM measurements analyzed, 89% were assessed as having an appropriate indication (Table5). Of the 32 assessed as inappropriate,

Table 3. Digoxin levels for 291 measurements.

Age range	n	Digoxin level; n (%)			Level (ng/mL)	Daily dose (ng/mL)
		<0.8 ng/mL	0.8 to 2.0 ng/mL	>2.0 ng/mL	$\bar{x}$ ± s	$\bar{x}$ ± s
<1 month	45	9 (20)	28 (62.2)	8 (17.7)	1.29 ± 0.58	6.35 ± 1.98
1 month to 1 year	184	65 (35.3)	112 (60.3)	7(3.8)	0.98 ± 0.46	7.34 ± 1.58
1 to 2 years	36	24 (66.7)	10 (27.8)	2(5.6)	0.81 ± 0.69	7.72 ± 1.43
>2 years	26	13 (50)	13 (50)	0	0.88 ± 0.34	5.87 ± 1.07

Table 4. Digoxin levels according to source of request for determination.

Source of digoxin TDM request	n	Digoxin level; n (%)		
		<0.8 ng/mL	0.8 to 2.0 ng/mL	>2.0 ng/mL
ICU	48	16 (33.3)	26 (54.2)	6 (12.5)
Cardiology	164	66(40.2)	95(57.9)	3(1.8)
Cardiac surgery	40	17(42.5)	19(47.5)	4(10)
Newborn room	22	4(18.2)	14(63.6)	4(18.2)
Other	17	8(47.1)	9(52.9)	0(0)

Table 5. Appropriateness of digoxin measurement.

Category	Reason	n (%)
Indication	(i) Appropriate	259 (89.0)
	(ii) Inappropriate	32 (11.0)
Appropriate indication	(i) Initiation of therapy	69 (23.7)
	(ii) High risk patient	26 (8.9)
	(iii) Initiation and high risk patient	89 (30.6)
	(iv) Dose adjustment	35 (12.0)
	(v) Suspected drug toxicity	22 (7.6)
	(vi) Sub-therapeutic response	18 (6.2)
Inappropriate indication	(i) Repeated measurement	28 (87.5)
	(ii) No digoxin therapy	4 (12.5)
Timing of sampling	(i) Appropriate	191 (67.7)
	(ii) Inappropriate	94 (32.3)
Inappropriate timing of sampling	(i) Duration of initiation therapy <6 days	46 (48.9)
	(ii) Duration since dose adjustment <6 days	18 (19.1)
	(iii) Interval since previous dose <6 h*	30 (32.0)

*Patients with samples taken <6 days and <6 h were included <6 h.

87.5% were unnecessary repeat determinations.

In 22.0% (n = 64) of the 291 determinations, digoxin monitoring was performed when steady state conditions had not been reached. Of these, 10.3% (n = 30) were taken during the distribution phase of digoxin, which may result in un-interpretable and usually clinically irrelevant digoxin concentrations. Overall, the timing was assessed as inappropriate in 32.3% of the 291 measurements (Table 5). When criteria for both indication and timing were considered, 56.7% of the digoxin level determinations were assessed as appropriate. The quality of completion of digoxin TDM order forms was analyzed and

Table 6. Appropriateness of digoxin TDM requests.

Requested item	Indication	Digoxin dose	Concurrent therapy	Liver and kidney function	Time last dose was given	Sampling time
Provided (n)	4	169	126	90	67	191
Not provided (n)	287	122	165	201	224	100
Percentage appropriateness	1.4	58.1	43.4	30.9	23.1	65.6

found to be generally poor. Problems included the use of a variety of codes, inadequate details about the requester and failure to record the time interval between the last dose of digoxin and blood sampling. The key information provided was complete in only 1.4% of requests (Table 6). More than half lacked adequate information about dose and other insufficiencies included information about concomitant drugs, liver and kidney function, timing of last dose and sampling time. None of the digoxin therapeutic monitoring orders had all of the information requested.

DISCUSSION

The therapeutic range for digoxin is narrow and there is a large inter individual variability in its pharmacokinetics. For these reasons therapeutic drug monitoring is an integral part of the management of digoxin use in children. Rational use of therapeutic drug monitoring can help determine appropriate drug dosage and avoid toxic reactions. However, in previous studies the proportion of inappropriate monitoring ranged from 32 to 84% (Clague et al. 1983; Copeland et al., 1992; Canas et al., 1999; Mordasini et al., 2002; Haim et al., 2002; Sidwell et al., 2003; Puche et al., 2004; Lippi et al., 2007; Orrico et al., 2011), suggesting that digoxin TDM is a tool that is difficult to use correctly. In these studies there was some variation in the criteria by which the quality of monitoring was assessed, making it difficult to directly compare findings. However, these studies do highlight how commonly there are problems associated with TMD of digoxin, and for this reason a study of the situation at the Children's Hospital of Fudan University was undertaken.

Determination of the appropriateness of digoxin TDM requires rigorous evaluation criteria and such criteria have been developed for adult patients, but adult criteria is not suitable for children in some cases such as indication of digoxin TDM for newborn or the patient in the newborn room.

