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Note

Frequency of Clinical Monitoring of Serum Concentrations of Digoxin, Potassium, and Creatinine, and Recording of Electrocardiograms in Digoxin-Treated Patients: A Japanese Claims Database Analysis

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Summary

Guidelines for cardiovascular drug therapy recommend monitoring serum digoxin concentration (SDC) in patients receiving digoxin treatment, especially those with renal dysfunction and hypokalemia. However, only a few studies have reported the prevalence of SDC monitoring and laboratory testing in clinical practice. Therefore, the aim of this study was to describe the frequency of SDC monitoring and laboratory testing in digoxin users and to assess the association between SDC monitoring and patient characteristics. We used the Japanese insurance claims data covering approximately 1.7 million patients aged 20–74 years between January 1, 2005 and March 31, 2014. All patients who had at least one prescription for digoxin were included. The frequency of SDC and laboratory tests was calculated and the association between patient characteristics and SDC monitoring was assessed using logistic regression analysis. A total of 98,867 prescriptions of digoxin were issued to 3,458 patients between 2005 and 2014. The annual mean frequencies of monitoring SDC, serum potassium level and serum creatinine level and of recording electrocardiograms was 16.8%, 34.8%, and 38.7% and 24.1%, respectively. Atrial fibrillation, chronic heart failure, renal diseases, and use of oral anticoagulants were associated with SDC monitoring. We found the frequency of SDC monitoring to be relatively low in Japanese clinical practice.

Keywords
Digoxin; therapeutic drug monitoring; frequency; laboratory test
INTRODUCTION

Digoxin is traditionally used as a positive inotrope in patients with heart failure (HF), and as a negative chronotrope in patients with atrial fibrillation.\(^1,2\) It is also used to reduce the incidence of hospitalization in HF patients with reduced ejection fraction,\(^3\) as well as to maintain the heart rate in patients with atrial fibrillation.\(^4\) However, emergency visits and hospitalization due to adverse reactions to digoxin occur frequently,\(^5,6\) since it has a very narrow therapeutic range.\(^7\) In addition, a higher serum digoxin concentration (SDC, \(\geq 1.2\) ng/mL) appears to increase the risk of hospitalization or all-cause mortality.\(^8\) In patients with a prescription for digoxin, therapeutic drug monitoring (TDM) may be critical for managing the beneficial and harmful effects of digoxin.

Measurement of SDC has been reported since the late 1960s.\(^9\) The package insert of digoxin and guidelines recommend TDM for digoxin.\(^3,4,10\) Studies from Japan and the United States (US) indicated that TDM was performed in 17–50% of patients receiving digoxin.\(^7,11,12\) However, there is not much information in the literature regarding the frequency of TDM for digoxin. In addition, the guideline\(^10\) recommends to simultaneously measure the serum creatinine and serum potassium levels as for SDC; while the monitoring frequency for these laboratory tests remains unknown.

The primary aim of this study was to describe the frequency of monitoring for SDC, electrocardiogram (ECG), and laboratory tests for serum creatinine and potassium in patients
prescribed digoxin. The secondary aim was to clarify the clinical factors associated with TDM for digoxin.

MATERIALS AND METHODS

Study Design and Population

This observational cross sectional study used the claims database in Japan. We used commercially available insurance claims and enrolment data of 1,707,346 beneficiaries maintained by the Japan Medical Data Centre Co., Ltd.\textsuperscript{13)} The insurance claims included healthcare utilization (outpatient visits and hospitalization), generic name for approved drugs, routes of administration (oral and intravenous), diagnoses coded by the International Classification of Diseases, 10\textsuperscript{th} edition (ICD-10), and medical procedures, including orders for TDM, monitoring of serum potassium and creatinine levels, and ECGs. Enrolment data contained information on patient demographics (year of birth and sex), date of enrolment, and de-enrolment of the insured patients. We selected all patients having at least one prescription of digoxin (oral or intravenous) from the database. To examine the baseline characteristics, we restricted the inclusion to patients with at least six months of insurance after the enrolment date, regardless of whether they were new or existing digoxin users.

Statistical Analyses

Descriptive statistics were used to characterize the patients with a first digoxin
prescription between January 2005 and March 2014. The number of digoxin prescriptions, TDM for drugs including digoxin, ECG, and measurements of serum potassium and creatinine in patients on digoxin therapy were tabulated. Similar to a previous study on lithium,\(^{14}\) the annual frequency of TDM in digoxin-treated patients was calculated by dividing the number of claims for TDM by the number of patients prescribed digoxin. Similarly, the frequencies of the measurement of serum creatinine and potassium per year were calculated. Prescription of digoxin, orders for TDM, and laboratory tests might have been issued multiple times per month as necessary. However, these were counted as once per month for the analysis, as patients whose SDCs are not stable may be measured more than once in the same month. The frequency was also calculated in patients (new users) who had not had a digoxin prescription in the six months preceding the first digoxin prescription during the study period. Among the digoxin users, the frequency of measuring serum potassium and creatinine levels and recording ECGs at baseline (six months before the issue of a prescription) was compared to those at follow-up and monthly intervals up to six months after the first prescription, by \(t\)-test.

