Clinical Investigations

Digoxin Use and Digoxin Toxicity in the Post-DIG Trial Era

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ABSTRACT

Background: The advent of medical therapies for congestive heart failure that have proven survival benefits, specifically angiotensin-converting enzyme (ACE) inhibitors, ß-adrenergic antagonists, and the aldosterone antagonists, have called into question the use of digoxin for patients with normal sinus rhythm, left ventricular dysfunction, and symptomatic heart failure. This issue appears to have been heightened after the publication of the results of the Digitalis Investigation Group (DIG) Trial in 1997 that did not demonstrate a statistically significant impact of digoxin on mortality.

Methods and Results: We used data from a large heart failure registry to examine digoxin use at the time of hospital admission for heart failure, a surveillance system for recording toxic drug exposures to describe patterns in digoxin toxicity and industry estimates for the use of digoxin antibody. Digoxin use has decreased significantly from 31.4% in late 2001 to 23.5% in late 2004 (P<.00001) independent of patient age, gender, or baseline creatinine. Conversely, the number of toxic or potentially toxic exposures to digoxin requiring hospitalization has not decreased.

Conclusion: Digoxin use is decreasing but there has not been a similar decline in cases of toxicity. Further analyses are required to delineate the reasons underlying these trends and the appropriateness of prescribing practices for both digoxin and its antidote.

Key Words: Digoxin, Practice patterns, Heart failure, Drug toxicity.

Over the last 20 years, with the advent of medical therapies for congestive heart failure that have proven survival benefits, specifically angiotensin-converting enzyme (ACE) inhibitors, ß-adrenergic antagonists (ß-blockers), and the aldosterone antagonist spironolactone, the use of digoxin for patients with normal sinus rhythm, left ventricular dysfunction, and symptomatic heart failure may have been called into question. This issue appears to have been heightened after the publication of the results of the Digitalis Investigation Group (DIG) Trial in 1997,6 which despite a decrease in hospitalization for heart failure, did not demonstrate a statistically significant impact of digoxin on mortality; rather, adverse effects were seen in certain subgroups.7 Indeed Packer stated that “as the list of (life extending) drugs increases in the coming years, the use of digoxin will gradually, but inevitably, diminish.”8

However, the impact of changes in background therapy on clinical practice is difficult to gauge, especially when the drug in question has been indelibly ingrained in the minds of generations of clinicians as a necessary therapy. Further, although the degree to which randomized clinical trials influence practice has been previously examined,9–11 these results may not apply when there are only observational data or when the results of a clinical trial provide intermediate results. Hence, although increases in the use of ACE inhibitors and ß-blockers have been clearly documented,12,13 little is known about prescribing patterns involving the cardiac glycosides.

We hypothesized that digoxin use has decreased over time and, as a corollary, that if changes have occurred in the prescription of digoxin, there should be a parallel change in the use of the polyclonal antibody to digoxin (Digibind [GSK, Research Triangle Park, NC] and DigiFab [Protherics, Brentwood, TN]) for cases of documented or presumed toxicity.
Methods

To evaluate this hypothesis, we obtained data from multiple sources in an attempt to describe and understand current practices with digoxin. Data on digoxin use were derived from the Acute Decompensated Heart Failure National Registry, which contains data on patients hospitalized with acute decompensated heart failure in a large sampling of community, tertiary, and academic centers across the United States; the overall design, methods, and patient characteristics in the registry have been previously described. We analyzed the use of digoxin on admission from the fourth quarter 2001 through the end of calendar year 2004 and examined 2 groups at higher risk for digoxin toxicity (age greater than 75 years and serum creatinine greater than 2.0 mg/dL). In light of retrospective data from the DIG Trial suggesting an increased mortality rate among women treated with digoxin as opposed to placebo, we also compared use in women and men. In addition, z-scores with corresponding P values were calculated to quantify the differences in the proportion of women versus men taking digoxin between October 2001 and December 2002 compared with the period between January 2003 and December 2004 (after publication).

Data on toxicity were derived from published data of the American Association of Poison Control Centers’ Toxic Exposure Surveillance System (www.aapcc.org) for calendar years 1998–2003. Toxicity was defined by the AAPCC as the occurrence of a “major morbid outcome” (the patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability such as respiratory compromise, ventricular tachycardia, or cardiac arrest) or a “moderate morbid outcome” (the patient exhibited signs or symptoms as a result of the exposure that were pronounced, prolonged, or systemic in nature; usually some form of treatment was indicated, but symptoms such as acid base disturbance or disorientation were not life threatening). The number of units of digoxin antibody sold (in the thousands) was obtained from pharmaceutical marketing data estimates for calendar years 2001–2004 based on information obtained from the US business development unit of GlaxoSmithKline, taking into account the sales to intermediaries of the two commercially available polyclonal antibody formulations (Digi-bind and DigiFab).

