Assessment of the Appropriateness of Serum Digoxin Concentration Measurement in a Medical Group Setting

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ABSTRACT

BACKGROUND: Recent quality initiatives require that the routine annual therapeutic drug-monitoring (TDM) parameters for the high-risk medication digoxin include a measure of renal function and a serum potassium level but not a serum digoxin concentration (SDC) measurement. Several studies have shown that the majority of the SDCs obtained in hospital settings provide little clinically actionable information.

OBJECTIVE: To evaluate the appropriateness and utility of SDCs ordered in a medical group practice setting by categorizing the reason the SDC was ordered and identifying action taken in response to the result.

METHODS: The descriptive study was conducted as a retrospective, electronic medical record (EMR) review of 90 primary care patients with continuous prescriptions for digoxin current on their medication profile with no gaps in therapy for at least 2 years prior to an SDC result entered into the EMR between January 1, 2009, and September 30, 2009. The reason the SDC was ordered was abstracted independently by 2 reviewers, who then assigned it to 1 of 8 predefined indication categories based on previously published criteria and practice guidelines. A third reviewer resolved inter-reviewer discrepancy ($n=1$).

RESULTS: A total of 90 patients with at least 1 SDC met inclusion criteria. Routine monitoring was the most frequent SDC order indication category with 35 patients (38.9%), 17 (48.6%) of whom did not have the recommended monitoring measures of potassium or renal function drawn concurrently. Patients were included in other categories as follows: confirmation of signs/symptoms of toxicity 30 (33.3%); assessment of factors altering pharmacokinetics 5 (5.6%); assessment of dosage change 5 (5.6%); assessment of drug interaction 3 (3.3%); assessment of clinical response 3 (3.3%); assessment of adherence 1 (1.1%); and other 2 (2.2%). Across all categories, a total of 19 (21.1%) of SDC results were outside the therapeutic range of 0.5 nanograms (ng) per mL and 2.0 ng per mL, 18 of which were below 0.5 ng per mL, with none of the subtherapeutic levels leading to a change in digoxin therapy. Only 1 patient (1.1%) had therapy changed in response to an elevated abnormal SDC result of 2.1 ng per mL and was in the routine monitoring category.

CONCLUSIONS: The majority of SDC results obtained in our medical group setting did not lead to clinical action, such as dose adjustment or drug discontinuation. SDCs were commonly measured as part of routine monitoring, which is considered an inappropriate indication, and often without being accompanied by better markers for digoxin toxicity such as serum potassium levels and measures of renal function as recommended by drug-monitoring quality initiatives. Provider education is needed regarding the most indicative digoxin TDM parameters to obtain in order to satisfy quality initiatives.

J Manag Care Pharm. 2011;17(9):695-700

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What is already known about this subject

- A quality initiative called “Annual Monitoring for Patients on Persistent Medications” is included as a National Committee on Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) effectiveness of care quality measure. Satisfying this quality measure requires that patients receiving digoxin have annual assessments of serum potassium and renal function but not a serum digoxin concentration (SDC). Results from the NCQA report for commercial health plans in 2009 showed that 16.4% of patients on persistent digoxin treatment did not receive the recommended monitoring.
- Previous studies have shown that 32%-84% of SDCs measured in the hospital setting are inappropriate based on criteria that include indication, timing, and interpretation of results. Whether SDC measurement adds value to clinical decision making in an outpatient setting has been largely unexplored.

What this study adds

- This descriptive, retrospective review explored the clinical utility of SDCs ordered for patients receiving persistent digoxin therapy in a multispecialty medical group setting. The most common reason an SDC was measured was for routine monitoring in 35 of 90 (38.9%) outpatients. For 17 of these 35 patients (48.6%), the SDC was the only monitoring parameter ordered; better markers for digoxin toxicity, such as measures of serum potassium and renal function, were not ordered concurrently.
- Our results showed that SDC results were seldom acted upon, especially when below the generally accepted therapeutic range. Of the 18 values (20.0%) less than 0.5 nanograms per milliliter, none led to a change in digoxin therapy including drug discontinuation.

