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THERAPEUTIC DRUG MONITORING OF DIGOXIN

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ABSTRACT

Background: Digoxin therapy requires close monitoring and proper handling because of its narrow therapeutic index and the wide variety of factors that affect digoxin serum level. **Objective:** This review attempts to examine papers that address why, when and how therapeutic drug monitoring (TDM) of digoxin is usually undertaken. **Method:** Articles were identified electronically using the following databases: Pubmed, Trip, Web of Science, Science Direct and Medline. Search was restricted to articles published in English during the period 2001 to 2012. The identified Studies were then examined for their relevance. Only full texts, human based studies were included.

Results: Sixteen studies were included based on the inclusion criteria. Three studies evaluated TDM practice of digoxin among medical group setting. Seven studies involved drugs that commonly interact with digoxin and in which interaction necessitates the monitoring process. Tow studies assessed the effect of non drug factors on digoxin serum level. One study evaluated how different immunoassay methods can give discordant results, three studies addressed renal function as a major determining factor of digoxin serum level and one study assessed the correlation between serum level and incidence of mortality. **Conclusion**: Digoxin monitoring should be undertaken in a response to certain indications and not as a part of routine medical practice. This process should be performed at least 8hours following the last oral dose. In addition, renal function as well as the concomitant use of p-glycoprotein inhibitor drugs is important determinants of digoxin serum level. Furthermore, this review revealed that how different immunoassay methods can lead in to different digoxin serum level and different clinical action as well. Among the difficulties that clinician might face is the negative or positive interference from drugs like canrenone,

spironolactone, prednisolone and hydrocortisone, subsequently this interference can lead in to false dose adjustment.

INTRODUCTION

Digoxin is cardiac glycosides that used mainly in the treatment of systolic heart failure and atrial fibrillation. This medication inhibits the sodium-potassium ATPa .This enzyme moves sodium out of the cells and brings potassium in to the cell. Digoxin inhibits this enzyme and causes an increase in the intracellular sodium. The inhibition is followed by sodium -calcium exchange and results in accumulation of intracellular Ca. The exact mechanism of this exchange is still unclear. Then the intracellular Calcium binds to tropin C, subsequently contractility of the cardiac muscle increases.[1]

Digoxin has very narrow therapeutic index (1-2.5) mmol/l. Toxicity related to this drug increases significantly with concentration over 2.6mmol/l. Digoxin serum level was introduced since 1969 then followed by TDM. Before the introduction of TDM, toxicity of digoxin was reported between 8 to 29%.[2]

Digoxin serum level is affected by many factors which include drugs, food, electrolytes, and renal function. Digoxin toxicity is quite common. The most common adverse effects associated with digoxin are ventricular tachycardia, ventricular ectopic beats, 2nd or 3rd degree heart block and SA node arrest. Non cardiac side effects are also common which include anaroxia, diarrhoea, fatigue, confusion and abnormal color vision (excess yellow/ green).[3]

This review highlights why digoxin is monitored, when & how? , and summarizes the important factors that affect digoxin serum level. It also identifies the common problems about the practice of TDM of digoxin.

METHOD

This review was conducted based on previously published studies about TDM of Digoxin. This search attempts to provide a vision on common challenges regarding TDM practice of Digoxin. The following databases were used: Google scholar, Science Direct, Pubmed, Med, Line, google scholar, Web of Science and trip database. Studies were identified through electronic searching using the following terms: therapeutic drug monitoring of digoxin, digoxin monitoring, how to monitor digoxin, digoxin and electrolyte and digoxin -drug

interaction. Some articles were obtained by searching the references at the end of the study. Search was restricted to papers published in the period 2001–2012.

The identified articles were then examined for their relevance to the objectives of this review which include: how to monitor digoxin, when and why digoxin is monitored? And what are the factors that affect digoxin serum level. Many papers were excluded if full text could not be accessed, or if the study was undertaken on laboratory animals. Full texts available in language other than English were also excluded.

Findings

The search resulted in identification of sixteen studies which include randomized controlled Trails (RCT), simple descriptive and observational studies. These studies highlighted many important areas about TDM of digoxin for instance: why digoxin is monitored, digoxin monitoring practice, drug and non drug factors that affect digoxin serum level and how different bioassay methods can produce discordant results. One study assessed the correlation between serum level and the incidence of mortality. The identified studies are summarized in the table below.

