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Therapeutic Ranges of Serum Digoxin Concentrations in Patients With Heart Failure

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Evidence-based medicine is an evolutionary process, intended to foster and disseminate the best practice guidelines from an ongoing critical analysis of available data. An underaddressed challenge relates to detecting and correcting delays where the evidence supports, but fails to effect, a timely change in practice. An example pertains to serum digoxin concentrations (SDCs) in the treatment of chronic heart failure (HF) because (1) the widely disseminated and used "therapeutic" SDCs for treating HF are not consistently aligned with considerably lower evidence-based values and (2) this discrepancy—a variant of the "clinical inertia" syndrome—may lead to unnecessary exposure of patients to potentially life-threatening toxicities.

Given its historic place in medical therapeutics, digoxin and related cardiac glycosides bypassed formal rigorous multiphase clinical trials designed to determine tolerability, toxicity, and efficacy. For more than two centuries, digitalis preparations have had a long-standing history in controlling the ventricular response in atrial fibrillation and treating HF.[1] Furthermore, several randomized trials performed beginning 30 years ago have demonstrated that digoxin confers benefits in patients with chronic HF related to improved exercise tolerance and quality of life.[2–7] However, these studies were small, with important limitations.[8] More convincing evidence was unavailable until publication of the Digitalis Investigation Group (DIG) trial in 1997.[9] This large-scale prospective randomized trial demonstrated that long-term treatment with digoxin had no effect on mortality alone but modestly decreased the combined risk of death and hospitalization in patients meeting entry criteria.

The American College of Cardiology/American Heart Association[10] and the European Society of Cardiology[11] currently recommend digoxin for the treatment of HF under specific clinical circumstances. Despite these recommendations, overall use of digoxin has decreased over the previous 10 years.[12] One report of a concomitant decrease in digitalis-related morbidity and mortality may reflect its decreased use.[13] Other reasons may be related to concerns about digitalis toxicity and the availability of multiple other approaches to treat HF, which are accompanied by a strong evidence base supporting mortality benefits—

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namely angiotensin-converting enzyme inhibitors,[14,15] angiotensin receptor blockers,[5] and β-adrenergic antagonists.[16,17] However, as a cautionary note, a recently published article has reported that, in elderly patients, digoxin is responsible for the third highest hospitalization rate for adverse drug events in the United States.[18] Therefore, at an estimated annual incidence of 4% to 5% per user[12] and a cost of >$6,500 per episode,[19] with associated morbidity and potential mortality, digoxin toxicity remains an important issue in contemporary clinical practice.

The development of a radioimmunoassay about 40 years ago was a breakthrough in relating SDC to risk of toxicity. As reported by Smith et al,[20] serum digoxin levels in 10 nontoxic patients (without atrial fibrillation) on oral doses of 0.25 mg/day were 1.1 ± 0.3 ng/ml (range 0.8 to 1.6) and 1.4 ± 0.4 ng/ml (range 0.9 to 2.4) for 11 clinically nontoxic patients on 0.50 mg/day (a dose rarely used in contemporary practice). Toxicity determined solely by electrocardiographic manifestations (e.g., atrial tachycardia with block, ventricular tachycardia, frequent or multifocal premature atrial or ventricular beats, second- or third-degree block, atrial fibrillation with slow ventricular response) was seen in 18 patients at a level of 3.3 ± 1.5 ng/ml (range 2.1 to 8.7). The findings from this small but seminal study became the basis for the unofficial but widely accepted guideline that the risk of toxicity is most likely to occur with serum concentrations >2.0 ng/ml and is almost certain at >3.0 ng/ml. Based on data derived from these 39 patients, a therapeutic range of 0.8 to 2.0 ng/ml was established.