In addition, we assessed the association between different factors (variables all listed in Table 1) and the measurements of TDM by using a logistic regression model. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC). A \(p\) value of \(< 0.05\) indicated statistical significance.
ETHICS APPROVAL

This study was approved by the ethics committee of the Nihon University School of Pharmacy (no. 17-015).

RESULTS

A total of 98,867 prescriptions, including 2,702 (2.7%) prescriptions for digoxin injection, were issued to 3,458 patients between January 2005 and March 2014. Since 2,975 patients received prescriptions for oral administration and 791 patients did for injection among 3,458 patients, 308 patients had prescriptions for both oral and injected medications. Among all prescriptions, a total of 96,718 were issued for digoxin to 3,022 patients (including 1,220 new digoxin users) who had information for a period of six months after the enrolment date of insurance and before the first prescription of digoxin. In total, 20,311 of the 96,718 prescriptions were issued to 1,220 new users. The baseline characteristics of the patients with or without SDC monitoring are shown in Table 1. The median age of the patients was 57 years (IQR: 49–63), and 2,059 (68.1%) patients were male. The proportion of patients with claims for SDC measurement at least once during the study period was 36.4% (95% confidence interval (CI): 34.7–38.1%). The initial daily dose in the first month of digoxin use was low dose regardless of the digoxin formulation. Although the primary reason
for starting digoxin could not be recovered from our claims database, the comorbidities included when digoxin prescription was started were, in order of frequency, hypertension (62.4%), HF (57.5%), diabetes mellitus (48.2%), and atrial fibrillation (39.1%). The frequency of concomitant medication use was highest with anti-hypertensives (73.2%), followed by direct oral anticoagulants (41.6%) and benzodiazepines (27.3%).

Table 2 shows the mean annual frequency of SDC, ECG, serum potassium, and serum creatinine by year. Among all cases, no significant change was observed regardless of the year, although those in all patients differed from those in new users. The mean annual frequency of SDC monitoring was 16.8% (95% CI: 15.7–18.0%, range: 15.1–20.4%) among all patients, whereas it was significantly higher at 20.5% (95% CI: 18.6–22.4%, range: 16.9–24.9%) (p = 0.002) in the new digoxin users. The mean annual frequencies of serum potassium measurement, serum creatinine measurement, and ECG recording in the patients were 34.8% (95% CI: 33.5–36.0%, range: 32.3–38.1%), 38.7% (95% CI: 37.1–40.3%, range: 34.1–42.3%), and 24.1% (95% CI: 23.0–25.3%, range: 22.5–27.6%), respectively, whereas among the new digoxin users, these values were significantly higher at 43.2% (95% CI: 40.1–46.3%, range: 36.0–46.8%), 48.1% (95% CI: 45.2–50.9%, range: 41.3–50.8%), and 37.4% (95% CI: 34.2–40.6%, range: 34.9–48.2%), respectively (p < 0.001).

Among the new digoxin users, the serum potassium and creatinine and the ECG were measured within six months of baseline in 61.0%, 65.2%, and 75.0% of patients,
respectively. These figures were significantly reduced to 49.1% ($p < 0.001$), 52.2% ($p < 0.001$) and 44.2% ($p < 0.001$), respectively, after initiation of digoxin.

We enumerated the clinical factors associated with SDC monitoring as shown in Table 3. Patients with atrial fibrillation, chronic HF, renal diseases, and patients on oral anticoagulants had an increased likelihood of SDC monitoring, but new use of digoxin, age, and sex were not significantly associated with SDC monitoring.

**DISCUSSION**

The annual mean frequency of SDC monitoring and measuring serum potassium, serum creatinine, and ECG in patients prescribed digoxin between January 2005 and March 2014 in Japan were found to be low (approximately 17%, 35%, 39%, and 24%, respectively) (Table 2). These figures were almost unchanged throughout the study period. Since the initial dose of digoxin was low, SDC monitoring may be less important than physical examinations (cardiac assessments), ECGs, and monitoring serum potassium and creatinine values. Among the new digoxin users, SDC monitoring and measurements of serum potassium and creatinine levels and recording ECGs were more frequent than those among all users. This finding suggested that due precaution was taken when initiating digoxin therapy.