Table 1: Summary of studies that examined therapeutic drug monitoring of digoxin

Authors	objective	Sample	Method	Result	Conclusion
1.Orrico et al., (2011)	To evaluate the reason for serum digoxin concentration (SDC) order and the clinical action taken in response to results.	90 patients on continuous digoxin therapy with no gab in the drug for 2 years.	The reason for each order SDC was abstracted for each patient. Then the appropriateness of each indication assessed based on predefined indication categories.	Of all 90 patients only one SDC order was considered appropriate. The indication for SDC order was summarized as follows: 38.9%of SDC order was conducted as a part of routine monitoring process, 33% to confirm signs of toxicity, 5.5% to assess factors altering the pharmacokinetic parameters of the drug, 3.3% to assess drug interactions and 5.5% to assess dosage change.	SDC orders were performed as a part of routine practice and did not lead to clinical action.
2. Englund et al (2004).,	To evaluate the effect of P-glycoprotein (P-gp) inhibitors on digoxin serum level.	618 patients on therapeutic drug monitoring of digoxin were included in the study.	P-gp inhibitors were classified into class 1 with known effect on digoxin, class 2 showing effect in vitro but no documented effect in vivo. Then the mean serum digoxin concentration was compared between patients.	47% of participants had one or more P-gp inhibitors. Patients with digoxin serum level > 2.5nmol/l were more likely co administered p- gp inhibitors compared with patients whose serum digoxin =2.5nmol/l.	The serum drug concentration significantly correlated to the number of co administered P-gp inhibitors.

3. Rogers et al .,(2008)	To assess how different immunoassay methods can lead to different result .	261 samples with sufficient volume of plasma were involved in the study.	Digoxin plasma samples were assayed in 5 laboratories using different Immunoassay methods .	46% of results were varied and led to different clinical decisions by physician.	digoxin concentration was different when using different immunoassay methods or when the same method was used by different laboratories.

Table 1 *continued*: Summary of studies that examined therapeutic drug monitoring of digoxin

Authors	objective	Sample	Method	Result	Conclusion
4. Ellington et al .,(2006)	To assess the quality of information provided when serum digoxin concentration (SDC) was ordered .	685 requests during 7 month period were included in the study.	Requests were assessed for the availability of the following information :contact details, reasons for request, dose, route of administration , concurrent therapy , treatment duration and time interval between the last dose and sampling .	19 % of requests contain contact details, 6.4% contain reasons for requests, 54.7% contain dose, 45.8% contain route of administration, 12.8% contain concurrent therapy, 32.9% ontain duration of the treatment and 47.1% contain the time interval between last dose and sampling .	The quality of information provided in each request was poor. Educational programs are needed to improve practice.
5. Sang Ling et al .,(2001)	To assess the relationship between increasing age and digoxin & digitoxin like immunoreactive substance (DLIS)&(DTLIS)	30 people older than 65 yrs and 25 younger than 50 without liver disease , uremia or volume expansion and none on digoxin therapy . In addition , 8younger than 50 and 14 older than 65 had	Serum samples from each group were examined for (DLIS&DTLIS) activity and compared with each other.	In elderly patients without liver disease or uremia , DLIS and DTLIS did not interfere with digoxin serum level . On the other hand , people who had uremic or liver disease had shown an elevated DLIS& DTLIS level .	DLIS&DLIS activity is not associated with age.

	.	digoxin therapy. Furthermore, 18 older than 65 yrs and 20 younger than 50 with liver disease or uremia.			