However, retaining the upper serum concentration limit ~2.0 ng/ml is no longer defensible. First, it may provide clinicians a false sense of reassurance that patients with lower levels are not at risk from digitalis excess. Some patients are more sensitive to digitalis (especially elderly individuals) and may show signs of toxicity with therapeutic SDCs.[21] Second, additional agents used in conjunction with digoxin in treating HF may further predispose a patient to toxicity (e.g., potassium-wasting diuretics). In addition, patients with chronic HF and paroxysmal or persistent atrial fibrillation may be placed on amiodarone or dronedarone, which increases the steady-state concentration of digoxin, necessitating a dose decrease by ≥50%.[22–25]

More concerning is that this therapeutic range is well above that indicated to be prudent based on published data. One small study of 20 patients with HF, published before the DIG trial, demonstrated that improved quality of life and functional exercise capacity could be derived from SDCs ranging from 1.2 to 1.8 ng/ml.[4] The DIG trial sought to maintain trough SDCs at 0.5 to 1.5 ng/ml in enrolled patients, and the mean SDC was 0.8 ng/ml.[9] Furthermore, 2 other large randomized trials published after the DIG trial, demonstrating that HF worsened with the withdrawal of digoxin, maintained SDCs of 1.2 ng/ml.[6,7] Another study demonstrated that patients with end-stage renal disease on hemodialysis—a group predisposed to potassium and other electrolyte instabilities—were at increased risk of overall mortality from concomitant digoxin therapy; the safest SDCs were <0.9 ng/ml.[26]

Post hoc analyses of the DIG trial further supported findings that higher SDCs were detrimental. One of these, although confirming that discontinuation of digoxin was associated with a worsening of HF in ambulatory patients, showed that continuation of digoxin at “low” SDCs (0.5 to 0.9 ng/ml) was associated with a significant decrease in all-cause mortality and hospitalizations compared to SDCs ≥1.0 ng/ml.[27] Another analysis has indicated that SDCs >1.2 ng/ml may be harmful[28] and that maintaining a trough concentration of 0.5 to 0.8 ng/mL seemed to provide the benefits of treatment with a lower risk of adverse effects.[29]

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In response to this evidence, the Heart Failure Society of America (HFSA), in its 2010 practice guidelines, stated the serum digoxin concentration should be <1.0 ng/ml and preferably 0.7 to 0.9 ng/ml.[30] Of note, these HFSA recommendations were strengthened from those previously issued in 2000, in which no target range was specifically mentioned.[31]

Thus, current data strongly support decreasing the widely used and recommended therapeutic trough SDC range from 0.8 to 2.0 ng/ml to much lower values (e.g., 0.5 to 0.8 ng/ml) in the treatment of chronic HF. Although some influential resources have adopted these narrower ranges, others have failed to do so. Even within some multiauthored texts, disparate recommendations are provided (Table 1). Multiple factors may contribute to the failure in adopting evidence-based medicine into daily practice.[32,33]

First, clinical inertia is usually defined as the failure of health care providers to initiate or intensify therapy when indicated.[34] Perhaps this definition should be broadened to include sluggishness or resistance in making any change in practice (not just intensification) despite strong evidence to support this alteration. The example of “downsizing” digoxin levels, although outside the classic definition of clinical inertia, may be related to the “refractoriness” to implementing new guidelines in a timely and effective way. This type of evidence-based “exit block” is not unique to digoxin.

Second, most studies examining digoxin and digitalis toxicity were published in specialty journals before the current era when summaries and electronic access of such literature became routinely available. Successful introduction of new clinical guidelines is dependent on many factors including the clinical context and methods of developing, disseminating, and implementing those guidelines.[35] HFSA guidelines are not likely as widely read by practitioners outside cardiology. However, this explanation is, at best, only partly explanatory because articles in nonspecialty journals have critically reviewed currently accepted SDCs and strongly encouraged the adoption of more appropriate (lower) serum reference ranges for the previous decade or so.[36,37]

Third, failure to adopt new practice guidelines may be more likely when the supporting data are not fully derived from “gold standard” randomized controlled trials. Calls for further basic and clinical research have been made.[38] Although post hoc and observational trials have well-described limitations—particularly those pertaining to digoxin[39]—new prospective randomized studies to address the optimal range of serum digoxin levels seem neither realistic nor required. The DIG trial and subsequent post hoc analyses are consistent and compelling, especially in light of the limited efficacy and high potential toxicity of this drug.

What are the next steps toward standardizing and disseminating appropriate guidelines for recommended digoxin SDCs? One suggestion is that expert panels from relevant medical societies be convened to explicitly address the “range of recommended ranges,” critically re-examine the literature, and then issue and widely disseminate updated evidence-based “accounts of the foxglove.”[1] Optimally, these guidelines should include graded recommendations on the use of digoxin not only in HF but also in atrial fibrillation and other supraventricular tachyarrhythmias. Expert panels should also address whether ranges for men and women should be the same or should be lower in the latter group.[40] Recommendations should note areas of nonconsensus and uncertainty to help guide and spur future research.