Results

Use of Digoxin

The overall use of digoxin has decreased significantly at the time of presentation to the hospital (31.4% to 23.5%, P < .00001 for trend) for a heart failure diagnosis (Table 1). This change has occurred independent of gender, age (<75 years vs. ≥75 years of age) or baseline serum creatinine (<2.0 mg/dL vs. ≥2.0 mg/dL) (all P values < .001). The use of digoxin was consistently and statistically greater in males than females and in patients with lower rather than higher creatinine values; at most time points, digoxin use was greater in patients age 75 years and older than in the younger cohort. Although the pattern of decreasing use of digoxin in both men and women continued after the publication of the DIG trial, the decrease in use among males was actually greater than among females (P < .001). The presence of a history of atrial fibrillation or presentation with atrial fibrillation was associated with a higher likelihood of digoxin use. The percentages of patients on digoxin with and without a history of atrial fibrillation were 41.3 and 20.1 respectively (P < .001); similar figures apply to patients with and without atrial fibrillation on admission (39.6 vs. 23.4% respectively; P < .001).

Digoxin Toxicity

The number of toxic or potentially toxic exposures to digoxin requiring hospitalization in any age group has not changed significantly from 1996 to 2003 though the total number of exposures reported among adults greater than 19 years has increased (Fig. 1). The incidence of morbid outcomes and death increased from 1996 to 2000 and subsequently remained relatively constant (Table 2). The number of cases for which digoxin antibody was prescribed has increased in absolute terms and as a percentage of admissions for toxicity (from 16.2% in 1996 to 30.7% in 2003, P < .001).

Table 1. Use of Digoxin

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Overall digoxin use</td>
<td>31.4</td>
<td>29.1</td>
<td>28.5</td>
<td>27.2</td>
<td>25.5</td>
<td>25.0</td>
<td>23.5</td>
</tr>
<tr>
<td>Females</td>
<td>26.4</td>
<td>26.0</td>
<td>25.6</td>
<td>24.7</td>
<td>22.6</td>
<td>22.0</td>
<td>20.5</td>
</tr>
<tr>
<td>Males</td>
<td>36.6</td>
<td>32.5</td>
<td>31.5</td>
<td>29.9</td>
<td>28.6</td>
<td>28.2</td>
<td>26.5</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>48.2</td>
<td>44.8</td>
<td>44.1</td>
<td>42.5</td>
<td>39.2</td>
<td>38.3</td>
<td>36.9</td>
</tr>
<tr>
<td>No history of atrial fibrillation</td>
<td>23.9</td>
<td>22.7</td>
<td>21.5</td>
<td>20.2</td>
<td>19.2</td>
<td>19.0</td>
<td>17.3</td>
</tr>
<tr>
<td>Atrial fibrillation on admission</td>
<td>47.8</td>
<td>43.9</td>
<td>43.0</td>
<td>40.7</td>
<td>37.4</td>
<td>35.5</td>
<td>35.2</td>
</tr>
<tr>
<td>No atrial fibrillation on admission</td>
<td>27.2</td>
<td>25.5</td>
<td>24.8</td>
<td>23.7</td>
<td>22.4</td>
<td>22.3</td>
<td>20.6</td>
</tr>
<tr>
<td>Age &lt;75 years</td>
<td>31.2</td>
<td>29.2</td>
<td>30.0</td>
<td>28.3</td>
<td>26.1</td>
<td>25.7</td>
<td>24.2</td>
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<tr>
<td>Age ≥75 years</td>
<td>31.5</td>
<td>29.1</td>
<td>27.0</td>
<td>26.1</td>
<td>24.9</td>
<td>24.3</td>
<td>22.8</td>
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<tr>
<td>Cr ≥2 mg/dL</td>
<td>29.0</td>
<td>25.4</td>
<td>24.1</td>
<td>22.8</td>
<td>22.4</td>
<td>21.2</td>
<td>18.9</td>
</tr>
<tr>
<td>Cr &lt;2 mg/dL</td>
<td>32.1</td>
<td>30.1</td>
<td>29.7</td>
<td>28.3</td>
<td>26.4</td>
<td>26.1</td>
<td>24.9</td>
</tr>
</tbody>
</table>

Source: ADHERE Registry.
There has been a slight downward trend in the estimated number of units of digoxin antibody sold in the United States since 2001, but no overall change comparing 2000 with 2004 (2000: 37,000; 2001: 43,000; 2002: 41,000; 2003: 39,000; 2004: 38,000). The average number of units per year sold is 39,600 ± 2408.