The study findings showed that mean values for digoxin in neonates were about 30% higher than in older children and the proportion of levels > 2.0 ng/mL was markedly higher in neonates (17.7% vs. 3.7%; Table 3). These findings are similar to those reported in other studies (Pinsky et al., 1979; Halkin et al., 1978) and reflect the lower capacity for renal excretion of digoxin by the relatively immature kidney (lisalo, 1977). In neonates renal excretion accounts for 57 to 80% of digoxin elimination, in the first few months after birth renal blood flow and glomerular filtration rate increase and there is a significant gain in renal function, leading to a gradual increase in digoxin excretion. It has been suggested that digoxin renal excretion capacity in children more than 1 month of age is equal to or slightly smaller than that of the adult (Wettrell, 1977); however, others think that the capacity does not reach adult levels until 3 to 4 months of age (Halkin et al., 1978; Suematsu et al., 1999). These considerations emphasize the importance of digoxin TDM in the very young and the need to consider these patients as being at high risk for incorrect dosing, while adult criteria is not mentioned. The study findings also showed that proportion of intensive care unit, cardiac surgery, newborn room patients with digoxin levels > 2.0 ng/ml (12.5, 10 and 18.2%) was higher than for other patients(1.8 and 0%)(Table 4), suggesting that ICU, newborn room, cardiac surgery patients should be considered to be at high risk. Hence, in the present study published standards for adult patients need to be altered to be make them more suitable for children (Table 1).

Our study suggests we do a better work than some departments, in particular in this study the proportion of digoxin levels determined without adequate indication was relatively low at 11.0%. Most of these determinations were repeat measurements associated mainly with incorrect sampling time. There may have three main reasons, first relating to the health condition in China. China is a developing country, many costs are out of the medical insurance range, hence if it is unnecessary, a digoxin monitoring will not be given in our hospital, secondly, this may be due to the reason that the characteristics of child patients are different from adult patients, congenital heart disease accounted for the majority (82.4%), most of them are receiving digoxin therapy for the first time as initiation of digoxin therapy and receiving operation therapy as a high risk. Moreover, in adequacies of health education to the care giver and the patients is another reason. Our study may suggest that we need to pay more attention to the sampling time problem of digoxin level monitoring in children hospital, for mistakes are more likely to happen

in such problems especially in the development country. Our findings also suggest that strategies to manage timing of blood collection will correct both inappropriate indication for and timing of digoxin TDM, for The test was repeated when the result did not answer the clinical question.

The halflife of digoxin is longer in infants less than 4 months of age than in adults, mainly because renal function is not fully developed (Halkin et al., 1978; lisalo, 1977; Wettrell, 1977; Suematsu et al., 1999). In adults receiving a fixed daily dose steady state is achieved after 6 to 7.5 days, whereas in neonates this still need more evidences to confirm, hence we have to use the adult standard, and a recommended time is need to establish for children. Judged by the criteria developed for this study, in 22% of the 291 samples digoxin monitoring was performed before steady state conditions had been achieved. The danger of early sampling is that the results may indicate that the digoxin level is safe when a further increase as steady state is achieved may result in exceeding the therapeutic window, thereby increasing the risk of toxicity. Digoxin level determination during the absorption and distribution phase is not meaningful. Of the 291 digoxin level measurements in this analysis, 30 were made less than six hours after digoxin dosing and most are less than three hours. Because distribution of digoxin is incomplete values are often high, especially if sampling occurred only one or two hours after dosing. Thus, a policy has been initiated that involves uniform digoxin dosing and timing of blood level measurements for all inpatients. Some caregivers are unaware that digoxin samples should be taken at least 6 hours after dosing and are confused by choices of multiple blood collection times (Matzuk et al., 1991; Bernard et al., 1996), the Fudan Children's Hospital has two main blood collection times, 13:30 and 15:00, and a common error is to reverse the timing. What's more, our study findings showed that the quality of requests was generally poor (Table 6), in fact, not a single digoxin therapeutic monitoring request had all the information codes required, this make hard for the pharmacists to correct the errors, another study reported similar findings (Ellington et al., 2007).

What strategies could be adopted to improve the quality of digoxin TDM? An accepted strategy to change physician behaviour is to offer educational lectures and tutorials, education is a key tool for changing physician opinions and a prerequisite to other interventions that are better for reinforcing behavior, however, this approach is labour intensive and the effect tends to decrease over time (Bates et al., 1998; Bates, 1998). Moreover, the development of national and/or international guidelines for TDM is needed (Norris et al., 2010), especially for children, adult criteria are not suitable for children in some cases, these are likely to be accepted by clinicians if they are evidence based. Whether through education or development of guidelines, multidisciplinary efforts play an increasing role in quality improvement, strengthening the cooperation between physicians and pharmacists to the benefit of managing TDM, the physician need to improve the quality of digoxin TDM requests. Computerization of requests offers the opportunity for decision support, including reminders and immediate feedback. In addition, when an assay is being performed specific information can be requested from the phlebotomist, such as time the specimen was obtained. This tool has been shown to be particularly effective in changing ordering behavior (Chen et al., 2003).

LIMITATIONS

This study has a number of limitations. We have to use the adult criteria and make a subtle change to evaluate the proportion of inappropriate digoxin level determinations in children at our hospital, for we do not have appropriateness criteria especially for children from available literatures. Moreover, the assessment of the appropriate time for digoxin level monitoring was based mainly on information from the TDM request form and patient charts, however, information on the exact timing of blood sampling was sometimes unavailable, instead, we used the time when the sample arrived in our department as a surrogate marker assuming that blood sampling usually occurred approximately one hour ago before arriving here, this might have lead to some misclassifications. Furthermore, the study included only certain laboratory parameters as markers for organ function and clinical condition, for example, we used creatinine serum urea nitrogen levels and we did not investigate the calcium levels of the patients in whom digoxin toxicity might have been enhanced due to a decrease in serum potassium levels with a concomitant increase in serum calcium levels.

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