A Case Series of Hospitalized Patients with Elevated Digoxin Levels

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PURPOSE: Although there is renewed enthusiasm for the use of digoxin in patients with heart failure, current dosing guidelines are based on a nomogram published in 1974. We studied the incidence of and risk factors for elevated digoxin levels in patients admitted to a community hospital, and compared their dosage regimens to published guidelines.

SUBJECTS AND METHODS: We reviewed the charts of all patients who had serum digoxin levels greater than 2.4 ng/mL during a 6-month period. We collected demographic and clinical data, indications for digoxin use, digoxin dosage, concurrent medications, laboratory data, and clinical and electrocardiographic features of digoxin toxicity.

RESULTS: Of the 1,433 patients with digoxin assays, 115 (8%) patients had elevated levels. Of the 82 patients with complete records and correctly timed digoxin levels, 59 (72%) had electrocardiographic or clinical features of digoxin toxicity. Patients with serum digoxin levels >2.4 ng/mL were slightly older (78 ± 8 versus 73 ± 9 years of age; P = 0.12) and had greater serum creatinine levels (3.1 ± 7.3 versus 1.4 ± 0.3 mg/dL; P = 0.01) than those with levels ≤2.4 ng/mL. Forty-seven patients had elevated digoxin levels on admission, including 21 patients admitted for digoxin toxicity. Impaired or worsening renal function contributed to high levels in 37 patients, and a drug interaction was a contributory factor in 10 cases. Twenty (43%) of these patients were taking the recommended maintenance dose based on the scheme employed in the Digitalis Investigation Group study. Thirty-five patients developed high digoxin levels while in hospital. In 26 patients, this followed a loading dose of digoxin for the control of rapid atrial fibrillation. Impaired renal function was implicated in all of these patients. Despite the elevated digoxin level, rate control was achieved in only 11 patients of these patients.

CONCLUSIONS: Elevated digoxin levels and clinical toxicity remains a common adverse drug reaction. Elderly patients, particularly those with impaired renal function and low body weights, are at the greatest risk. As published digoxin nomograms often result in toxicity, clinical variables need to be monitored. In patients with congestive heart failure and normal sinus rhythm the potential benefit of digoxin is small; thus, patients should receive a dose that minimizes the risk of toxicity. For patients with new onset atrial fibrillation, other agents may be preferable for rate control. Am J Med. 1998;105:110–115.

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assays obtained, length of hospital stay, concurrent medications, laboratory data including blood urea nitrogen, serum creatinine and electrolytes, and all electrocardiographic (ECG) data. Any medical record without this information was considered incomplete and nonevaluable.

Each patient’s creatinine clearance was calculated using the Jelliffe formula (15). The maintenance dose prescribed was compared with the dosing scheme followed in the DIG study (7,11,13,14). The recommended loading dose was based on ideal body weight and whether renal dysfunction was present, using the guidelines published by the manufacturer (Glaxo-Wellcome, Research Triangle Park, North Carolina). Determination of the time of blood sampling in relation to digoxin administration was assessed from nursing records, physician orders, and laboratory records. A digoxin level drawn within 6 hours of an intravenous dose or within 12 hours of an oral dose was considered a sampling error (mistimed specimen). Patients were grouped as to when the elevated digoxin levels were obtained: on admission to hospital; during hospitalization; after an initial loading dose; and after a supplementary loading dose in patients already receiving digoxin (reloading).

Digoxin toxicity was defined as the development of signs or symptoms commonly associated with digoxin toxicity that resolved after digoxin withdrawal or dose reduction. Signs and symptoms included anorexia, nausea, vomiting, weakness, visual disturbances and arrhythmias, including ventricular bigeminy, ventricular tachycardia, ventricular fibrillation, atrioventricular junctional escape rhythm, paroxysmal atrial tachycardia with atrioventricular block, atrial fibrillation with slow ventricular response (<60 beats/min), Mobitz type 1 second degree atrioventricular block, and sinus bradycardia (<60 beats/min) (16,17). Patients were followed until discharge or death. Digoxin toxicity was considered the probable cause of death if an arrhythmia associated with digoxin toxicity was the primary cause of death, and the digoxin level was above 2.4 ng/mL at the time of death. Digoxin toxicity was considered a contributory cause of death if the patient had organ system failure that led to death and a digoxin level above 2.4 ng/mL was obtained within 24 hours of death.