Table 1 *continued*: Summary of studies that examined therapeutic drug monitoring of digoxin

Authors	objective	Sample	Method	Result	Conclusion
6. Levine et al .,(2009)	To assess the relationship between calcium and development of digoxin toxicity .	Sample of 159 patients with digoxin toxicity from January 1, 1989 to May 31, 2005 .	The frequency of life threatening dysrhythmia within 1 hour of calcium administration was compared among those who received calcium and those who did not .	22%is the mortality rate among patients who received calcium compared with 20% in patients who did not receive calcium . In addition, no life threatening dysrhythmia occurred within 1 hour of calcium administration .	No evidence supports the claim that calcium increases life threatening events in digoxin toxic patients.
7. Steimer et al. ,(2002)	to evaluate the interference of Spironolactone, Canrenone, , hydrocortisone and prednisolone on digoxin assays.	3089 samples were assessed over 16.5 months.	The interference by Spironolactone, Canrenone and Steroids on digoxin serum level was assessed using the following assay methods: (AxSYM , IMx®, TDx®, Emit®, Dimension®, aca®, TinaQuant®, Elecsys® and Vitros®) .	Canrenone suppressed digoxin level in AxSYM IMx and Dimension assays .In addition , positive false results was documented in aca, TDx and Elecsys .Twenty five out of 669 had shown false negative results and 19 of these had toxic concentration of digoxin(Emit; >2.0 µg/L). This figures were led by the	False low or high results can lead to disastrous consequences because dose adjustment could be conducted based on false results .

				interference of spironolactone, canrenone , hydrocortisone,and prednisolone .	

Table 1 *continued*: Summary of studies that examined therapeutic drug monitoring of digoxin

Authors	objective	Sample	Method	Results	Conclusion
8. Sharma et al ., (2009)	To evaluate the usefulness of measurement of free digoxin level as indicator for digoxin toxicity in patients with chronic kidney disease (CKD) .	Two heamodialysis dependant cases suffering from chronic kidney disease (CKD) we included in the study.	In the first case , the patient had some signs of digoxin toxicity and treated with digoxin spacific FAb .Total and free digoxin levels were measured for both cases . .	In case no 1 ,free digoxin was bound to Fab therapy , this caused a reduction in free digoxin level and an increase in the total value(pharmacologically inactive drug). In case no 2 ,total digoxin level was high(3.98mcg/L) compared with the free level (8mcg/L) . This suggested interference by (DLIS).	Digoxin free level along with the total level must be measured in CKD stages at steady state level .
9.Hallberg .,(2004)	To assess the relationship between s-digoxin and the GFR markers(S-creatinine and S-cystatin C).	A sample of 149 hospital patients .	The correlation between s-digoxin and s-cystatin C vs s-creatinine was examined .	Researchers found that s-digoxin is greater correlated to s-cystatin C (p=0.00001, R=0.35, n=149) when compared to s-creatinine (p=0.00003, r=0.34, n=149) .	S-cystatin C is a better marker for GFR when compared with S-creatinine .

Table 1 *continued*: Summary of studies that examined therapeutic drug monitoring of digoxin

Authors	objective	Sample	Method	Results	Conclusion
10. Young et al	To assesses	81 patients on stable	Participants were	Serum magnesium level is	hypomagnesaemia is the

.,(2012)	the relationship between low magnesium level and digoxin toxicity .	digoxin dose for more than 10 days were included.	classified into groups based on presence or absence of digoxin toxicity. Serum digoxin, sodium, potassium, calcium, creatinine, magnesium and monocyte magnesium concentrations were compared .	much lower in those suffering from toxic digoxin. Magnesium level (0.80 (0.76-0.84) in toxic vs 0.88 (0.85-0.91) mmol 1-1, P < 0.01) in non toxic patients. monocyte magnesium (6.40 (5.65-7.16) in toxic patients vs 8.76 (7.81-9.71) mg g-1 DNA, P < 0.01) in patients without toxicity. There is no significant difference in other parameters.	most important electrolyte disturbance that determine digoxin toxicity. Cellular magnesium check is needed as the magnesium level could be depleted in spite of normal serum concentration.
11. Mordasini ., (2002)	To assess the appropriateness of digoxin monitoring practice .	210 randomly selected digoxin plasma samples.	Digoxin monitoring was assessed based on the following criteria: (1) There was a good reason for digoxin monitoring; (2) the blood sample had been taken at least 6 h after the last oral dose (3) the laboratory result had to be assessed by a physician(4) digoxin therapy should be conducted based on patient's individual status.	59% of digoxin monitoring were considered inappropriate, 39% appropriate and 2% could not be evaluated .	Educational strategies are needed for health care providers to conduct appropriate digoxin monitoring .