Clinicians have been conducting therapeutic drug monitoring (TDM) for the medication digoxin for more than 30 years. Historically, pharmacists and physicians have been taught to maintain serum digoxin concentrations (SDC) within a narrow therapeutic window of safety and efficacy by using pharmacokinetic analysis to guide drug initiation and dose adjustment.¹ In spite of this practice, digoxin toxicity continues to be a major cause of preventable hospitalizations due to adverse drug events (ADE). The National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance project (NEISS—CADES) quantifies and

characterizes ADEs caused by outpatient drugs that result in emergency department visits. Budnitz et al. (2006) reported that NEISS—CADES data over the 2-year time period in 2004-2005 showed that approximately one-third of the 4,492 ADEs occurring in people aged 65 years or older were caused by 1 of 3 drugs that require safety monitoring—digoxin, warfarin, and insulin.²

In 2009, the “Annual Monitoring for Patients on Persistent Medications” was added as a National Committee on Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) Effectiveness of Care quality measure.³ Included in this quality measure is the requirement that all patients maintained on digoxin (at least 180 days in the 12-month measurement period) receive an annual assessment of serum potassium and renal function (serum creatinine or blood urea nitrogen) as TDM because hypokalemia and decreased drug clearance are known to predispose patients to digoxin toxicity. Results from the NCQA report for commercial health plans in 2009 showed that 16.4% of patients on persistent digoxin treatment did not receive the recommended monitoring.³ Routine safety surveillance does not include measurement of an SDC because once stabilization on a maintenance dose is achieved, random SDC sampling has never been shown to be predictive of toxicity and is best used to supplement clinical judgment.^{4,5}

The 2009 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for Heart Failure state that once the therapeutic range has been reached, SDC measurement is recommended and appropriate in the following circumstances: in response to a change in a toxicity-provoking physiologic parameters, such as decreased renal function; after the addition or discontinuation of an interacting drug; to assess clinical response; to assess adherence; or in the presence of clinical signs of digoxin toxicity.⁶ A 2002 retrospective study conducted at the University Hospital of Basel evaluated the usefulness of SDCs through comparison to researcher-developed, *a priori*-designed appropriateness criteria that considered indication, timing, and interpretation of results.⁴ Of 210 SDCs measured in the hospital, 125 (59.5%, 95% confidence interval [CI]=52%-66%) were rated as inappropriate, and 67 (31.9%, 95% CI=25%-38%) had an inappropriate indication for SDC measurement. A small but similar study sampled SDC values measured between October 1995 to March 1996 at Brigham and Women's Hospital and associated medical clinics.⁵ Results showed that only 16% (95% CI=11%-20%) of 162 inpatient SDCs and 52% (95% CI=44%-61%) of 117 outpatient SDCs had an appropriate indication when matched to appropriateness criteria. Among patients with inappropriate tests, none of the abnormal levels led to a change in therapy or revealed toxicity in inpatients, whereas only 1 outpatient result in the inappropriate testing group was clinically actionable.

The aim of the present study was to evaluate the appropri-

ateness and utility of SDCs ordered in a medical group practice setting by determining the reason the level was ordered and identifying action taken in response to the result. Through retrospective electronic medical record (EMR) review of SDCs measured in outpatients with evidence of continuous digoxin prescriptions during a 24-month time period, we abstracted and categorized the reason a level was ordered and evaluated whether the SDC result informed clinical decision making. The study was conducted to help plan strategies to improve drug-monitoring quality initiative activities at the study center and to better understand the role that SDC measurement may play in routine TDM.