The frequency of SDC monitoring (17%) was low in our study compared to that of previous studies. Although the frequency of SDC monitoring in the US was 32–50%, the
frequency at four hospitals in Japan in 2005 was 17–35%.\textsuperscript{11} Despite the difference across the study populations, the low frequency of SDC monitoring in Japan has not changed. However, although TDM of digoxin was found to be low in this study, the frequency of measurement of serum creatinine level at baseline among new digoxin users was high approximately 61%. To prevent digoxin intoxication in clinical practice, it may be necessary to recommend monitoring of SDC, serum potassium, and serum creatinine, as well as the recording of ECGs, at a certain time after initiation of digoxin therapy.

In this study, SDC monitoring was significantly associated with comorbidities, including atrial fibrillation, HF, and renal dysfunctions, but not with age, sex, and new digoxin use. In a study performed among ambulatory patients, Raebel et al.\textsuperscript{7} showed that SDC monitoring was approximately 1.3–1.5 times higher in patients with arrhythmia or HF than in patients without these diseases, and these findings were similar to those in our study. We found that SDC monitoring was frequent in patients with renal dysfunctions. Renal dysfunction is a well-known predisposing factor for digoxin intoxication.\textsuperscript{10} Our findings also may support the 2017 recommendation\textsuperscript{10} of SDC monitoring in patients with arrhythmia and HF, although its effect is unknown.

In our study, monitoring of serum potassium and creatinine levels was performed in approximately 40% of all digoxin users, which was significantly increased in new users by 8–9%. Raebel et al. reported that the frequency of monitoring the serum potassium and
creatinine levels in new digoxin users was 73\% using a dataset of 10 healthcare organizations.\textsuperscript{15} In another study including an elderly population of Medicare beneficiaries in the US,\textsuperscript{16} the frequency of measurement of serum potassium and creatinine was found to be as high as 96\% at six months prior to initiation of digoxin therapy. Laboratory tests were significantly more frequently performed in patients using drugs with black box warnings (BBWs)\textsuperscript{12} than in those not using them. For monitoring serum potassium and creatinine levels to prevent digoxin toxicity in Japan, regulatory actions like BBWs may be needed for digoxin. A higher frequency of SDC monitoring may help in early detection of digoxin intoxication in clinical practice.\textsuperscript{6,10}

Our study has some limitations. First, our data did not contain the actual values of SDC, serum potassium, and creatinine levels, and findings of ECG. Therefore, we could not estimate the proportion of patients developing digoxin intoxication, hyperkalemia, hypokalemia, or renal dysfunctions. Second, our study population did not include the elderly population (>75 years). The prevalence of SDC monitoring and performing laboratory tests in the elderly population might be higher than those in the middle-aged population.\textsuperscript{7,16} Hence, our findings cannot be generalized to elderly patients on digoxin therapy. Third, although the frequency of SDC monitoring was higher in new digoxin users than in long-term users, the factor of new use was not associated with performing TDM for digoxin, but the details are not known. Fourth, although we could not validate the data of SDC and serum potassium and
creatinine levels and ECG, it is likely that the recorded clinical laboratory tests in claims
database were indeed conducted.

In conclusion, the annual frequency of performing TDM for digoxin was low
(approximately 17%) in Japan, although measurements of the serum potassium creatinine
levels, as well as the ECGs, prior to initiation of digoxin therapy were performed in more
than 61% of the patients initiating digoxin, the baseline assessments of serum potassium,
serum creatinine, and ECG should be continued in new digoxin users to prevent digoxin
intoxication.

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**Conflict of Interest** The authors declare no conflict of interest.
|                            | Monitoring of serum digoxin concentration |               |               |
|---------------------------|------------------------------------------|---------------|---------------|
|                            | Total number of patients (n = 3,022)     | Yes (n = 1,100) | No (n = 1,922) |
| Median age (years, IQR)   | 57 (49–63)                               | 57 (49–63)    | 57 (49–63)    |
| Male (%)                  | 2,059 (68.1)                             | 775 (70.5)    | 1,284 (66.8)  |
| New users                 | 1,220 (40.4)                             | 356 (32.3)    | 864 (45.0)    |
| No. of prescriptions in first month | 5,489                                    | 2,185         | 3,304         |
| i.v.                      | 1,042 (n = 508)                          | 262 (n = 85)  | 780 (n = 423) |
| oral                      | 4,075 (n = 2,423)                        | 1,741 (n = 975)| 2,334 (n = 1448)|
| i.v. and oral             | 372 (n = 91)                             | 182 (n = 40)  | 190 (n = 51)  |
| Average initial oral daily dose (mg)# |            |             |               |
| Digoxin                   | 0.18                                     | 0.18          | 0.19          |
| Metildigoxin              | 0.09                                     | 0.09          | 0.1           |
| Digitoxin                 | 0.06                                     | 0.05          | 0.07          |
| Comorbidities* (%)       |                  |                  |                  |
|-------------------------|------------------|------------------|------------------|
| Hypertension            | 1,885 (62.4)     | 703 (63.9)       | 1,182 (61.5)     |
| Heart failure           | 1,739 (57.5)     | 739 (67.2)       | 1,000 (52.0)     |
| Diabetes mellitus       | 1,458 (48.2)     | 574 (52.2)       | 884 (46.0)       |
| Atrial fibrillation     | 1,183 (39.1)     | 513 (46.6)       | 670 (34.9)       |
| Liver diseases          | 625 (20.7)       | 247 (22.5)       | 378 (19.7)       |
| Renal diseases          | 320 (10.6)       | 142 (12.9)       | 178 (9.3)        |
| Hyperkalemia            | 25 (0.8)         | 14 (1.3)         | 11 (0.6)         |

