Prediction of Serum Concentrations of Digoxin in a Family Practice Center

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Physicians and clinical pharmacists were compared in their ability to predict serum digoxin concentrations and to discriminate among patients who were subtherapeutic, therapeutic or toxic. Physicians correctly predicted patients having therapeutic serum digoxin concentrations 77 percent of the time, but they were unable to reliably identify subtherapeutic and toxic patients. By incorporating more compliance and pharmacokinetic data into their assessment, pharmacists proved to be more accurate than physicians both in the prediction of serum digoxin concentrations ($P < .01$) and in therapeutic classifications ($P < .001$). The clinical pharmacist can be a valuable aid to the physician in the prediction and interpretation of serum digoxin concentrations.

Digoxin is one of the most commonly used medications in clinical practice today. Unfortunately, the drug has a narrow therapeutic index, making it difficult to maintain patients at a therapeutic serum drug concentration. As a result, up to 15 percent of hospitalizations for adverse drug reactions are due to digoxin toxicity.[1-3]

The purpose of this study was to examine the clinical application of serum digoxin concentrations in a family practice setting to determine how accurate physicians are at predicting the serum drug concentrations of their patients on digoxin. Also at issue were whether the physicians were able to identify which patients are subtherapeutic, therapeutic or toxic, and to what extent the clinical pharmacist can help with therapy.

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Methods

Data were collected during an eight-month period from July 1981 to March 1982 on patients seen at the Family Practice Center in Gainesville, Florida. For each serum digoxin concentration requested, both the prescribing physician and a pharmacy student under the supervision of a clinical pharmacist (JDR) were asked to complete a data collection form and predict the serum drug concentration. Each had access to the information obtained by the other.

The physician data collection form contained 18 questions that ascertained the following background information: (1) the dose and the length of time the patient had been taking digoxin; (2) the reason the patient was on digoxin; (3) pertinent laboratory, radiographic, electrocardiographic or physical findings; (4) the patient's clinical status and whether his condition had changed; and (5) other medical problems.

The physician was asked to indicate the reason for requesting a serum digoxin concentration read-

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Table. 1. Therapeutic Guidelines for Serum Digoxin Levels

Condition/Type of Level	Therapeutic Range (ng/mL)
Congestive heart failure	
Trough*	0.4-1.2
Peak**	0.5-1.5
Atrial fibrillation	
Trough	1.0-2.0
Peak	1.5-2.5

*Trough—the level drawn just before the next dose
**Peak—the level drawn 6 hours following the administration of the last dose

ing; to indicate whether he thought the concentration would be subtherapeutic, therapeutic, or toxic; to predict an actual value for the concentration; and to estimate the patient's compliance in taking the medication.

The pharmacy data collection form contained 42 questions covering the patient's personal characteristics (height, weight, ideal body weight, etc), pertinent laboratory data, and a detailed account of other medications the patient was taking. The pharmacist was asked to estimate compliance on the basis of talking with the patient ("estimated compliance") and then to refine this estimate with the benefit of pill counts, verification of prescription refills, and the results of any previous digoxin assays. This "corrected" compliance estimate was known as the "overall compliance rating," and was used in the final computation of the pharmacist's predictions. Patients were not aware that their compliance was being monitored.

Based on the above information, predicted mean serum digoxin concentration at steady-state ($\overline{Cpss}$) was calculated by the following formula:[4]

$$\overline{Cpss} = \frac{1.44 \times F \times D \times T_{1/2}}{Vd \times \tau}$$

where F = bioavailability (68 percent for Lanoxin tablets), D = dose, $T_{1/2}$ = half-life of digoxin, as estimated from the patient's renal function, Vd = volume of distribution (6-8 L/kg normally, 5 L/kg in renal failure),* and τ = dosing interval.

From this answer, peak and trough values were calculated, predicting serum digoxin concentrations at 6 and 24 hours after the last digoxin dose. Corrections for drug interactions were made if the patient was on quinidine** or ibuprofen.† A final prediction was then made taking into account the number of hours since the patient's last dose. Serum digoxin concentrations that were obtained less than 6 hours following the patient's last dose were adjusted to reflect what the concentration would be if the blood had been drawn after the completion of the distribution phase (ie, at 6 hours after oral administration of the drug), since the physicians had no way of knowing this information at the time they made their predictions. The pharmacist was then asked to predict whether he thought the serum digoxin concentration would be subtherapeutic, therapeutic, or toxic.