**Statistical Methods**

Group means were compared by the t test for unpaired data. Chi-square analysis was used to compare categorical data. Unless otherwise stated, all data are expressed as mean ± SD, with statistical significance set at P <0.05 or less.

**RESULTS**

During the study period, 2,483 digoxin assays were obtained on 1,433 patients. One hundred and fifteen patients (8%) had serum digoxin concentrations greater than 2.4 μg/mL. Complete clinical data were available for 102 of these patients, 20 of whom had an elevated level due to sampling error. Thus, 82 (5.7%) patients had appropriately sampled digoxin assays with a level greater than 2.4 ng/mL (Table 1). Fifty-nine (72%) of these patients had ECG or clinical features of digoxin toxicity. The mean age of the 1,318 patients with serum digoxin concentrations ≥2.4 ng/mL was 73 ± 9 years; their mean serum creatinine level was 1.4 ± 0.3 mg/dL. The mean age of the 82 patients with serum digoxin levels ≥2.4 ng/mL was 78 ± 8 years (P = 0.14) while their mean serum creatinine level was 3.1 ± 7.3 mg/dL (P = 0.01). Twenty-four patients had both ECG and clinical features suggestive of digoxin toxicity, 12 had ECG features alone, while 23 had clinical symptoms alone. ECG features of digoxin toxicity included junctional rhythm (n = 9), paroxysmal atrial tachycardia with atrioventricular (AV) block (n = 6), Mobitz type 1 second degree AV block (n = 5), bigeminy (n = 5), sinus bradycardia (n = 4), slow atrial fibrillation (n = 3), AV dissociation (n = 2), and ventricular tachycardia (n = 2). Three patients were treated with digoxin-specific Fab fragments. Four hundred and thirty-seven digoxin assays were performed on the 102 patients with high levels, with a range of 1 to 18

<table>
<thead>
<tr>
<th>Table 1. Demographic and Clinical Data in Patients with Serum Digoxin Concentrations ≥2.4 ng/mL.</th>
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<tr>
<td>Digoxin level (ng/dL)</td>
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<td>Age (years)</td>
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<td>Men</td>
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<td>Weight (kg)</td>
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<td>Serum creatinine (mg/dL)</td>
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<td>Creatine clearance (mL/min/1.72m²)</td>
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<td>Time of elevated levels</td>
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<td>After loading dose</td>
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<td>After “reloading”</td>
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<td>Died during hospitalization</td>
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Data are expressed as mean ± SD (range). There were no significant differences between the groups.
Table 2. Digoxin Levels and Renal Function in Patients Who Received a Loading Dose

<table>
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<th>&quot;Full” Digitalization (n = 21)</th>
<th>Reloading* (n = 5)</th>
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<tr>
<td>Loading dose given (mg)</td>
<td>0.89 ± 0.26</td>
<td>0.75 ± 0.27</td>
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<tr>
<td>Recommended loading dose (mg)†</td>
<td>0.45 ± 0.18</td>
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<tr>
<td>Calculated creatinine clearance</td>
<td>27 ± 15</td>
<td>40.8 ± 8.3</td>
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<tr>
<td>Digoxin level (ng/mL)</td>
<td>3.5 ± 1.2</td>
<td>2.8 ± 0.6</td>
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Data are expressed as mean ± SD.

* Received additional loading dose while already receiving digoxin.
† According to manufacturer, based on ideal body weight and renal function.