| Concomitant medications (%) |                  |                  |                  |
|----------------------------|------------------|------------------|------------------|
| Antihypertensives          | 2,212 (73.2)     | 836 (76.0)       | 1,376 (71.6)     |
| Oral anticoagulants        | 1,257 (41.6)     | 548 (49.8)       | 709 (36.9)       |
| Benzodiazepines            | 825 (27.3)       | 291 (26.5)       | 534 (27.8)       |
| Antihyperlipidemics        | 765 (25.3)       | 285 (25.9)       | 480 (25.0)       |
| Antidiabetics              | 521 (17.2)       | 209 (19.0)       | 312 (16.2)       |
| Antiplatelets              | 176 (5.8)        | 54 (4.9)         | 122 (6.3)        |

IQR, interquartile range; i.v., intravenous

#The average oral initial daily dose (mg) in 2,514 patients with oral prescription is provided using the generic name.
* We present comorbidities at the time of starting digoxin treatment, although the primary reason for starting digoxin was not identified in our database.
Table 2. Frequency of serum digoxin concentration monitoring, electrocardiogram, and laboratory tests of serum potassium and creatinine levels between 2005 and 2014

| Year | SDC monitoring (%) | Electrocardiogram (%) | Laboratory test of serum potassium (%) | Laboratory test of serum creatinine (%) |
|------|-------------------|-----------------------|---------------------------------------|----------------------------------------|
|      | All users | New users | All users | New users | All users | New users | All users | New users |
| 2005 | 17.6      | -         | 23.6      | -         | 32.3      | -         | 34.1      | -         |
| 2006 | 20.4      | 24.9      | 27.6      | 48.2      | 34.8      | 44.3      | 37.9      | 48.9      |
| 2007 | 17.7      | 17.3      | 25.7      | 35.5      | 34.0      | 36.9      | 38.4      | 42.3      |
| 2008 | 18.0      | 19.0      | 24.5      | 34.9      | 33.1      | 36.0      | 38.0      | 41.3      |
| 2009 | 16.6      | 21.7      | 22.6      | 35.8      | 33.8      | 42.9      | 38.0      | 50.8      |
| 2010 | 15.8      | 16.9      | 23.1      | 35.4      | 33.7      | 43.6      | 38.0      | 48.0      |
| 2011 | 15.1      | 20.1      | 22.9      | 36.7      | 35.2      | 46.5      | 39.2      | 50.3      |
| 2012 | 15.2      | 21.3      | 23.1      | 36.6      | 35.9      | 46.8      | 40.2      | 50.8      |
| 2013 | 15.8      | 21.1      | 23.0      | 35.3      | 36.7      | 45.9      | 41.3      | 49.9      |
| 2014* | 16.1     | 21.9      | 24.9      | 38.4      | 38.1      | 45.9      | 42.3      | 50.6      |

*From January 2014 to March 2014. SDC, serum digoxin concentration.
Table 3. Clinical factors associated with SDC monitoring in patients with digoxin prescription

| Factors                  | Unadjusted odds ratio (95% CI) | Adjusted odds ratio (95% CI) |
|--------------------------|---------------------------------|-----------------------------|
| Age                      | 1.00 (0.99–1.01)                | 0.99 (0.98–1.00)            |
| Male                     | 1.19 (1.01–1.39)                | 1.05 (0.89–1.25)            |
| New use                  | 0.59 (0.50–0.68)                | 0.71 (0.59–0.85)            |
| Atrial fibrillation      | 1.63 (1.40–1.99)                | 1.24 (1.02–1.49)            |
| Heart failure            | 1.89 (1.62–2.20)                | 1.67 (1.42–1.96)            |
| Renal diseases           | 1.45 (1.15–1.84)                | 1.47 (1.15–1.88)            |
| Oral anticoagulants      | 1.70 (1.46–1.97)                | 1.38 (1.17–1.64)            |

CI, confidence interval.
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