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MINIREVIEW

Evidence Based Digoxin Therapeutic Monitoring A Lower and Narrower Therapeutic Range

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ABSTRACT
Cardiac glycosides have been used for congestive heart failure and certain cardiac arrhythmias for more than 200 years. Despite the introduction of a variety of new classes of drugs for the management of heart failure, specifically angiotensin-converting enzyme (ACE) inhibitors, b-adrenergic antagonists (b-blockers), and the aldosterone antagonist spironolactone, digoxin continues to have an important role in long-term outpatient management. However, a narrow margin exists between therapeutic and toxic doses of digoxin, resulting in a high incidence of digoxin toxicity in clinical practice.
A wide variety of placebo-controlled clinical trials have unequivocally shown that treatment with digoxin can improve symptoms, quality of life, and exercise tolerance in patients with mild, moderate, or severe heart failure. The clinical relevance of digoxin therapeutic monitoring is also proved but the SDC (Serum Digoxin Conentrations) required for optimal clinical efficacy and acceptable toxicity remains controversial. In the last years, international guidelines recommend 1.2 ng/mL as acceptable high level.
In this bibliographic synthesis, we aim to collect pertinent informations from MedLine database about exposure-effect relationship in order to assess the evidence level scientific of new digoxin therapeutic monitoring.

KEY WORDS: Digoxin, drug monitoring, pharmacokinetic-pharmacodynamic, digitalics, heart fealure.

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INTRODUCTION
Digoxin is the oldest (more than 200 years) and probably the least expensive drug for heart failure (HF) [1]. Its effectiveness was not completely known until recently. Results of the Digitalis Investigation Group trial [2] showed that adding digoxin to standard heart failure therapy had no effect on mortality. However, adding digoxin decreased hospitalizations related to heart failure and improved symptoms in patients treated for heart failure.
Digoxin should be given without a loading dose in stable patients with sinus rhythm. A single daily maintenance dose of 0.25 mg is commonly employed in adults with normal renal function. In the elderly and in those with renal impairment, a reduced dose of 0.125 or 0.0625 mg/day should be used [3].
There are many problems encountered in trying to choose an effective dose for a drug such as digoxin. It is difficult because of such components as narrow therapeutic index, difficulty to define therapeutic endpoints, patients' variability, and varying effects of pathological states and drugs on digoxin disposition [4]. The determination by radioimmunoassay (RIA) of efficacious and toxic serum digoxin concentrations in 1969 dramatically improved

digoxin therapy [5]. The use of digoxin must be adjusted to each patient individually according to patients' age, weight, and renal function [6]. In suspected toxicity or ineffectiveness, serum digoxin concentration (SDC) should be measured, but the SDC required for optimal clinical efficacy and acceptable toxicity remains controversial [7].

SAFETY DATA

Because of the low therapeutic index of cardiac glycosides, their toxicity is a common clinical problem [8]. Arrhythmias, nausea, disturbances of cognitive function, and blurred or yellow vision are the usual manifestations. Elevated serum concentrations of digitalis, hypoxia, and electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypercalcemia) predispose patients to digitalis-induced arrhythmias. With severe intoxication (suicidal ingestion), severe hyperkalemia owing to poisoning of Na+/K+ATPase and profound bradyarrhythmias, which may be unresponsive to pacing therapy, are seen.

Minor forms of cardiac glycoside intoxication may require no specific therapy beyond monitoring cardiac rhythm until symptoms and signs of toxicity resolve. Any serious arrhythmia should be treated with antidigoxin Fab fragments, which are highly effective in binding digoxin and digitoxin and greatly enhance their renal excretion. Serum glycoside concentrations rise markedly with antidigitalis antibodies, but these represent bound (pharmacologically inactive) drug.