■ Methods

Study Setting

The study was conducted as a descriptive, retrospective, EMR database review at the Palo Alto Division of the Palo Alto Medical Foundation for Health Care, Research, and Education (PAMF/PAD) located in northern California. For nearly a decade, PAMF/PAD has utilized a full-featured EMR produced by Epic Systems to document all clinical activity including computerized prescription and laboratory order entry. The PAMF/PAD Department of Quality and Planning can query the EMR to abstract patient-specific demographic information, physician assignment, prescription, and over-the-counter medication orders, laboratory results, diagnoses, appointment date and type, and a combination of factors. All documentation of visit (encounter) activity, including summaries of telephone encounters as well as electronic mail correspondence between patients and physicians, is contained in the EMR. Documents not available electronically, such as laboratory result reports conducted outside of PAMF/PAD, are scanned into the record. The study was approved by the PAMF Institutional Review Board.

Data Attributes and Study Population

An EMR query was conducted by the PAMF Department of Quality and Planning and initially identified 180 patients meeting the inclusion criteria of aged 18 years or older; PAMF/PAD primary care physician (PCP) assignment; not deceased; with at least 1 visit to any department between January 1, 2007, and September 30, 2009; and with at least 1 prescription for digoxin and an SDC result entered into the EMR between January 1, 2009, and September 30, 2009. An Excel (Microsoft, Redmond, WA) worksheet generated from the query included the patient's name, medical record number, sex, age, and the name of the assigned PCP. Other abstracted parameters included the result and date of the last measure of serum potassium, creatinine, and SDC. In order to satisfy study inclusion criteria and select patients stabilized on digoxin, chart review was necessary to ascertain that a continuous prescription for digoxin remained active on each patient's medication list for

TABLE 1 Categories of SDC Indication

Category	Definition
Confirmation of signs or symptoms of toxicity	Documentation explicitly states SDC ordered to evaluate cardiac and noncardiac signs of toxicity including palpitations, fatigue, mental status change, visual and auditory disturbances, hallucination, dizziness, headache, lightheadedness, weakness, N/V/diarrhea, abdominal pain, or other described as indicative of toxicity. ⁷
Assessment of factors altering pharmacokinetics	Documentation explicitly states SDC ordered in response to suspected change in digoxin absorption or dosage form, renal elimination, or factors altering the volume of distribution such as worsening heart failure or hypothyroidism.
Assessment of drug interaction	Documentation explicitly states SDC ordered to assess impact of initiation or discontinuation of a known interacting drug.
Assessment of clinical response	Documentation explicitly states SDC ordered to assess therapeutic response or failure.
Assessment of adherence	Documentation explicitly states SDC ordered to assess adherence.
Assessment of dosage change	Documentation explicitly states SDC ordered to assess dose increase, decrease, interruption, or discontinuation.
Routine monitoring	Documentation explicitly states SDC ordered for routine monitoring with no other precipitating factor present.
Other	Documentation explicitly states SDC ordered for other reason.
Could not determine	Reason not explicitly stated.

N/V = nausea/vomiting; SDC = serum digoxin concentration.

the entire 24-month time period prior to the date the SDC value was entered into the EMR (SDC index date; if more than 1 SDC value was recorded, the date closest to September 30, 2009, was defined as the SDC index date). For example, if a prescription for digoxin was ordered on September 1, 2007, and expired 1 year later, another prescription would need to have been entered on or before September 1, 2008, or the patient would be excluded because a gap in therapy would have been possible. Patients who did not have continuous digoxin orders during the 24-month time period were excluded. The review identified 90 patients who composed the study group.

EMR Review Process

The review process commenced on December 13, 2009, and was conducted by 4 reviewers: 1 pharmacist and 3 fourth-year doctor of pharmacy students. Individual patient records were accessed through entry of the medical record number into the EMR. A standardized Excel worksheet containing predefined data points was placed on a password protected share-drive and used by each reviewer to enter the abstracted information. Each patient was independently reviewed by 2 researchers, who completed separate worksheets. The worksheets were then reviewed for agreement, and any identified discrepancies were reconciled by a third reviewer, who conducted an independent review.