**Table 2. Outcome of Cases of Digoxin Toxicity Exposure**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Exposures in Hospitals</th>
<th>Number of Major Morbidity or Death (%)</th>
<th>Number of Exposures, Digoxin Antibody Administered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>1454</td>
<td>681 (46.8)</td>
<td>446 (30.7)</td>
</tr>
<tr>
<td>2002</td>
<td>1469</td>
<td>656 (44.6)</td>
<td>346 (23.6)</td>
</tr>
<tr>
<td>2001</td>
<td>1493</td>
<td>665 (44.5)</td>
<td>314 (21.0)</td>
</tr>
<tr>
<td>2000</td>
<td>1535</td>
<td>673 (43.8)</td>
<td>328 (21.4)</td>
</tr>
<tr>
<td>1999</td>
<td>1404</td>
<td>581 (41.4)</td>
<td>334 (23.8)</td>
</tr>
<tr>
<td>1998</td>
<td>1509</td>
<td>533 (35.3)</td>
<td>296 (19.6)</td>
</tr>
<tr>
<td>1997</td>
<td>1400</td>
<td>428 (30.6)</td>
<td>231 (16.5)</td>
</tr>
<tr>
<td>1996</td>
<td>1477</td>
<td>479 (32.4)</td>
<td>239 (16.2)</td>
</tr>
</tbody>
</table>

Source: American Association of Poison Control Centers’ Toxic Exposure Surveillance System Data.

For definition of “major” or “moderate” morbidity, see text for details.

we observed in digoxin use extends to 2004, several prior studies have suggested conflicting trends both before and after the publication date of the DIG trial, using data from single centers, observational registries, and clinical trials. Although baseline use in heart failure trials may be decreasing, applying these data to infer real trends is made difficult by interstudy differences in the demographics of study subjects (eg, distribution by New York Heart Association classification and the geographic location of the study center). At the same time, use in the elderly with heart failure has been noted to be almost twice the rate observed in our report. The decrease in use of digoxin we observed may be due in part to the increasing recognition of its limited role when patients are on β-blockers and possibly reflect concern about the effects in women, although the gender data from the DIG Trial was published after the trend in decreasing digoxin use began and the rate of decline was actually greater in men. It is likely that the overall decline in use will continue, despite the fact that digoxin remains a part of heart failure guidelines for symptomatic heart failure patients on standard medical therapy and the gender difference may be explained by differences in serum digoxin concentrations. Indeed, this trend suggests that there may be other influences on practice that can supercede the guidelines and that digoxin may be relegated to a significantly less important role in heart failure management over time. Conversely, continued advocacy for and interest in digoxin may also occur, in part, because of the recognition that efficacy may be achieved when lower serum levels are targeted.

Further, we observed no parallel trends for digoxin toxicity; in fact, the number of reported exposures may be increasing. Given the absence of a clear downward trend in the incidence of digoxin toxicity, it is possible that the use of the drug is continuing in those heart failure patients who may be at high risk for complications from the drug, for example, we found that use was higher in the elderly. This is important because when toxicity occurs, the associated costs are considerable. In this analysis, digoxin antibody use has increased for cases of toxicity while industry estimates for digoxin antibody sales suggest a downward trend during some of the same years. Whether this reflects a more conservative estimate of the number of vials needed to treat each episode cannot be established from these data sources.

The study is limited by the fact that not all prescriptions for digoxin antibody or cases of toxicity occur in patients with heart failure. Indeed, with an increased emphasis on rate versus rhythm control for patients with atrial fibrillation, the use of digoxin for this diagnosis may lead to a concomitant increase in the incidence of toxicity. We demonstrated that the use of digoxin in patients with either a history of atrial fibrillation or atrial fibrillation on admission was much higher than in patients without such characteristics. However, there are no reliable data that describe patterns of use of digoxin in an atrial fibrillation population.
We cannot assess the appropriateness of the prescription of digoxin or the antidote, control for changes in the estimated size of the heart failure population, or differentiate use between systolic and diastolic heart failure.

Clearly, further multivariable analyses of data derived from observational and administrative databases are required to establish whether digoxin use is changing in specific patient subgroups such as patients with preserved left ventricular systolic function and in settings outside clinical trials and registries. In addition, heart failure registries generally enroll patients with a principal admission or discharge diagnosis of heart failure, not digoxin toxicity, limiting their usefulness in evaluating practice patterns with digoxin antibody. Data are also lacking about contemporary physician attitudes toward and beliefs about the role for digoxin in patients with advanced heart failure symptoms. Nevertheless, the decline in digoxin use is clear. The major outstanding issue is the extent to which digoxin will remain a conventional therapy for heart failure.

References