PHARMACOKINETICS

Most digoxin tablets average 70% to 80% oral bioavailability; however, approximately 10% of the general population harbors the enteric bacterium Eubacterium lentum, which can convert digoxin into inactive metabolites, and this may account for some cases of apparent resistance to standard doses of oral digoxin [9]. Liquid-filled capsules of digoxin (LANOXICAPS) have a higher bioavailability than do tablets (LANOXIN) and require dosage adjustment if a patient is switched from one dosage form to the other. Digoxin is available for intravenous administration, and maintenance doses can be given intravenously when oral dosing is impractical. Digoxin administered intramuscularly is erratically absorbed, causes local discomfort, and is not recommended.

Digoxin exhibits a high degree of tissue binding, resulting in a large volume of distribution that averages 4–7 L/kg.

The elimination half-life for digoxin is 36 to 48 hours in patients with normal renal function [10]. This permits once-a-day dosing; near steady-state blood levels are achieved one week after initiation of maintenance therapy.

Digoxin is excreted by the kidney with a clearance rate that is proportional to the glomerular filtration rate [11]. In patients with congestive heart failure and marginal cardiac reserve, an increase in cardiac output and renal blood flow with vasodilator therapy or sympathomimetic agents may increase renal digoxin clearance, necessitating adjustment of daily maintenance doses. Conversely, the half-life of the drug is increased substantially in patients with advanced renal insufficiency (to approximately 3.5 to 5 days); both the volume of distribution and the clearance rate of the drug are decreased in the elderly.

Despite renal clearance [12], digoxin is not removed effectively by hemodialysis due to the drug's large (4 to 7 L/kg) volume of distribution. The principal tissue reservoir is skeletal muscle and not adipose tissue, and thus dosing should be based on estimated lean body mass.

EXPOSURE-EFFECT RELATIONSHIP

During last years, serum digoxin concentrations (SDC) window is getting lower and narrower. It was at 0.8 to 2.0 ng/mL in the last seventies and eighties [13]. Till the last five years, optimal SDC was fixed at 0.8 to 1.5 ng/mL [14]. American and European guidelines in 2008 suggest a new decrease of SDC level to 1.2 ng/mL [3].

An initial digoxin level should be obtained 10–14 days after initiation of maintenance therapy.

Concentration-Efficacy Relationship

Current data suggest that up to 80% of the maximum inotropic effect of digoxin is obtained when the serum concentration is within the range of 1.0–1.5 nanograms/mL at the 24-hour trough point [15].

The first retrospective post-hoc analysis of the DIG trial was published in 2003 by S.S RATHORE and Al [16]. Authors compared three ranges of SDC (n=1171) with a placebo group (n=2611). SDC ranges were 0.5 – 0.8 ng/mL (n=572), 0.9 – 1.1 ng/mL (n=322), ≥1.2 ng/mL (n=277). Analysis showed a significant ($p<0.01$) gain in all-cause mortality with low SDC under 0.8 ng/mL.

The second comprehensive retrospective post-hoc analysis [17] taken from DIG trial data witch compares a digoxin group (An add-on trial: Associatioted with diuretics and converting enzyme inhibitor) with placebo (n=3861). Low SDC (0.5 – 0.9 ng/mL) group (n=982) and high SDC (≥1 ng/mL) group (n = 705) where chosen according to there significant association with heart failure outcome. Authors succeed to show different all cause mortality and hospitalization between different groups (See figures 3,4). The same author shows similar results in elderly (Patients ≥ 65 years) [18]. However, because less than one third of patients had a concentration measurement at one month, there was insufficient statistical power to determine whether digoxin use was associated with benefit or harm or had a neutral effect for women in this or any serum digoxin concentration range.

Another retrospective analysis [19] from DIG trial data demonstrated a significant linear relationship between SDC and mortality in women ($p=0.008$) and men ($p=0.002$, $p=0.766$ for gender interaction). Averaging hazard ratios (HRs) across serum concentrations from 0.5 to 0.9 ng/ml in women produced a HR for death of 0.8 (95% confidence interval [CI] 0.62 to 1.13, $p=0.245$) and for death or hospital stay for worsening HF of 0.73 (95% CI 0.58 to 0.93, $p=0.011$). In contrast, SDCs from 1.2 to 2.0 ng/ml were associated with a HR for death for women of 1.33 (95% CI 1.001 to 1.76, $p=0.049$).