Assignment to a PAMF/PAD PCP was verified by viewing the PCP field. The "Chart Review" option was selected next, which allows access to sections of EMR documentation such as the medication list, visit summaries, laboratory results, vital signs, and patient correspondence including electronic messaging and telephone encounters. To view the patient's prescription information, the "Medications" tab was selected to display 2 views entitled "Current" and "History." A chronological listing of digoxin prescription orders was produced by filtering the "History" medication list by the generic name, digoxin, and sorted (ordered) by Start Date. The list was reviewed to make

certain that a continuous active order for digoxin was present throughout the time period of October 1, 2007, through September 30, 2009. It is important to note that the EMR medication list documentation captures the prescribing of all prescription drugs ordered by PAMF physicians due to computerized prescription order entry activity but does not include actual medication fill information. The diagnosis or indication for treatment with digoxin that was associated or linked to the current prescription was captured and categorized as atrial fibrillation, heart failure, both, or other. If the indication for digoxin could not be determined from the associated diagnosis, it was abstracted from the problem list and other chart documentation.

Next, the rationale or reason for each SDC order was abstracted and assigned to 1 of 8 predefined SDC indication categories in accordance with the parameters listed in Table 1. The routine monitoring category is the only indication considered to be inappropriate based on recommendations from the ACC/AHA guidelines, references, and criteria used in other studies.^{6,8} Also, the HEDIS quality measure for annual monitoring for patients on persistent digoxin does not include an SDC.³

Reviewers next viewed SDC results documented in the EMR. The results were filtered to identify the index SDC listed on the data query. A displayed laboratory result report also contains a link to the associated encounter where the SDC order was placed. This link was accessed for each index SDC in order to review the visit documentation where the decision to place the order was most likely noted. Linked encounters could be office visits, telephone encounter, or a laboratory order only. For example, a patient may have telephoned to inquire if laboratory assessments were needed prior to an office visit. If testing was needed, the laboratory order was placed at that time and linked to the telephone encounter.

The EMR system requires that an SDC laboratory order must be associated with a diagnosis code. Typically, an order

FIGURE 1 Sample Selection Flow Diagram

^aDefined as the 24-month period prior to the date that the SDC result was entered into the EMR.

^bDefined as the SDC retrieved by data query.

EMR=electronic medical record; PAMF/PAD= Palo Alto Medical Foundation Palo Alto Division; SDC=serum digoxin concentration.

was associated with the indication for digoxin or the order diagnosis (TDM). In other cases, the SDC order was associated with a chief complaint or visit diagnosis (e.g., malaise, fatigue, nausea), which indicated the reason for the laboratory order. The comment section of the original lab order was also reviewed because it allows the provider to enter a reason as free text for the SDC order. Laboratory results scanned into the EMR, which are not identifiable by query, were manually reviewed and recorded on the Excel spreadsheet.

Reviewers next identified the date of the SDC immediately preceding the index SDC and calculated the elapsed time in days between 2 results. Of note, the laboratory display flags an SDC result as high or low if it lies outside a defined therapeutic range of 0.5 nanograms per milliliter (ng per mL) and 2.0 ng per mL. During the study period, no standardized recommendations or guidelines for SDC monitoring were in effect at PAMF.

Results

After the initial review of 180 patients identified by an EMR

TABLE 2 Characteristics of Patients with SDC Measurement^a

Age in years mean (range)	78	(54-98)
Female % (n)	60.0	(54)
Indication % (n)		
Atrial fibrillation	57.8	(52)
Heart failure	12.2	(11)
Both	15.6	(14)
Other	14.4	(13)

^aTotal N=90.

SDC=serum digoxin concentration.

