Nighttime dosing assures postdistribution sampling for therapeutic drug monitoring of digoxin

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To study the appropriateness of phlebotomy for digoxin therapeutic drug monitoring (TDM) in outpatients, we conducted a retrospective chart review, a computer search of all previous TDM testing, and a questionnaire of all outpatients (n = 86) who had serum digoxin determinations between April 10 and April 28, 1992 (585 tests). In patients who took digoxin at the same time daily (40 patients, 300 tests), 52% of tests were performed on inappropriate samples drawn within 6 h of the last dose. No patient who took digoxin after 1700 had inappropriate tests. Phlebotomy for serum digoxin determinations before distribution of digoxin is complete is a common problem in outpatients, leading to clinically uninterpretable test results. Postdistribution sampling can be assured by nighttime dosing, and this recommendation has been implemented at our hospital.

INDEXING TERMS: blood sampling • pharmacokinetics

Digoxin is one of the most widely prescribed drugs for both inpatients and outpatients [1], and digoxin serum concentration is the most commonly ordered therapeutic drug monitoring (TDM) test in the US. Digoxin serum concentrations have been shown to be useful in corroborating the clinical diagnosis of digoxin toxicity as well as correlating with therapeutic effects of digoxin [2, 3]. Digoxin pharmacokinetics are complex but well characterized (for a review see [4]). For oral dosing of digoxin, rapid absorption occurs in the intestine [4]; reaching distributional equilibrium after a digoxin dose requires at least 8 h, the time at which the semilog plots of plasma and tissue concentrations vs time reach terminal linear and parallel slopes [4, 5]. Samples obtained within 8 h after a digoxin dose can be very misleading as an index of digoxin response [4].

For TDM to be used effectively, several criteria must be fulfilled: There must be a rational indication for the test; accurate analysis of the drug concentration performed on an appropriate sample; correct interpretation of the results; and, ultimately, an appropriate response of the physician to the digoxin concentration [6]. Failure to comply with one or more of these criteria will compromise the utility of TDM. In this study, we focused attention on the collection of an appropriately timed sample. We examined outpatient digoxin TDM in a university hospital setting to determine the appropriateness of the timing of measurements of digoxin concentrations with respect to the time of drug administration.

Patients and Methods

Patients. All outpatients (86 patients) who had serum digoxin determinations between April 10 and April 28, 1992, were studied. In addition, results of any prior digoxin determinations on these patients performed in the toxicology laboratory since May 1990 were included in the study. A search of the clinical laboratory databank for each patient identified 585 individual tests. Clinical data were collected via a retrospective outpatient chart review. A questionnaire and accompanying letter describing the nature of this study were mailed to the patients, with the consent of their physicians, and a second letter was sent after 2 months if no response was obtained. Data collected by questionnaire included whether the patient took digoxin at the same time daily, the time at which the patient took digoxin (before 0900, 0900–1200, 1200–1700, or after 1700), and whether the patient took digoxin at the same time on days when blood was drawn for digoxin determinations.

Methods. Digoxin concentrations were measured in serum samples with the Abbott TDx (Abbott Laboratories, Abbott Park, IL) fluorescence polarization immunoassay. The therapeutic range of postdistribution concentrations at steady state in use at our hospital was 0.9–2.0 μg/L. The supratherapeutic range was >2.0 μg/L. Subtherapeutic concentrations were <0.9 μg/L, with a detection limit of 0.5 μg/L.

Since exact dosing times were not elicited in the questionnaire, for calculation purposes we assumed the time of daily digoxin dosing to be 0730 for those patients indicating before
0900, 1030 for between 0900 and 1200, 1430 for between 1200 and 1700, and 1930 for after 1700. The time from the last digoxin dose was determined as the time of phlebotomy (recorded for each test) minus the time of the last dose (as above). For analyses of the timing of digoxin measurements in relation to the last digoxin dose, only those patients fulfilling the following criteria were included: completion of the questionnaire, digoxin dose taken at the same time daily, digoxin taken by the patient at the same time on the days of blood draws. Serum concentrations determined on specimens obtained <6 h from the last dose (before the distribution phase was complete) were considered inappropriate and clinically uninterpretable.

Statistics. Statistical analyses ($\chi^2$, Student's $t$-test) were performed with a commercial statistical program, InStat (GraphPad, San Diego, CA).