The therapeutic range for serum digoxin levels used in this study is defined in Table 1. Consideration was given both to the clinical situation and the actual serum digoxin concentration in determining whether borderline values were classified as subtherapeutic, therapeutic, or toxic. Each patient's

*A Vd = 5 L/kg was used if estimated creatinine clearance was less than 15 mL/min.
**If the quinidine-serum digoxin concentration was therapeutic, the pharmacy digoxin prediction was doubled.[5-7]
†If the patient was on therapeutic anti-inflammatory doses of ibuprofen (ie, ≥ 1200 mg/d), the pharmacy digoxin prediction was increased by 50 percent.[8,9]

Table 2. Patient Profile

Number of patients	81 (36% male, 64% female)
Average age	69.4 yr (range 39-93)
Average estimated creatinine clearance (Cl_{Cr})*	45.7 mL/min (40% of patients had $Cl_{Cr} \leq 35$ mL/min
Reasons for digoxin administration	
Congestive heart failure	65%
Atrial fibrillation	11%
Congestive heart failure and atrial fibrillation	15%
Supraventricular tachycardia	3%
Reason unclear	6%
Reason for obtaining serum digoxin concentration	
Worsening of symptoms	18%
Suspicion of toxicity	11%
Suspicion of noncompliance	14%
Routine check	57%

*Where $Cl_{Cr} = \frac{(140 - \text{Age}) \times \text{IBW (kg)}}{\text{Serum Cr} \times 72 \text{ kg}}$ for men[10] (multiply by 0.85 for women)

IBW (men) = 50.0 kg + 2.3 × (inches over 5 feet)
IBW (women) = 45.5 kg + 2.3 × (inches over 5 feet)
IBW = ideal body weight

medical record was further reviewed to determine whether physician prediction errors were predominantly pharmacokinetic or compliance in origin. All of the data were reviewed by the authors for accuracy. Statistical evaluation of the data was performed using chi-square analysis, and significance was established at $\alpha = .05$.

Results

A total of 117 serum digoxin concentrations obtained from 81 different patients were included in this study. For each concentration requested, a data collection form was given to the prescribing physician and a pharmacy student. Seventeen residents, 4 attending physicians, and 22 pharmacy students of varying experience participated. Eighty-one percent of the data collection forms were completed and returned to one of the authors (KG) before the digoxin value was determined. Six serum digoxin concentrations could not be used because of technical difficulties (ie, breakage of the test tube, laboratory error), leaving a total of 188 forms from which data were collected. The profile of patients used in the study is shown in Table 2.

Pharmacists' errors were almost entirely of overprediction (25 out of 27 cases) compared with physician errors, which were more evenly distributed between overprediction (27 cases) and underprediction (13 cases) ($P < .025$). Thirty-eight percent of physician errors were attributed to not adequately understanding digoxin pharmacokinetics, 40 percent to inaccurately estimating compliance, and the remaining 22 percent to a combination of these factors.

The accuracy of identifying whether patients had subtherapeutic, therapeutic or toxic concentrations was examined. When physicians predicted that a patient would have a therapeutic concentration, they were correct in 48 out of 62 cases (77 percent). Of the 14 patients who did not have therapeutic serum digoxin concentrations, six were toxic and 8 were subtherapeutic.

Pharmacists were correct in predicting that 77 out of 83 serum digoxin concentrations (93 percent) would be therapeutic, which was significantly better than the physicians ($P < .001$). Among the six errors, one patient had a toxic level and the other five were subtherapeutic.

For patients thought to be subtherapeutic, physician predictions were accurate in only 7 out of 20 cases, whereas the pharmacists correctly predicted that 9 out of 10 patients would be subtherapeutic. Two out of 5 patients were thought to have toxic levels by physicians compared with 5 out of 7 patients who were accurately predicted to have toxicity by pharmacists.

Comparison was made between physician and pharmacist assessment of patient compliance. Physician and pharmacist estimations of patient compliance were considered to be in agreement if they differed by 25 percent or less. Among the 81 serum digoxin concentrations for which both the physician and pharmacist made predictions, agreement was reached in 49 cases (60 percent).