query, 90 met inclusion criteria (Figure 1). Characteristics of the study patients are shown in Table 2. Reviewer disagreement occurred with 1 patient (1.1%), and the discrepancy was reconciled by a third reviewer through independent review and final agreement with the original 2 reviewers. A total of 19 (21.1%) SDC results were outside the generally accepted therapeutic range, defined in the PAMF/PAD EMR as a value between 0.5 ng per mL and 2.0 ng per mL. Of the 19 abnormal results, 18 were below 0.5 ng per mL, none of which led to a change in digoxin therapy. Only 1 patient (1.1%) had therapy changed in response to an abnormal SDC result of 2.1 ng per mL. This SDC was ordered upon receipt of a refill request (routine monitoring) in a male aged 96 years with atrial fibrillation and was accompanied by a measure of potassium (3.8 milliequivalents [mEq] per mL) and a serum creatinine (1.4 milligram [mg] per deciliter). Of the 8 indication categories, routine monitoring was determined to be the most frequent reason an SDC was ordered (35 patients, 38.9%; Table 3). Of this group of 35 patients, 17 (48.6%) did not have measures of potassium or renal function drawn concurrently (i.e., on the same date). The average time since the last SDC was measured was 552 days (range 17 to 1,635 days), and the average age of the patients in this group was 79 years (range 55 to 96 years).

The second most common indication category was confirmation of signs and symptoms of toxicity, which included 30 patients (33.3%), yielding 5 abnormal SDC results. All 5 abnormal values were below 0.5 ng per mL and did not lead to any changes in digoxin therapy. The most common symptoms reported in 16 of the 30 patients with signs of toxicity (53.3%) were central nervous system complaints including fatigue, dizziness, auditory and visual hallucinations, and other mental status changes. The average time since the last SDC for the group was 426 days (range 14 to 1,246 days), and the average age of the patients was 82 years.

The next most common indication categories were assessment of factors altering pharmacokinetics and assessment of dosage change, each containing 5 patients (5.6%). The pharmacokinetics category included 3 patients with worsening renal function and 2 patients where a concern existed that they had

TABLE 3 Frequency of SDC Indications

SDC Indication Category	% (n) ^a	Abnormal SDCs		Action Taken in Response to Abnormal Result?	Average Time in Days Since Last SDC Measurement (Range)
		SDC <0.5 ng per mL	SDC >2.0 ng per mL		
1. Routine monitoring	38.9 (35)	8	1	Yes—1 dose lowered	552 (17-1,635)
2. Confirmation of signs/symptoms of toxicity	33.3 (30)	5	0	No	426 (14-1,246)
3. Assessment of factors altering pharmacokinetics	5.6 (5)	2	0	No	222 (144-942)
4. Assessment of dosage change	5.6 (5)	2	0	No	152 (26-431)
5. Assessment of drug interaction	3.3 (3)	1	0	No	189 (130-573)
6. Assessment of clinical response	3.3 (3)	0	0	0	151 (137-261)
7. Assessment of adherence	1.1 (1)	0	0	0	2,031
8. Other	2.2 (2)	0	0	0	195 (288-677)
9. Could not determine	6.7 (6)	0	0	0	392 (64-715)

^aTotal N = 90.

mL = milliliters; ng = nanograms; SDC = serum digoxin concentration.

received digoxin tablets subject to a nationwide recall.⁹ The SDCs ordered to assess dosage changes were ordered following dose reductions, one of which led to a further decrease in digoxin dosage, although the SDC value was within the therapeutic range (1.2 ng per mL).

The indication category of drug interactions included 3 patients (3.3%) who had an SDC drawn after the addition of azithromycin, carvedilol, and sotalol. The other category included 1 SDC ordered per patient request and another level ordered as part of a standardized pre-surgical evaluation. One patient had an SDC ordered to assess adherence, and in 6 patients (6.7%), the reason the SDC was ordered could not be ascertained from EMR documentation.

Discussion

Our results and those from similar reviews of hospitalized patients indicate that the majority of SDCs measured in clinical practice contribute little useful information to either improve clinical decision making or digoxin safety surveillance and are rarely acted upon even when abnormal.^{4,5,10} Our results also suggest that a rigid therapeutic range for SDCs may be an outdated concept that should be redefined.

The most common reason an SDC was ordered for outpatients stabilized on digoxin in our medical group setting was for routine safety monitoring (38.9%), an indication considered to be inappropriate.⁴⁻⁶ This problem has been documented in countries other than the United States. Sidwell et al. (2003) studied the utility of 100 SDCs drawn at Christchurch Hospital in New Zealand in September and October 2002 and categorized 53% of requests as inappropriate because they were ordered with no identifiable indication.¹⁰ Of more concern was our finding that 49% of the patients in the routine monitoring indication category did not have concurrent measures of serum creatinine and potassium, which are known to better correlate with digoxin toxicity, indicating that safety surveillance is being conducted suboptimally in some cases.