Results

During our survey of outpatient serum digoxin concentrations between April 10 and April 28, 1992, we identified 86 patients. The patients' physicians were contacted and chart reviews were performed. Also, questionnaires were sent to each patient at the address provided by the physician. Of the 86 patients, 44 returned completed questionnaires. The results of the questionnaire and chart review are summarized in Table 1. A search of the computer data bank revealed a total of 585 outpatient digoxin tests performed on these 86 patients between May 1990 and April 1992.

To evaluate the timing of digoxin testing relative to the patient's last dose, we grouped those patients who took digoxin at the same time every day, including days on which blood samples had obtained for digoxin concentrations. Forty of the 44 patients who returned questionnaires fulfilled these criteria and accounted for 300 of the 585 total serum digoxin concentrations performed. These patients routinely took each dose of digoxin at the same time: 14 before 0900, 18 between 0900 and 1200, 3 between 1200 and 1700, and 5 after 1700.

The blood sample collection times for the 300 serum digoxin concentrations available for full analysis were: 16 (5%) before 0900, 25 (8%) between 0900 and 1200, 245 (82%) between 1200 and 1700, and 14 (5%) after 1700. The distribution of the digoxin determinations falling within specified intervals is shown in Table 2. For all patients, there were few (4%) digoxin serum concentrations >2 µg/L and 55% were between 0.9 and 2.0 µg/L. The remainder (~40%) were below the therapeutic range. Comparison of the percentage distribution of digoxin concentrations according to concentration range between non-responders to the questionnaire and the selected responders (patients fulfilling inclusion criteria as above) showed no significant difference.

To evaluate the appropriateness of these tests with regards to the timing from the last dose of digoxin, we analyzed the 300 tests on the selected patients. As shown in Table 2, 52% (125 tests) were inappropriate (performed on specimens obtained <6 h from the last digoxin dose). For the few serum digoxin concentrations above the therapeutic range, 64% (7 of 11) were from inappropriate timed samples. Of the tests in the therapeutic range, 56% (104 of 186) were drawn before the distribution phase was complete and 43% (44 of 103) of the subtherapeutic concentrations were measured in inappropriate drawn specimens.

The number of tests with relation to the last digoxin dose is shown in Fig. 1. A majority (69%) of the tests were performed on serum samples obtained <8 h after the last dose. In Fig. 2, the percentage of patients who were always appropriately (all tests >6 h from the last dose) monitored is shown vs the time of usual dosing. As can be seen, <30% of the patients who took their digoxin before 1700 were always appropriately monitored.

<table>
<thead>
<tr>
<th>Table 2. Evaluation of timing of serum digoxin concentrations stratified by digoxin concentration.</th>
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<td>All patients</td>
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<td>Nonresponders</td>
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Serum digoxin measurements on all patients (86) and selected patients who fulfilled study criteria (see Methods) were calculated as subtherapeutic (<0.9 µg/L), therapeutic (0.9-2.0 µg/L), and supratherapeutic (>2.0 µg/L) as shown. Tests on selected patients were further analyzed with respect to timing of blood sampling relative to last digoxin dose. Digoxin concentrations drawn within 6 h of the last dose were considered inappropriate. Percentages are of the total tests (n) within each row. $\chi^2$ analyses showed no significant difference among the percentage of tests in each concentration range between nonresponders and selected responders and between appropriate and inappropriate tests within the selected group.

Table 1. Characteristics of outpatients who had serum digoxin tests performed between April 10 and April 28, 1992.

<table>
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<th>n</th>
<th>All patients</th>
<th>Responders</th>
<th>Nonresponders</th>
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<tbody>
<tr>
<td>Average age (range), years</td>
<td>64 (30-95)</td>
<td>62 (30-91)</td>
<td>66 (41-95)</td>
</tr>
<tr>
<td>Male:female</td>
<td>52:34</td>
<td>25:19</td>
<td>27:15</td>
</tr>
<tr>
<td>Average daily dose (range), mg</td>
<td>0.2 (0.036-0.375)</td>
<td>0.183 (0.036-0.375)</td>
<td>0.219 (0.065-0.312)</td>
</tr>
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Information was obtained from outpatient chart review and patient questionnaires. Responders are those patients who completed questionnaires. All others are nonresponders. Average daily digoxin dose between responders and nonresponders is not significantly different ($P > 0.05$) by Student's $t$-test for independent means.