Table 1 *continued:* Summary of studies that examined therapeutic drug monitoring of digoxin

Authors	objectives	Sample	Method	Result	Conclusion
12. Levy et al ., (2001)	To determine the interaction between digoxin and levotiracetam .	A sample of 7 men and 4 women.	This study conducted as randomized, placebo controlled trial (double blind- two way cross over study).	Pharmacokinetic parameters including: AUC_{ss}, C_{max}, C_{min}, and PTF along with the pharmacodynamic parameters for digoxin did not differ between the two groups. Combination between these drugs is well tolerated	No interaction was suspected between the two drugs.
13.Rengel shausen et al·,(2003)	To determine the interaction between digoxin and clarithromycine.	A sample of 12 healthy men.	Randomized controlled trials (double blind - cross over design) was adopted in the study . Men were randomized in to tow groups:12 men co administered oral digoxin with clarithromycine or placebo. In addition, 3 of them received iv digoxin with clarithromycine or placebo.	Oral co administration of digoxin and clarithromycine resulted in 1.7 fold increase in area under the curve(AUC) . Non glomerular renal clearance of digoxin was reduced ,the mean ClRng is (0, 24) ± SD 34 ± 39 in those who co administered clarithromycine with digoxin compared with . 57 ± 41 mL min−1 in placebo receiving patients . After intravenous co adminstration AUC was increased by 1.2% .	Clarithromycine increases the bioavailabilty and reduces the non glomerular renal clearance of digoxin .

Table 1 *continued*: Summary of studies that examined therapeutic drug monitoring of digoxin

Authors	objective	Sample	Method	Results	Conclusion
14. Rathore et al .,(2003)	To assess the association between digoxin serum concentration , mortality and hospitalization among heart failure patients .	3782 men with left ventricular ejection fraction of 45% or less were included in this study	This study was conducted as randomized, double-blinded, placebo-controlled trial . Patients were randomly assigned either to receive digoxin or placebo. Patients who received digoxin were then divided into three groups according to SDC level for a period of one month and compared with patients who received placebo .	Mortality rate and SDC were assessed according to digoxin serum level . Digoxin was not associated with a reduction in mortality in patients with serum level of 0.9-1.1 ng/mL , meanwhile, patients with SDC of 1.2 ng/ml had higher mortality rate compared with placebo receiving patients.	There is a strong correlation between mortality rate and digoxin serum level .
15.Mahgoub et al .,(2002)	To evaluate the potential pharmacokinetic and pharmacodynamic interactions between diltiazem , isosorbide	A sample of 8 patients with chronic heart failure secondary to ischemic disease aged	The study was designed as a double blind , randomized cross over study. Patients were assigned to receive digoxin , hydrochlorothiazide, amiloride and dipyridamole for 10 days then randomly placed into two groups. The groups were received either digoxin plus diltiazren or digoxin	Co administration of digoxin and diltiazem resulted in an increase in area under the curve (AUC)by 51% , 50% increase in the mean steady state serum digoxin concentration, 37% increase in the peak serum digoxin concentration. Elimination half life had also increased by 29% .	Co administration of digoxin and diltiazem results in a modification in the pharmacokinetic Parameters .Mean while, combination

	dinitrate and digoxin .	between 48 and 61 years.	plus isosorbide dinitrate for 10 days.	Patients received diltiazem and isosorbide dinitrates showed improvement in symptoms when compared with digoxin alone.	between diltiazem , isosorbide dinitrates and digoxin results in an improvement in the clinical outcome.

DISCUSSION

This review revealed that digoxin monitoring practice had several limitations. First, the indication for serum digoxin concentration measurement (SDC) was inappropriate and insufficient clinical action was taken in response to the results (Orrico et al., (2011). There are, however, very few indications for SDC include: confirmation of drug toxicity, assessing the effect of the factors altering drug pharmacokinetic parameters, assessment of dosage change, drug adherence, drug interactions and clinical action taken in response to the results (Orrico et al., (2011). Another study conducted at Christchurch hospital on 100 digoxin TDM requests, revealed that 50% of digoxin TDM requests had no specific indication. In addition, SDC measurement should be conducted at least 8 hours following the last oral dose. According to Christchurch hospital study, one third of the sample was taken too soon after oral dose and 20% of samples were taken before steady state had reached.

