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Effect of digoxin noncompliance on hospitalization and mortality in patients with heart failure in long-term therapy: a prospective cohort study

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Abstract Background: As outpatients with long-term chronic illness often show a high incidence of medication noncompliance, we investigated the influence of digoxin noncompliance on hospitalization, left ventricular ejection fraction, and mortality in outpatients in long-term therapy having congestive heart failure with tachycardia at a rate over 100 beats/min before starting digoxin therapy, but abnormal sinus rhythm.

Methods: Before starting this study, the digoxin compliance/noncompliance of patients was determined by measuring the serum digoxin concentration (SDC). SDC was determined once a month, followed for six consecutive months, and patients were defined as noncompliant if their SDC was zero (0.0 ng/ml) on at least three consecutive occasions. According to SDC data, 218 patients were assigned to the compliant group and 213 patients were assigned to the noncompliant group. All 431 patients received diuretics, angiotensin converting-enzyme inhibitors, or nitrates as well as conventional therapy with digoxin throughout the trial. The duration of follow-up was 72 months.

Findings: After 72 months of follow-up, the digoxin noncompliant patients showed significant increases in the number and duration of hospitalizations compared with the compliant patients. The digoxin noncompliant patients had a marked decrease in the left ventricular ejection fraction from 49.1% to 41.8%. The cumulative rate of mortality from any cause in noncompliant patients was twofold higher (15.0%) than in compliant patients (7.8%; risk ratio when noncompliant was compared with compliant: 1.95; 95% confidence interval 1.11, 3.45; $P=0.029$) at the 72-month follow-up. The higher mortality in digoxin noncompliant patients was exclusively attributed to worsening heart failure rather than other cardiac and noncardiac causes (risk ratio 2.13; 95% confidence interval 1.12, 4.07; $P=0.033$). In addition, multiple regression analyses demonstrated that patient noncompliance as well as lower left ventricular ejection fraction at baseline were significantly involved in increased mortality.

Conclusion: These results indicate that digoxin noncompliance, at least in part, increases the rate of both hospitalization and mortality due to worsening heart failure in outpatients who have congestive heart failure with tachycardia in long-term therapy.

Key words Digoxin noncompliance · Hospitalization · Mortality

Introduction

Despite recent advances in drug therapy and health management, congestive heart failure (CHF) is a difficult condition to manage in clinical practice. Although new therapeutic modalities have been developed to reduce mortality, their general applicability may be limited by drug toxicity, cost of medication, and other problems [1, 2].

Recent clinical studies have demonstrated that patient medication noncompliance is also a serious factor limiting the effectiveness of medical treatments. Many such problems are related to maintaining long-term therapy in patients with chronic disease such as hypertension [3, 4, 5, 6, 7, 8, 9]. Various factors encouraging noncompliance in long-term therapy include the cost of medication, lack of written instructions, nonparticipation of the patient in designing the treatment plan, lack of patient education about disease, side effects, and inconvenient dosing schedules [10, 11, 12, 13,
14, 15, 16, 17]. These factors may enhance the frequency of patient noncompliance as the duration of drug therapy is prolonged.

Recent clinical trials [18, 19] to evaluate the effect of patient noncompliance on functional status in patients with CHF were short-term studies, so patient noncompliance has been not implicated as a major impediment in achieving the desired goal of disease control in patients with CHF. Little or no information about the effect of the noncompliance on hospitalization and mortality in patients with CHF is available in long-term therapy. Therefore, in the present study to determine the effect of patient noncompliance on therapeutic efficacy in long-term therapy we followed the subsequent history with regard to hospitalization and mortality of patients having CHF with tachycardia who received digoxin therapy for 72 months.

Materials and methods

Patients

Patients who had heart failure with supraventricular tachycardia at a rate over 100 beats/min before starting digoxin therapy and had received oral maintenance therapy with digoxin at the Department of Medicine at Kosei Hospital, Anjo, Japan, were recruited to this prospective cohort study. A total of 431 patients were enrolled in the study between April 1985 and March 1986. All study patients with chronic stable heart failure who required no alteration of medication were considered for entry. The patients, consisting of 342 men and 89 women with a mean age of 63.0 years (range 42–78 years), were enrolled in the study after written informed consent was obtained from each of them. Patients were responsible for administering their own medication. Throughout the trial, all patients received digoxin and any combination of drugs such as diuretics, angiotensin converting-enzyme inhibitors, and nitrates used to treat heart failure with tachycardia. Patients were excluded from the study if they had any of the following conditions: lung disease or claudication, angina requiring continuous treatment, myocardial infarction within the past 6 months or stroke within the past 12 months, or severe primary pulmonary, renal, or hepatic disease.