* 50 questionnaires were returned, of which 44 were completed. Forty patients met the inclusion criteria specified in Methods.
Thus, take digoxin according to the following criterion.

Methods

Last evening or morning serum digoxin concentrations were determined for all 86 outpatients, who took digoxin at the same time daily. Tests were grouped into hourly intervals from the last dose.

We examined the subtherapeutic digoxin tests in more detail. Fifteen patients had one subtherapeutic concentration and 45 had more than one subtherapeutic concentration; only 26 patients had no subtherapeutic digoxin concentrations (data not shown). Also, nearly 10% (n = 58) of the total tests in this study were less than the lower limit of detection of our assay, 0.5 μg/L (data not shown). To determine the relative frequency of subtherapeutic tests among patients with multiple tests, we examined all patients with 5 or more serum digoxin determinations (40 patients, range 5 to 34 tests per patient) and calculated the percentage of subtherapeutic concentrations for each patient. As shown in Fig. 3, 16 of 40 patients were subtherapeutic >50% of the time and 3 were subtherapeutic >90% of the time. In these three patients 18 of 18, 12 of 13, and 6 of 6 serum digoxin determinations were subtherapeutic.

Time of Digoxin Dosing

The small number of patients who took digoxin in the evening (five patients) were always appropriately monitored and none of these patients had inappropriately timed tests. This is not unexpected, considering that 270 (90%) of the blood samples for digoxin concentration were drawn between 0900 and 1700. Thus, virtually all samples obtained from patients taking digoxin in the evening would meet the >6-h-after-the-last-dose criterion.
risk of toxicity or the beneficial effects of digoxin [4]; they were clinically uninterpretable.

The difficulties of the timing of phlebotomy for TDM of digoxin in patients have been described previously. Clague et al. [7] examined 200 consecutive requests for digoxin assays and (using 8 h or more from the last oral dose of digoxin as an appropriate time interval) found that <6% of these samples were inappropriate. Others have subsequently found that a higher percentage of tests were inappropriately timed. In a 12-week survey of digoxin TDM, Gibb et al. [8] showed that 35% of outpatient tests and 25% of inpatient tests were inappropriate (within 6 h of the last dose). Kumana et al. [9] demonstrated that 31% of the digoxin assays over a 6-month period were performed on blood samples drawn within 6 h of the last digoxin dose. Copeland et al. [10] evaluated the digoxin assays performed during a 7-week period and determined the appropriateness of digoxin TDM with respect to clinical indications for the test and the action taken in response to the test results. Of these tests performed for an appropriate indication (n = 48), 6 (12%) were performed before steady state was achieved and 13 (27%) were performed on samples within 6 h of the last dose. In our hospital, Matzuk et al. [11] investigated inpatient digoxin monitoring and dosing patterns. They showed that increased serum digoxin concentrations were often measured in samples drawn within 6 h of the last oral dose and demonstrated that nonuniform dosing times were a major cause. A uniform dosing policy for all inpatient units in conjunction with a standardized phlebotomy time for serum digoxin tests was adopted to assure collection of postdistribution serum specimens and thereby decrease the number of increased digoxin concentrations obtained in nonpostdistribution samples. Recently, Howanitz and Steindel [12] examined the digoxin TDM data from the Q-probe studies of 666 institutions. They report only the results of supratherapeutic concentrations but show that 22% of inpatient and 45% of outpatient tests were drawn within 6 h of the last dose. Piergies et al. [13] audited 92 patients with serum digoxin concentrations >3.0 µg/L. They found that 30 patients (33%) had blood drawn <6 h after digoxin administration. None of these patients exhibited signs of digoxin toxicity. On the other hand, 44 of the 62 patients (71%) whose blood samples were appropriate had one or more signs of digoxin toxicity [13].