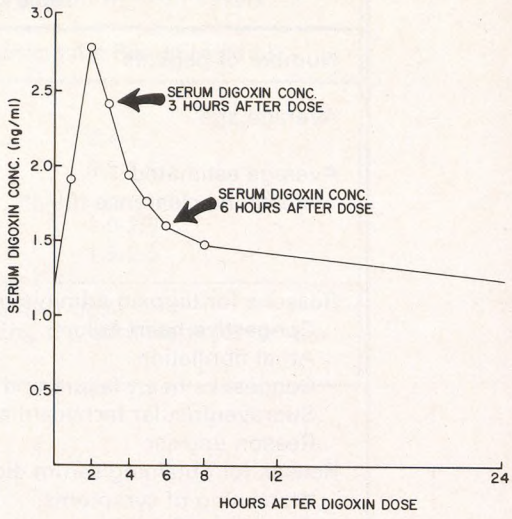

Figure 1. Serum digoxin concentrations in the hours following oral administration (adapted from Walsh and Sode[13])

Discussion

Pharmacokinetic factors important to consider in the assessment of serum digoxin concentrations include (1) the daily maintenance dose of digoxin and the time the last dose was administered, (2) the age of the patient, (3) the condition being treated (ie, congestive heart failure or atrial fibrillation), (4) the presence of other significant medical conditions (such as coronary artery disease, chronic obstructive pulmonary disease, hyperthyroidism), (5) renal and electrolyte status, and (6) other medications that the patient is taking (ie, quinidine, ibuprofen). To better understand the results of this study, the application of these factors will be reviewed.

The brand of digoxin used by all of the patients in the study was Lanoxin, which has a bioavailability of 68 percent in the tablet form.[11] The drug is passively absorbed by the gastrointestinal tract and reaches its maximal serum concentration approximately 2 hours after administration. Following this, serum drug concentrations rapidly decline as the drug is distributed into the various tissue compartments over the next 6 to 12 hours[11-13] (Figure 1). During this time, the concentration of digoxin becomes greatest in the myocardium, where it may reach concentrations greater than 30 times higher than those in the serum.[11] However, if blood is drawn prior to the completion of this distribution phase, the serum concentration will not yet accurately reflect the concentration of digoxin at its active receptor site in the myocardium.[11,13] For example, a serum digoxin concentration of 2.4 ng/mL obtained 3 hours following administration of the last dose would correspond to a serum concentration of 1.6 ng/mL if one had waited for 6 hours before drawing the blood (Figure 1). It is only after the distribution phase has been completed and a state of equilibrium has been established between serum and myocardial concentrations that the serum concentration of digoxin will

closely reflect the myocardial effect of the drug.[14]

The therapeutic range of digoxin has been the subject of much controversy in the literature. Most investigators agree that the beneficial effects of the drug begin at concentrations under 1.0 ng/mL, and that toxicity usually does not develop until serum concentrations of 2.0 ng/mL have been surpassed.[1,11,12,14-16] In a study by Smith and Haber,[14] 87 percent of patients with cardiac signs of toxicity had a serum digoxin concentration greater than 2.0 ng/mL while 90 percent of patients without any evidence of toxicity had concentrations under 2.0 ng/mL. Serum digoxin concentrations close to 2.0 ng/mL constitute an area of overlap in which it may be difficult to distinguish between therapeutic and toxic concentrations.[17] Patients with previous myocardial infarction, chronic obstructive pulmonary disease, or with low serum potassium levels are extremely sensitive to seemingly low serum digoxin concentrations and may be toxic at values well below 2.0 ng/mL.[14] Others with thyrotoxicosis or atrial fibrillation with a rapid ventricular response may require serum concentrations of 3.0 ng/mL or higher for control of their condition without the development of toxicity.[16,18] In those patients with atrial fibrillation who do not have complicating medical diseases (ie, acute myocardial infarction, infection, etc), control of the ventricular response rather than measurement of serum digoxin concentrations may provide a more suitable end-point of digitalization.[1,18] For this study, the authors used the guidelines indicated in Table 1 in conjunction with the patient's clinical situation to determine whether a serum digoxin concentration was subtherapeutic, therapeutic, or toxic.