Our results also support findings from other studies showing that the generally accepted clinical signs and symptoms of digoxin toxicity were only fair predictors of an elevated SDC (more than 2 ng per mL).^{8,11,12} In fact, all 5 abnormal values in this indication category were actually below the lower limits of the therapeutic range. For all categories, no SDC below 0.5 ng per mL was acted upon with either a dose increase, an appraisal of the continued need for digoxin therapy, or drug discontinuation. Thus, we are measuring SDCs and then doing little with the results even when abnormal.

Information from large clinical studies and vetted practice guidelines call for a redefinition of the once generally accepted safe, therapeutic range for digoxin therapy of 0.8 ng per mL to 2.0 ng per mL.¹ *Post hoc* analysis of the Digitalis Intervention Group (DIG) study, which was limited to males, challenged this once accepted SDC therapeutic range for heart failure by demonstrating symptom relief for heart failure at SDCs between 0.5 ng per mL and 0.8 ng per mL with an increase in risk-adjusted mortality at values greater than 1.0 ng per mL.^{11,12} The DIG trial also showed that SDC values below 0.5 ng per mL provided effective symptom control for heart failure in many patients. A study by Miura et al. (2000) evaluated the relationship between SDC values and the incidence of digoxin toxicity in 899 Japanese patients receiving digoxin for heart failure, atrial fibrillation, or atrial fibrillation with tachycardia.¹³ Noncardiac symptoms of toxicity were common when SDC values were between 1.4 ng per mL and 2.0 ng per mL but did not occur with SDC values less than 1.4 ng per mL. Increasing age was shown to be a major predisposing factor for digoxin toxicity independent of renal function, and the authors suggested that the SDC therapeutic range for patients aged 70 years or older be redefined as 0.5 ng per mL to 1.4 ng per mL. The present study showed similar findings, with an average age of 82 years in the signs and symptoms of toxicity category and with no levels exceeding 2.0 ng per mL.

Limitations

First, all retrospective chart reviews rely heavily on the accuracy and completeness of EMR documentation. However, use of the EMR for more than 10 years in our setting should contribute to a more accurate patient record. Second, retrospective reviews are also subject to interpreter bias when data are abstracted, which we attempted to minimize by agreement between multiple reviewers; disagreement occurred in only 1 case. Third, we assumed that evidence of continuous prescription orders was a proxy for stabilization on digoxin and recognize this as a weakness of the study because interruptions or gaps in therapy may not have been identified. Fourth, because prescription fill data were not available, no assessment of patient adherence was possible. Fifth, we did not attempt to evaluate the appropriate timing of SDC draw (6 hours post-dose administration). Finally, this evaluation is descriptive in nature, and its sample size was too small to draw statistically significant conclusions.

Conclusions

Routine monitoring was the most common indication for SDC measurement in our medical group setting, occurring 38.9% of the time often without the recently recommended routine monitoring parameters for digoxin safety surveillance. When clinical signs and symptoms of digoxin toxicity were present (30 patients, 33.3%), no SDC was greater than 2 ng per mL, and the average age of this group was 82 years. The majority of SDCs ordered in our medical group setting for stabilized patients provided little clinically actionable information. A continued focus on achieving drug-monitoring quality goals and provider re-education regarding the measures most associated with digoxin toxicity, such as renal function and electrolyte serum levels, is an ongoing quality improvement activity at PAMF.

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DISCLOSURES

There was no external funding for this research, and the authors report no financial or other potential conflicts of interest related to the subject of this manuscript.

Concept and design were performed by Orrico with the assistance of Wilson and Wu. All authors contributed equally to data collection and interpretation. The manuscript was written and revised primarily by Orrico.

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