DISCUSSION

Several studies in the 1970s reported digitalis intoxication in up to 23% of patients admitted to the hospital while taking digoxin (18–20). With the widespread use of digoxin assays and the attempt to keep serum levels within the therapeutic range, the incidence of digoxin toxicity has diminished to less than 6% (21–23). A recent study of more than 280,000 digoxin levels from 666 institutions in the United States found that 6.7% were in the toxic range (21). However, between 22% and 31% of these specimens were obtained before distribution had occurred. The relatively high (5.7%) frequency of elevated digoxin levels in our study may reflect the advanced age, low body weight, and poor renal function of our patients, and the failure to recognize the interplay of these factors in the pharmacokinetics of digoxin. Our study confirms the observation that most patients receive a 0.25 mg dose of digoxin regardless of age, weight, or renal function (16,24). Indeed, 20 patients became toxic after receiving the correct maintenance dose based on the Jelliffe and Booker nomogram (which was modified and used in the DIG study) (7,11,13,14).

We do not know why digoxin-specific Fab fragments were not administered to the 8 patients in whom digoxin toxicity was thought to be the cause or a contributory cause of death. Lack of familiarity with digoxin-specific Fab, as well as the indications for its use, may have played a role.

Renal Function

In the DIG study, 2% of patients in the digoxin group and 0.9% in the placebo group were admitted to hospital for suspected digoxin toxicity (11). This low incidence is probably attributable to the exclusion of patients with significant renal dysfunction from the study. Also, most patients were less than 70 years of age, and digoxin doses were determined according to weight and calculated creatinine clearance (7,11,14). Although the median digoxin dose was 0.25 mg/day, the mean serum digoxin level was only 0.8 ng/mL (7).
Both renal function and age are independent predictors of digoxin toxicity (25). The mean serum creatinine concentration is between 2.5 and 3.4 mg/dL in patients with digoxin toxicity (16,22,23,25). In patients with normal renal function, elimination of digoxin is primarily renal (50% to 80%), with a β half-life of 36 hours (26). In addition to glomerular filtration, digoxin is actively secreted by the renal tubular cells via the P-glycoprotein drug efflux pump (27). In patients with chronic renal failure, renal and total digoxin clearance is decreased with a β half-life of up to 5 days (26). Consequently, the maintenance dose of digoxin must be reduced. In addition, patients with impaired renal function may be particularly susceptible to digoxin toxicity because myocardial Na+ -K+-ATPase is partly inactivated. Thus, less digoxin is required to cause toxicity (28,29). Furthermore, it is generally not appreciated that the apparent volume of distribution of digoxin is significantly reduced in patients with renal failure (26,28,30,31). Jelliffe and Brooker (12) and Jelliffe (32) suggested that it was not necessary to reduce the loading dose of digoxin in these patients. However, as is apparent from our study, patients with impaired renal function are at high risk of developing excessive digoxin levels if they receive a 1.0 mg intravenous loading dose.

Effects of Age
The elderly use about 80% of digitalis products, with 25% of the population over the age of 85 years using digoxin (33). The risk of an adverse event caused by digoxin increases significantly with advancing age, such that a person older than 85 years is twice as likely to experience an adverse event as someone aged 65 through 74 years (33). Older individuals have relatively fewer binding sites for digoxin and a decreased volume of distribution (25,29). Elderly patients with poor renal function are at particularly high risk for digoxin toxicity and should be treated very cautiously. Moreover, in the elderly with apparently normal serum creatinine serum levels, the glomerular filtration rate may be substantially decreased, slowing digoxin excretion and prolonging its half-life.

Drug Interactions
Several drugs alter digoxin pharmacokinetics, increasing the risk of toxicity. Quinidine, verapamil, amiodarone, propafenone, cyclosporine, and itraconazole reduce renal excretion of digoxin (24,34–36). These drugs have been demonstrated to inhibit P-glycoprotein mediated digoxin secretion by the renal tubular cells (36–38). Macrolide antibiotics, particularly clarithromycin, erythromycin, and roxithromycin, have been implicated in causing digoxin toxicity (39,40). It has been suggested that these antibiotics eliminate Eubacterium lentum from the gastrointestinal tract, leading to increased absorption and elevated serum digoxin concentrations (39,40). Eubacterium lentum, an anaerobic gram-positive rod, converts digoxin to digoxin reduction products (41).