The current study is unique in that we have examined the digoxin TDM of individual outpatients over 2 years. Our study was designed to investigate the frequency of appropriate (postdistribution) blood sampling for digoxin TDM. We assumed that patients were unlikely to take their medication at exactly the same time daily over 2 years; therefore, we did not attempt to elicit exact dosing times in the questionnaire. Also, the questionnaire included a question asking if the patients had made a change in their dosing habit over the 2 years of the study. No responder indicated a change in the time they took digoxin. For calculation purposes, we assigned the time of the last dose to a time within each range (see Methods). Generally, this assignment could lead to a maximum error of 2.5 h. To examine if this error skewed the results, we also analyzed only those tests that could be definitely assigned to appropriate or inappropriate timing (e.g., digoxin concentrations from tests performed on samples obtained before 1500 are inappropriate for patients taking digoxin between 0900 and 1200). This alternative analysis yielded similar results (data not shown). Also, our cutoff of 6 h from the last dose is conservative. Indeed, the observation has been made that digoxin concentrations measured in serum obtained within 8 h of the last dose can be misleading as an index of inotropic response to digoxin [4]. Given these caveats, some interesting questions arise from the data and await further study. We found that a large number (52%) of the blood samples were inappropriately drawn <6 h from the last dose. Stratifying all tests by concentration range of digoxin showed that 40% were subtherapeutic. Examination of the patients with multiple serum digoxin determinations revealed a high frequency of subtherapeutic concentrations per patient. These patients were obviously maintained at low concentrations. Evaluation of whether or not these patients derived benefit from this therapy was beyond the scope of this study. In the selected patients, 62% of the serum digoxin concentrations were in the therapeutic range but 56% of these were performed on samples drawn within 6 h of the last dose. Whether true postdistribution concentrations would have been in the therapeutic range is unknown. Of the digoxin concentrations and patients studied here, only 14 patients had supratherapeutic concentrations (only 4% of all tests). Seven (64%) of the supratherapeutic tests in the selected patients were inappropriate. Therefore, exposure to potentially toxic concentrations of digoxin was not a major problem in this study.

Ideally, the solution to the problems identified in this study would be that each physician would educate his/her patient about the timing of their laboratory tests. This is probably unattainable, considering the increasing demands on medical caregivers' time in medical management and nonmedical issues. In our experience, physician educational programs work best when coupled with practical procedures that will maximize assurance of compliance with stated therapeutic goals. Since none of the patients who took digoxin after 1700 had any inappropriately timed digoxin concentrations, a practical approach would be nighttime dosing by patients. Although the number of patients (n = 5) who took digoxin after 1700 in our study is small, the fact that the majority of blood sampling was performed between 0900 and 1700 provides the assurance that morning or afternoon blood draws would be >6 h from the last dose. The serum digoxin concentrations from these blood draws would represent true postdistribution values. This is analogous to the uniform inpatient digoxin dosing policy adopted by our teaching hospital [11]. Except for the administration of digoxin loading doses, all inpatients prescribed this medication receive it at 1700 and phlebotomy for requested serum digoxin concentrations is performed at 0700.

After review of the data presented here and our recommendation to establish an after-1700 dose time for outpatients, our hospital Medical Board instituted a physician practice guideline that includes the following: All physicians prescribing digoxin have received a summary of the study results and conclusions and the recommendation that all patients be switched to nighttime dosing, and all prescriptions filled by our pharmacy are now given with instructions to take digoxin at night. As a preliminary assessment of
the effects of these measures on digoxin TDM, we conducted a questionnaire survey of those patients refilling prescriptions at our pharmacy, asking for their regular digoxin dosing time. Of 39 patients, 22 (or 56%) took digoxin after 1700, compared with just 12% in the original study group. A search for recent digoxin concentrations performed on these patients revealed that 12 patients had tests performed in our laboratory and none was performed on inappropriately timed blood samples. These initial results are encouraging and suggest that a simple change in dosing schedule will lead to better TDM and patient care while reducing costly, inappropriate testing.

We thank the physicians in the Departments of Medicine, Cardiovascular Medicine, Hematology/Oncology, and Surgery of the University of Pennsylvania Medical Center for their participation and cooperation with the chart review and contacting their patients. We thank the members of the Drug Use and Effects Committee of the University of Pennsylvania Medical Center for their valuable suggestions regarding the design of this study. We thank Jonathan C. Fox, Arthur Atkinson, and David Shulkin for their critical review of this manuscript and helpful discussions. Finally, we thank Erika S. Roberts and the Laboratory Medicine computer room staff for performing the searches for all digoxin tests performed on the patients in our study.

References