Reanalysis of the PROVED and RADIANCE trials indicated that patients with low serum digoxin concentrations (0.5 to 0.9 ng/mL [1.2 nmol/L]) experienced similar benefits regarding symptoms of heart failure, improvement in LVEFs, and increased treadmill time compared with patients with moderate (1.0 to 1.2 ng/mL [1.5 nmol/L]) to high (more than 1.2 ng/mL) serum digoxin concentrations [20] but showed that patients in the low SDC (≤0.9 ng/ml) category were significantly less likely than placebo patients to experience worsening heart failure during follow-up ($p = 0.018$).

Concentration-Toxicity Relationship

Major signs of digoxin toxicity include: cardiac arrhythmias; gastro-intestinal symptoms (anorexia, nausea, and vomiting); and neurologic complaints (visual disturbances, disorientation, and confusion). Digoxin

toxicity is commonly associated with serum levels over than 2 ng/mL.

Although there is no single ECG abnormality that is pathognomonic of digoxin excess, the combination of enhanced automaticity and impaired conduction (atrioventricular block accompanied by an accelerated junctional pacemaker) is highly suggestive of toxicity even when serum levels are within the ‘‘accepted’’ therapeutic range [21].

The exposure-response relation between cardiac glycosides toxicity has previously been established. An old retrospective study [22] of 5 I00 patients on digoxin, with a four-week follow up after digoxin levels were measured, was done to determine the mortality rate. A significant increase in mortality was correlated with an increasing serum digoxin level, up to 50% at a level of 6.0 ng/mL and more. Clinical toxicity was suspected in only 0.25% of all patients on digoxin, although almost 10% had levels above the therapeutic range. Deliberate digoxin overdoses were fatal in 50% of cases. This study showed a correlation between increasing digoxin levels and increasing mortality rates. Writers recommanded to seriously consider the indications for initiating or continuing digoxin treatment in any patient because of an increased mortality in patients with levels of more than 1.0 ng/mL.

PHARMACO-ECONOMIC STUDIES

Digoxin remains the less expensive heart failure drug. Its clinical benefit is now clearly assessed by terminal endpoints hospitalization). EISENSTEIN et al. [23] in a post-hoc economic analysis, compared hospitalizations and medical costs. On average, there were fewer hospitalizations in digoxin-treated patients. These patients had lower heart failure yet higher non–heart failure hospitalization costs than placebo patients. Digoxin therapy was cost saving versus placebo in only 27% of 1000 bootstrap samples using Medicare costs (mean costs $12,648 vs. $12,362) and in 44% of samples using commercial carrier costs (mean costs $ 17,400 vs. $17,306). However, digoxin was cost saving in >50% of samples for several higher-risk patient subgroups.

Authors concluded that the use of digoxin therapy versus placebo was associated with reduced hospitalizations. Moreover, the resulting cost-savings could cover the costs of this inexpensive therapy in selected subgroups of higher-risk patients. In the remainder, there is a modest cost associated with this therapy.

PHARMACOKINETIC VARIABILITY

Inter-individual variability

A healthy volunteer pharmacokinetic study assessed the disposition of intravenous digoxin in healthy subjects following 0.5, 1.0, and 1.5 mg. doses. None of the identifiable pharmacokinetic variables changed significantly with dose, suggesting that digoxin pharmacokinetics in healthy humans are dose-independent over a relatively wick range of doses [24].

Elderly and Renal failure

Age-related changes in the pharmacokinetics of digoxin contribute signiticantly to the increased predisposition of the elderly to toxicity. Age-related differences in absorption, protein binding, and extrarenal clearance of digoxin are not well defined but do not appear to be clinically important [25]. A major pharmacokinetic factor contributing to the increased predisposition to digoxin toxicity relates to the change in volume of distribution of digoxin with aging [26]. Older persons have a decrease in muscle mass and an increase in fat mass. This smaller volume of distribution leads to higher serum digoxin levels.