Ellington C et al.,(2006) study revealed that insufficient information were provided when SDC was ordered by clinician **.** Mordasini et al.,(2002) assessed the appropriateness of digoxin monitoring practice on 210 plasma samples based on a certain criteria: there is appropriate indication for digoxin monitoring, blood sample had been taken at least six hours after the last dose , laboratory results had to be assessed by a physician and digoxin therapy should be conducted based on patient's individual status.

This study revealed that only 39% considered appropriate. According to the previously mentioned studies, educational programs are needed for health providers to improve digoxin monitoring service.

Rathore et al.,(2003) argued that mortality rate increased in patients with serum level higher than 1.2ng/ml . However, digoxin serum level is affected by several factors. According to Englund et al., (2004), digoxin serum level increased proportionally with the increase in the number of co administered p-gp inhibitors. Therefore, combination between digoxin and these drugs necessitates appropriate handling.

This review had also identified some of the misleading considerations about digoxin effect and the agents that might alter digoxin serum level. In contrast to the theoretical belief that co administration of calcium and digoxin could increase mortality, Levine et al., (2011) found that there was no difference in the mortality rate among those who received calcium and

those who did not. There is also another misconception that digoxin beneficial effect is less observed among elderly patients. Digoxin therapy has beneficial clinical outcome including reduction in mortality, reduction in patient's admission among patients of all ages Michael W Rich et al (2001).

Digoxin serum level is affected by many factors other than drugs include: DLIS, renal function and immunoassay methods. A study conducted by Rogers NM et al., (2008) had revealed that different immunoassay methods can lead to discordant results. In addition, different results can be also obtained from different laboratories even when the same immunoassay method was used. Immunoassay methods can be adversely affected by interference mediated by many drugs eg : spironolactone , prednisolon and canrenone steimer W et al .,(2002). This interference can result in to false negative or positive digoxin level. Digoxin dose can be increased or decreased based on these results and many patients could be adversely affected.

Recommendation

There are few indications for digoxin concentration measurement include confirmation of drug toxicity, assessing the effect of the factors altering drug pharmacokinetic, assessment of dosage change, assessment of drug adherence, assessment of drug interaction and assessment of clinical response. Orrico et al., (2011).

Digoxin concentration should be measured at least 8 hours after the last oral dose when the drug has reached steady state Sidwell et al, (2003).

Digoxin serum level increases proportionally with the increase in the number of co administered p-gp inhibitors. Combination between digoxin and these drugs necessitates appropriate handling Englund et al. (2004).

Assessment of renal function is essential in TDM practice of digoxin. Maintainance dose calculation based on calculation of patient's creatinine clearance using Cockcroft and Gault formula. Sidwell et al., (2003).

Toxicity related to digoxin can occur even when the drug concentration falls within the normal therapeutic range. Digoxin should be withheld after toxicity for a period of time according to drug concentration and the half-life of the drug in that patient . For example, in a patient with normal renal function (half-life approximately 30 h) and a concentration of

3.0nmol/l, the drug should be withheld for 1–2 days before changing the dose. On the other hand, in patient with renal impairment and prolonged digoxin half-life, doses may need to be withheld for several days Sidwell et al., (2003).

In case of therapeutic failure, dose adjustment need to be performed when the drug reached steady state. Change in the dose will normally result in a proportional change in the drug concentration in patients with normal renal function. In patients with unstable renal function, dose adjustment should be estimated according to patient's creatinine clearance using Cockcroft and Gault formula. For example, if the patient's renal function is a half of the normal patients then only half of the maintenance dose will be required to keep the same steady state Sidwell et al .,(2003).

Limitations

Some of the studies were conducted as descriptive, retrospective studies. This type of studies, however, is subject to bias when the data is abstracted. Systematic review was not conducted. Some articles assessed TDM practice in hospitals located in California, Australia and Basil. Therefore, the generalizability of the results especially in the developing countries is questionable. This review was restricted to studies published between 2001 to 2012 thus many studies out of this period that might contain significant results were not included. Although this study was not restricted to one age group, children and neonates were not included.

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