Digoxin is eliminated from the blood by renal excretion and hepatic metabolism. In the presence of normal renal function, the half-life of digoxin is about 1.6 days, and over 70 percent of the drug is renally excreted.[11,12] With progressive renal impairment, the half-life is prolonged, and metabolism becomes the principal route of elimination. This is the case in elderly individuals in whom renal function may be decreased by over 50 percent, necessitating a corresponding reduction in the daily maintenance dose. In the extreme case of a patient without any renal function, digoxin is entirely metabolized by the liver, and the half-life may be as long as five days.[11,19]

Finally, one must be aware of several interactions between digoxin and other medications. The best documented example is the addition of quinidine, which on the average causes a doubling of the serum digoxin concentration.[5-7] Canine experiments have shown increased serum digoxin concentrations when some of the nonsteroidal anti-inflammatory agents are used,[8] and preliminary results of a 14-patient study performed at the University of Florida suggest a 50 percent increase in the serum digoxin concentration when ibuprofen is added.[9] Recently nifedipine has also been reported to increase serum digoxin concentrations by about 50 percent.[20]

In this study, physicians fared relatively poorly in predicting the actual serum digoxin concentrations of their patients. They were better at predicting therapeutic classification. Although unable to reliably identify subtherapeutic and toxic patients, physicians were correct 77 percent of the time at predicting which patients would have therapeutic serum concentrations, supporting the premise that routine monitoring of serum digoxin concentrations is generally not needed in patients who are clinically controlled on the drug.[15,21] Serum concentrations of digoxin seem to be most useful when toxicity or noncompliance is suspected or when the state of digitalization is difficult to assess.[7,12,22]

Pharmacists proved to be more accurate than physicians in predicting actual serum concentrations ($P < .01$). In addition, pharmacists surpassed physicians by correctly predicting 93 percent of patients who had therapeutic serum digoxin concentrations and in being better able to identify patients who were subtherapeutic or toxic ($P < .001$).

It is of interest to compare the types of predictive errors made in this study. The pharmacists' errors were consistently due to overestimation of serum digoxin concentrations, whereas physician errors were of both overprediction and underprediction ($P < .025$). In predicting serum digoxin concentrations, knowledge is needed both of patient compliance and of the pharmacokinetics of the drug. Since the pharmacy students were specifically trained to apply pharmacokinetic principles in their predictions, the predominance of overprediction errors is attributed to an overestimation of compliance on their part. In contrast, physician errors of both overprediction and underprediction were divided almost equally into

pharmacokinetic and compliance errors.

Compliance remains the most important determinant of serum digoxin concentrations.[22,23] Nevertheless, in this study physicians and pharmacists were unable to agree in their estimates of patient compliance 40 percent of the time.

Pharmacists evaluated compliance by regularly questioning patients on how they took their medication, when they took their last dose, and whether they were experiencing any adverse effects. They also encouraged patients to bring their medication with them so that pill counts could be performed, consulted the patient's pharmacy regarding prescription refill dates, and reviewed the results of previous serum digoxin assays.

Physicians had an equal opportunity to employ compliance data plus the advantages of a long-term relationship and a better appreciation of the patient's clinical status. Although physicians were not so accurate as pharmacists in estimating compliance, their assessment may be viewed as complementary, since physicians were correct in a number of instances in which pharmacists overestimated compliance.

Use of pharmacokinetic and compliance data by the pharmacist resulted in more accurate predictions of serum digoxin concentrations and therapeutic classifications. This may be attributed to the greater effort routinely put forth by pharmacists in acquiring such data (ie, calling pharmacies, performing pill counts, etc). Physicians were not encouraged to seek out data to any greater extent than they normally would in their practice setting. Given an equal knowledge of pharmacokinetics and the time to record detailed compliance histories, physician accuracy would be expected to be similar to that of the pharmacist.

Physicians are accurate at predicting patients with therapeutic serum digoxin concentrations. They can improve their accuracy in predicting subtherapeutic and toxic levels by attending to the timing of dosing, renal and electolyte status, the condition for which digoxin is being prescribed, concomitant medical problems, other medications as well as a more thorough evaluation of compliance. Time-consuming pharmacokinetic calculations and meticulous questioning of patients regarding compliance may not be cost effective, considering the busy schedule of the practicing family physician. In these cases the inclusion of a clinical pharmacist as a member of the health care team may improve the assessment of patients on digoxin.

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