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Digoxin Toxicity and Use of Digoxin Immune Fab

Insights From a National Hospital Database

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ABSTRACT

OBJECTIVES This study was developed to determine contemporary management of digoxin toxicity and clinical outcomes.

BACKGROUND Although the use of digoxin in heart failure management has declined, toxicity remains a prevalent complication.

METHODS The Premier Perspective Comparative Hospital Database (Premier Inc., Charlotte, North Carolina) was used to retrospectively identify patients diagnosed with digoxin toxicity and/or who received digoxin immune fab (DIF) over a 5-year period (2007 to 2011). DIF was evaluated using treatment date, number of vials administered, and total cost. Clinical outcomes included length of stay (total hospitalization; days after DIF), cost of hospitalization, and in-hospital mortality. Exploratory multivariate analyses were conducted to determine predictors of DIF and effect on length of stay, adjusting for patient characteristics and selection bias.

RESULTS Digoxin toxicity diagnosis without DIF treatment accounted for 19,543 cases; 5,004 patients received DIF of whom 3086 had a diagnosis of toxicity. Most patients were >65 years old (88%). The predictors of DIF use were urgent/emergent admission, hyperkalemia, arrhythmia associated with digoxin toxicity, acute renal failure, or suicidal intent (odds ratios 1.7, 2.4, 3.6, 2.1, and 3.7, respectively; $p < 0.0001$ for all). The majority (78%) of DIF was administered on days 1 and 2 of the hospitalization; 10% received treatment after day 7. Digoxin was used after DIF administration in 14% of cases. Among patients who received DIF within 2 days of admission, there was no difference for in-hospital mortality or length of stay compared with patients not receiving DIF.

CONCLUSIONS Digoxin toxicity diagnoses are clustered in the elderly. One-fifth of cases receive treatment with DIF, most within 2 days of admission. Opportunities exist for improved diagnosis and post-DIF management. Prospective data may be required to assess the impact of DIF on length of stay. (J Am Coll Cardiol HF 2016;4:357–64)

Digoxin remains a therapeutic intervention in both atrial fibrillation and heart failure (HF), as described in current clinical practice guidelines (1,2). Although digoxin use has declined in HF and meta-analyses have raised questions about efficacy in atrial fibrillation, toxicity remains clinically relevant largely as a consequence of the drug's narrow therapeutic window (3,4). The risk factors for digoxin toxicity have been amply described (5) and include advanced patient age (6), renal failure (7), metabolic disorders, and drug interactions (8). However, little is known about hospitalizations related to toxicity

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ABBREVIATIONS AND ACRONYMS

APR-DRG = All Patients Refined Disease-Related Group

DIF = digoxin immune fab

Dx = coded diagnosis of digoxin toxicity

ICD-9-CM = International Classification of Diseases-Ninth Revision-Clinical Modification

HF = heart failure

OR = odds ratio

including contemporary management and resource utilization. Since 1986, antidotal therapy has been available; however, its use has only been indirectly quantified (9–11). Therefore, the primary objectives of the study were to describe patient characteristics, hospital utilization, and outcomes of patients with digoxin toxicity, and to compare patients treated with and without digoxin immune fab (DIF).

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METHODS

A retrospective cohort design was followed using the Premier Perspective Comparative Hospital Database (Premier Inc., Charlotte, North Carolina) for the 5-year period from 2007 to 2011 (excluding quarter 4). Premier collects data voluntarily submitted from more than 450 hospitals including detailed information about day-of-service resource use. Hospital region, patient, and payer distributions compare well to national statistics, although they tend to include larger hospitals (68% of discharges recorded in Premier are provided by hospitals with more than 300 beds, compared to 37% nationally; [12]). The database contains the data elements available in most hospital or payer datasets including patient demographics, marital status, gender, race, diagnosis and procedure codes, length of stay, total cost of inpatient care, and a date-stamped log of all billed items, including medications, laboratory, and diagnostic and therapeutic services at the individual patient level.

Member hospitals benchmark their clinical and financial performance against their peers. The underlying data undergo quality checks, and cost information is reconciled with the hospitals' financial statements. The Premier data are subsequently de-identified and rendered Health Insurance Portability and Accountability Act (HIPAA) compliant to ensure patient confidentiality (12).

STUDY DESIGN. This is a retrospective study designed to characterize patients with digoxin toxicity and to compare patients with and without treatment with DIF. Inclusion criteria were:

1. Record of administration of DIF (brand names DigiFab [BTG International Inc., West Conshohocken, Pennsylvania] or DigiBind [formerly manufactured by GlaxoSmithKline, no longer commercially available]; procedure codes Current Procedural Terminology [CPT] J1162 or Q2006); and/or
2. International Statistical Classification of Diseases-Ninth Revision-Clinical Modification (ICD-9-CM) diagnosis of digoxin toxicity (listed as admitting, discharge, or secondary diagnosis) with code 972.1 (poisoning by cardiotonic glycosides and drugs of similar action—digitalis glycosides, digoxin, strophanthins) or code E942.1 (causing adverse effects in therapeutic use, cardiotonic glycosides, and drugs of similar action—digitalis glycosides, digoxin, strophanthins).

If an individual patient had more than 1 inpatient hospitalization fulfilling either criterion, the earliest hospitalization was selected. Exclusion criteria included patient visits for use of DIF for reasons other than digoxin toxicity, including any diagnosis indicating possible severe pre-eclampsia or a related diagnosis (ICD-9-CM code 642.x).

Patients were assigned to 1 of 2 cohorts, depending on their exposure to DIF. The day of exposure to DIF and the presence of a diagnosis of digoxin toxicity were also noted to define possible subgroup analyses or covariates.

The following variables were obtained: patient demographics (age, gender, race); evidence of acute ingestion (e.g., any diagnosis of suicidal intent); principal (discharge) diagnosis (1 per patient; e.g., digoxin toxicity, arrhythmias, HF, renal failure, hyperkalemia); admission diagnosis (reliably populated in 2009 and after); secondary diagnoses; admission type (emergency, urgent, elective); hospital characteristics (bed size, teaching status, rural vs. suburban/urban location and region); admitting physician specialty; and month/year of discharge. In addition, the APR-DRG group (All Patients Refined Disease-Related Group) (3M Health Information Systems, Salt Lake City, Utah) was recorded. APR-DRGs are similar to Medicare DRGs, classifying patients to predict intensity of resource use based on diagnosis and key surgical procedure codes but enhanced to define separate disease severity and mortality subclasses (1 through 4, with 4 being extreme).

DIF was evaluated using the date of administration, the number of vials administered, and cost. Data related to medications used for treating arrhythmias (potentially as a consequence of digoxin toxicity) were obtained, including anticholinergic agents (atropine sulfate) and lidocaine, as well as other potential therapies (magnesium, activated charcoal, and the placement of a temporary transvenous pacemaker). Use of digoxin after administration of DIF was also evaluated by day of administration.

Clinical outcomes of interest included length of stay (total and in intensive care) measured for both total