Determination of digoxin noncompliance

The serum digoxin concentration (SDC) was used to evaluate medication noncompliance of patients. To determine “real” and/or “true” noncompliance, SDC was determined once a month, followed for six consecutive months, and patients were defined as noncompliant if their SDC was zero (0.0 ng/ml) on at least three consecutive occasions. When their drug level was zero, medical doctors always advised outpatients about their illness and medications. Once patients were labeled as digoxin noncompliant, the patients remained in this group.

In the current study, at least 2 months after the initiation of digoxin therapy at 0.125–0.5 mg/day (digoxin tablets, Yamanochi Pharmaceutical Co. Ltd., Tokyo, Japan), SDC was measured about 24 h after administration of the last dose of digoxin using fluorescence polarization immunoassay (FPIA, Dainabot, Tokyo, Japan). When the assays were not carried out within 12 h after obtaining blood samples, the samples were stored at –10°C until analyzed. In our laboratory, the lower limit of quantification of the serum digoxin level was 0.2 ng/ml, and there was a cross reactivity of FPIA to spironolactone, a digoxin-like substrate, at 0.1 ng/ml. In the main study, routine biochemical variables, electrocardiogram (ECG), and SDC were monitored once a month as safety and patient medication compliance indexes. In addition, the resting heart rate of all patients was monitored whenever blood samples were collected for SDC measurement.

Follow-up

When patients were recruited into the study, a case record form detailing baseline clinical and demographic data was completed for all patients. To identify the effect of digoxin noncompliance on patient outcomes, we determined changes in the patients outcomes as follows: the number and duration of hospitalizations, left ventricular ejection fraction (EF), and resting heart rate. Additionally, to further clarify the factors influencing mortality in all study patients, we determined the relationship between mortality and the following factors: digoxin noncompliance, gender, age, baseline EF, and complications. The left ventricular EF was assessed using two-dimensional echocardiography. Numbers of compliant/noncompliant patients with hypertension, hyperlipidemia, and diabetes mellitus were 62/66, 25/27, and 44/44, respectively.

Statistical analysis

All the analyses were performed between the baseline and 72-month follow-up and between the digoxin compliant and noncompliant patient groups with two-sided P values. Analysis of variance (ANOVA) was used to determine any differences in the number and duration of hospitalizations and the left ventricular EF between the two patient groups, followed by Student’s t-test. A stratified log-rank statistic was used to compare the survival distributions in the two patient groups. Kaplan-Meier analysis was used to construct life-table plots. In comparing the digoxin compliant and noncompliant patient groups, we estimated the risk ratio associated with an event and calculated the 95% confidence interval from the Cox proportional hazards model. In comparing both patient groups, we estimated the odds ratio associated with an event and calculated the 95% confidence interval from the logistic regression model. Multiple regression analysis was used to evaluate the involvement in patient mortality of digoxin noncompliance, gender, age, baseline EF, and complications such as hypertension. After ANOVA, the Scheffe-type multiple comparison test was also used for comparing differences in the resting heart rate at each period between patient groups. Differences were considered significant if the P value was less than 0.05.

Results

Patient characteristics

Before starting the present study, we performed SDC measurements in all outpatients with CHF to determine the digoxin compliant and noncompliant patient groups. Moreover, to evaluate the reliability of SDCs from six measurements we determined the difference between maximum and minimum SDC to be less than 10%. The mean SDCs in compliant and noncompliant patients were 0.79 ng/ml (range 0.63–1.57 ng/ml) and 0.0 ng/ml, respectively. On the basis of these SDC data, 431 patients were assigned to either the compliant (218) or the noncompliant (213) group. The mean duration of follow-up was 69 months (range 10–72 months). During the follow-up of 72 months, an average of 92.6% of the compliant patient group had SDCs within the therapeutic range of 0.5–2.0 ng/ml at every monthly visit. The baseline characteristics of the two patients groups at the beginning of the study are summarized in Table 1. There