The normal age-related decrease in renal clearance and the loss of renal function due to chronic disease are probably the other major factors that increase the risk of toxicity in the elderly. This problem is compounded by the fact that the serum creatinine level may not adequately reflect the decrease in renal function in the elderly because of decreased muscle mass; this may lead the clinician to use too high a dose of digoxin [27]. Because of that, clinician have to be aware about apparent normal serum creatinine level in elderly. Using Glomerular Filtration Rate (GFR) using Cockroft-Gall equation or more recently aMDRD equation is more effective to evaluate renal function especially in elderly.

Drug–drug interactions

Concomitant drug administration may directly alter the pharmacokinetics of digoxin or indirectly alter their action on the drug by pharmacodynamic interactions [28]. Amiodarone administration has been found to increase steady-state digoxin concentration significantly, and maintenance doses should be decreased by 50% or more. Examples of pharmacodynamic interactions include decreased gastrointestinal (GI) absorption of digoxin during cholysteramine administration, and increased incidence of digoxin toxicity during diuretic administration caused by volume depletion and induction of electrolyte disturbances, including hypokalemia and hypomagnesemia. The concomitant use of amiodarone, verapamil, spironolactone, flecainide, and propafenone can increase serum digoxin levels and may increase the likelihood of toxicity.

Monitoring free (Unbound) digoxin concentrations

Digoxin is only 25% bound to serum proteins mainly albumin. Monitoring free digoxin concentration can be useful only under special circumstances [29];

a) In patients overdosed with digoxin and being treated with FAB fragment of anti-digoxin antibody (digibind)

b) To eliminate interference of endogenous and certain exogenous digoxin-like immunoreactive factors on serum digoxin measurement.

ANALYTIC INFORMATIONS

Therapeutic drug monitoring for digoxin is carried out by immunoassays that are well established in routine clinical practice. Literature reviews the considerable variation in the routine monitoring of digoxin. This makes therapeutic drug monitoring difficult to interpret and complicates clinical management when treating physicians are endeavouring to avoid toxicity and optimize dosing. A study published in 2008 analyses results on 261 sample aliquots [NM. Rogers, TE. Jones, RG. Morris. Frequently discordant results from therapeutic drug monitoring for digoxin: clinical confusion for the prescriber. Internal Medicine Journal, 2008 Volume 40 Issue 1, Pages 52 - 56]. The results showed that 119 (46%) of 261 samples were so varied that a different clinical outcome was indicated when reviewed by the treating physician. The differences between the highest and lowest readings from any one sample were also substantial, with 45% of the measurements exceeding 0.3 µg/L.

The immunoassay methods used world wide are:

DGNA Digoxin Assay method run on a Dimension RXL analyser (Dade Behring, Cupertino, CA, USA)

DRI (Microgenics Diagnostics, Fremont, CA, USA) run on a Hitachi 911 analyser (Boehringer Mannheim, Indianapolis, IN, USA)

DRI (Microgenics Diagnostics) run on an Olympus 5400 analyser (Olympus Diagnostic Systems, Center Valley PA, USA)
Digoxin-II assay run on an AxSYM analyser (Abbott Diagnostics Division, IL, USA)
Kinetic Immunoinhibition Microparticle Assay (KIMA, Roche Diagnostics, Basel, Switzerland) run on an Integra analyser (Roche Diagnostics, Basel, Switzerland).
Digoxin serum levels should be drawn at least 4 hours after an intravenous dose and at least 6 hours after an oral dose (optimally 12-24 hours after a dose).

CONCLUSION AND EVIDENCE LEVEL

The appropriate therapeutic range for digoxin in chronic heart failure patients continues to be debated. The target serum digoxin concentration should be 0.5 to 1.0 ng/mL (0.6 to 1.3 nmol/L). Evidence rating is at B level (inconsistent or limited-quality patient-oriented evidence) [16,20,30].

AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

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COMPETING INTERESTS

The authors declare no competing interests.

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