SDC ranges should be annotated with cautions that digitalis toxicity may become manifest even within “therapeutic” serum levels, that the probability of toxicity is increased by certain metabolic abnormalities (e.g., hypokalemia, hypomagnesemia, and hypercalcemia),

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and that serum levels and risk of digoxin toxicity may be increased by some medications and by intrinsic or extrinsic factors that decrease its renal clearance.

Pending the issuance of “official” new guidelines, clinicians should consider whether it is time to adopt an upper therapeutic range of ~0.8 ng/ml for trough SDCs and thus preserve one of the few timeless guidelines of medicine: “first do no harm.”

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Table 1

Serum digoxin concentrations: selected reference therapeutic trough ranges

Resource	Range (ng/ml)
Online/electronic references	
POISINDEX®	0.6–2.6*
Lexi-Comp®	0.5–0.8†
UpToDate®	0.5–0.8†; 0.8–2.0§§
DynaMed™	0.5–2.0
Epocrates	0.5–0.8†; 0.8–2.0‡§
DRUGDEX®	0.8–2.0•
Specialty society heart failure guidelines	
American College of Cardiology/American Heart Association 2005 guideline update	0.5–1.0
European Society of Cardiology 2008	0.6–1.2
Reference textbooks	
Braunwald's Heart Disease, 9th Ed., 2012	<1.0†; 0.5–1.0†; 0.8–2.0‡¶
Goldman's Cecil Medicine, 24th Ed., 2012	0.5–1.0¶¶
Harrison's Principles of Internal Medicine, 18th Ed., 2012	<1.0#
Tintinalli's Emergency Medicine, 7th Ed., 2011	0.5–2.0
Rosen's Emergency Medicine, 7th Ed., 2010	0.7–1.1†##
Goldfrank's Toxicologic Emergencies, 9th Ed., 2010	0.5–2.0**
Physicians' Desk Reference, 2011	0.8–2.0††
Pharmacotherapy: A Pathophysiologic Approach, 8th Ed., 2011	0.5–1.0
2012 CURRENT Medical Diagnosis and Treatment	0.5–0.9†; 0.5–2.0†∞
Conn's Current Therapy, 2012	0.6–2.0
Oxford Textbook of Primary Medical Care, 2011	1.0–2.0
Hurst's The Heart, 13th Ed., 2011	0.5–1.1
Commercial laboratory	
Quest Diagnostics	0.8–2.0

* Notes that toxicity has been reported within this "normal" therapeutic serum digoxin concentration.

† Range cited for heart failure.

‡ Range cited for control of ventricular response with atrial tachyarrhythmias.

§ Notes that "arrhythmias may require higher level."

¶ "Effective serum or plasma concentration" for atrial tachyarrhythmias.

Range cited in the text for treating heart failure, but table on "toxicology and therapeutic drug monitoring" cites a therapeutic range of 0.5 to 2.0 ng/ml, with toxicity at >3.9 ng/ml.

** Level cited for "most institutions." Specifies that current evidence suggests upper limits of 1.0 ng/ml.

†† Notes that about 2/3 of adults considered adequately digitalized (without evidence of toxicity) have serum drug concentrations ranging from 0.8 to 2.0 ng/ml but that concentrations of 0.5 to 1.0 ng/ml may be "appropriate."

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¶¶ Range cited in the text, but table in Appendix “Drugs: Therapeutic and Toxic” cites a therapeutic range of 0.8 to 1.5 ng/ml, a range for CHF and arrhythmias as 1.5 to 2.0 ng/ml, and a toxic range of >2.5 ng/ml.

§§ Therapeutic range in chapter on Digitalis (Cardiac Glycoside) Poisoning.

∞ Notes that the positive inotropic effect is apparent with serum digoxin levels between 0.7 ng/mL and 1.2 ng/mL, and levels above this range may be associated with a higher risk of arrhythmias and lower survival rates.

Serum steady-state digoxin levels of 1.1 to 3.0 ng/mL are equivocal.

• This level is based on the Product Information for Lanoxin®, from Glaxo Wellcome, Inc.