Monitoring Digoxin and Target Levels
Our study reconfirms the extensive overlap of serum digoxin levels in patients with and without symptoms (17,42). Moreover, there were no significant baseline differences between the patients who were asymptomatic and those who had signs or symptoms of digoxin toxicity (16). The trend toward higher mortality in our symptomatic patients has been seen in other studies (16).

The digoxin assay is the most widely used drug assay and represents a considerable medical cost (11,21). A major error in its use is the failure to wait for the postdistribution phase, which requires 12 hours after an oral dose and 6 hours after an intravenous dose (24). Administering digoxin in the evening has been recommended in the hospitalized patient, with the drug assay being performed in the morning (24,43). The time of the last dose should be noted on the laboratory requisition form to assure specimens have been appropriately drawn (43). When ordering a digoxin assay, the clinician must consider whether steady state has been achieved, remembering that this takes 4 to 5 half-lives (range of 10 to 25 days) following any change in dose. In our study, a digoxin assay was performed on average every 2.1 days in patients with elevated levels, reflecting a poor understanding of digoxin’s pharmacokinetics.

Disease progression in heart failure is related not only to hemodynamic but also to neurohumoral factors (44). Neuroendocrine inhibitory effects of digoxin in patients with cardiac failure have been noted (45–49). Low maintenance dosages of digoxin (0.125 mg) reduce sympathetic activity with no additional benefit when the dose is increased (45,47). Four recent clinical trials, including the DIG study, suggest that high serum digoxin levels (>1.1 ng/mL) or full dose digoxin (≥0.25 mg/day) is associated with increased risk of death (8–11). In 1974, Jelliffe and Booker (12) demonstrated that the risk of arrhythmias increases with increasing digoxin serum levels. Furthermore, although the DIG trial suggested a trend toward a beneficial effect from digoxin on death from pump failure, there was a trend toward increased mortality due to other cardiovascular causes (7). Thus, digoxin in low doses may be beneficial through modulating sympathetic activity, while at higher doses the risks of arrhythmias outweigh these benefits. Moreover, in patients with congestive heart failure and normal sinus rhythm, the potential benefits of digoxin are small when compared with ACE inhibitors. If digoxin is given to patients with normal sinus rhythm, it should be used in doses that do not carry a risk of toxic effects with serum levels between 0.7 and 1.2 ng/mL (11,50). The serum digoxin level should be monitored in the elderly, in patients with deranged renal function, and when used in conjunction with agents that alter the drug’s disposition. Furthermore, the dosage should be adjusted and the serum level
monitored in patients with an acute decline in renal function.

Atrial Fibrillation
Rapid digitalization has been considered the treatment of choice for patients with new-onset atrial fibrillation to facilitate conversion to sinus rhythm or to achieve rate control (51,52). Rapid digitalization is also recommended for paroxysmal atrial fibrillation and for rate control in patients with chronic atrial fibrillation (51,52). Despite elevated digoxin levels, adequate rate control was only achieved in 11 (42%) of 26 patients in our study. Two recent randomized placebo-controlled studies demonstrate that digoxin does not increase the rate of conversion to sinus rhythm and provides weak rate control in patients with acute atrial fibrillation (53,54). Furthermore, intravenous diltiazem was superior to intravenous digoxin for ventricular rate control in acute atrial fibrillation (55). These data suggest that digoxin may have a limited role in the management of acute atrial fibrillation.

In conclusion, our study shows that digoxin toxicity remains a common and serious adverse drug reaction. Elderly patients, particularly those with impaired renal function, are at the greatest risk. The current dosage guidelines will frequently result in toxicity in these patients, and therefore a lower dose is recommended, together with therapeutic drug monitoring. Clinicians should be aware of drugs that increase digoxin serum concentrations. In patients with congestive heart failure and normal sinus rhythm, the potential benefit of digoxin is small, and patients should receive a dose that minimizes the risk of toxicity. Digoxin may no longer be the drug of first choice for patients with acute atrial fibrillation. If digoxin is used for this indication, calculation of the loading dose must take into account the patient’s ideal body weight and renal function.

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REFERENCES