Effect of Congestive Heart Failure on Mexiletine Pharmacokinetics in a Japanese Population

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Objective: The goal of this study was to evaluate the influence of congestive heart failure (CHF) on the clearance of mexiletine. Methods: The mexiletine clearance/bioavailability (CL/F) ratio was estimated in 584 inpatients receiving mexiletine therapy. The study population consisted of 210 patients with CHF (CHF group; 116 inpatients with New York Heart Association (NYHA) class I—II (group NYHA I—II) CHF) and 94 inpatients with NYHA class III—IV (group NYHA III—IV) CHF, and 374 inpatients without CHF (Non-CHF group). Serum levels of mexiletine were determined by high performance liquid chromatography (HPLC). Results: Mexiletine clearance was significantly lower in the CHF group when compared with the Non-CHF group (0.264±0.093 vs. 0.393±0.082 l/h/kg, mean±S.D., p<0.05). Further, the CL/F ratio was 50% lower in group NYHA III—IV when compared with the Non-CHF group, and the CL/F ratio tended to change in inverse proportion to NYHA class. Conclusion: CHF status significantly affects mexiletine clearance. Therefore, dose adjustments and careful monitoring are likely required in CHF patients receiving mexiletine.

Key words clearance; congestive heart failure; New York Heart Association (NYHA); mexiletine

Mexiletine is a class 1b antiarrhythmic agent that is used for the treatment of ventricular arrhythmias. The therapeutic window of mexiletine is narrow, so monitoring of the serum concentration is necessary.

Congestive heart failure (CHF) may result in altered pharmacokinetics of various drugs. Although Vozeh et al. previously reported that clearance of mexiletine was not affected by the presence of CHF, the study population number may have been insufficient to make definitive conclusions. Therefore, the purpose of this study was to investigate the effect of CHF on the pharmacokinetics of mexiletine in a large Japanese cohort.

MATERIALS AND METHODS

Subjects Data was collected from the records of 584 patients (412 males, 172 females) hospitalized at the National Cardiovascular Center and National Sengokuso Hospital between April 1986 and March 2004. All patients received oral mexiletine for ventricular arrhythmias and gave informed consent for participation in this study. Of the patients with CHF, 116 patients (90 males, 26 females) were NYHA class I or II (Group NYHA I—II), and the other 94 patients (67 males, 27 females) were NYHA class III or IV (Group NYHA III—IV). The other 374 patients (255 males, 119 females) in the study population did not have CHF (Non-CHF group). Assessments of the presence and severity of CHF were performed by cardiologists. All patients received mexiletine 3 or 4 times daily (0700, 1200, 1800, 2200 h), and patients in Group NYHA III—IV received concomitant catecholamines (dobutamine) at doses >3 µg/kg/min and had a cardiothoracic ratio >50%. Blood samples were collected at 0600 h from an arm vein at least 5 d after the initiation of mexiletine therapy, and serum was separated by centrifugation at 3000 rpm for 10 min. None of the subjects were receiving any other drugs that might have influenced the pharmacokinetics of mexiletine (e.g., rifampicin, phenobarbital, quinidine, cimetidine, paroxetine, or fluvoxamine). Since previous reports have suggested that mexiletine clearance was decreased in patients with dilated cardiomyopathy (DCM), patients with DCM were not included in the study population. None of the patients were actively smoking cigarettes within one year prior to enrolling in the study. Further, none of the patients experienced concomitant infections, adverse effects, or significant hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase >100 units/l).

Assay Serum mexiletine concentrations were determined by a slight modification of the high-performance liquid chromatography (HPLC) method described by Mastropaolo et al. In brief, mexiletine was extracted with diethyl-ether and then crystallized by evaporation. The residue was reconstituted in 0.044 M phosphate buffer containing 0.5% triethylamine (pH 2.6) before injection into the HPLC system, which consisted of a reverse-phase column (STR ODS-2, Shimadzu Corp., Kyoto, Japan) and an ultraviolet absorbance detector operating at 210 nm. The mobile phase was a mixture of 0.044 M phosphate buffer containing 0.5% triethylamine (pH 2.6) and acetonitrile (75:25 by volume), and the flow rate was set at 1.2 ml/min. The retention times of mexiletine and its internal standard were 5.3 and 8.8 min, respectively. The minimum measurable concentration was 50 ng/ml when 0.5 ml of serum was used as the sample. The inter-day and intra-day variation was less than 5.0%. 4-Methyl mexiletine was used as the internal standard (ISMEX).

Pharmacokinetic Analysis The mexiletine clearance/bioavailability (CL/F) ratio was estimated by the Bayesian method using population pharmacokinetic analysis, which was performed by NONMEM using a 1-compartment model to describe the pharmacokinetics of mexiletine.

Statistical Analysis Data are expressed as the mean±standard deviation (S.D.). Statistical analysis was performed using Fisher’s PLSD and Student’s t-test. All analyses were performed with Microsoft Office Excel 2003 software (Microsoft, Redmond, WA, U.S.A.), and p<0.05 was considered statistically significant.
RESULTS

The clinical characteristics and CL/F ratios of the subjects are shown in Table 1. There were no significant differences in age and body weight when comparing the CHF Group and the Non-CHF group. Figure 1 shows the distribution of CL/F ratio values in the Non-CHF and CHF groups. The distribution was nearly unimodal in both groups. The mean CL/F ratio was significantly lower in the CHF group than in the Non-CHF group (0.246 ± 0.093 l/h/kg vs. 0.393 ± 0.082 l/h/kg). The effect of age on the CL/F ratio was comparatively larger in the Non-CHF group than in the CHF group (Figs. 2, 3). Further, mean CL/F ratio decreased as the NYHA class increased in all age groups examined (Fig. 4).

DISCUSSION

Antiarrhythmic agents such as lidocaine and mexiletine are effective for controlling arrhythmias in patients with CHF. However, clearance of many drugs may be decreased in the context of CHF secondary to decreased cardiac output and renal blood flow. Indeed, previous studies have reported that lidocaine clearance was reduced in patients with CHF.11,12 By contrast, Vozeh et al. performed a study of 58 patients receiving mexiletine and reported that CHF did not have a significant effect on drug levels. Their report was a study of small numbers and they did not refer NYHA classification. However, the present study of 584 patients does suggest that CHF reduces mexiletine clearance. As shown in Table 1, the mean CL/F ratio was significantly lower in the CHF group than in the Non-CHF group, and this decrease in CL/F ratio was inversely proportional to the NYHA class. Because of the slight effect of age on in the Non-CHF group as shown in Fig. 2, it needs to evaluate the effect of CHF status on the CL/F ratio in each age group. That is, CL/F ratio varied with CHF status in each age group investigated (Fig. 4).
Further, the mean CL/F ratio was lower in the CHF group than in the non-CHF group among all age groups investigated. Of note, the CL/F ratio was approximately 50% lower in the NYHA III—IV group than in the Non-CHF group in each of the age groups investigated. These results suggest that clearance of mexiletine is markedly decreased in patients with CHF.

Cardiac output and hepatic blood flow are decreased in the context of CHF. Mexiletine is metabolized by cytochrome P450 (CYP) 2D6 and by CYP 1A2, with a lower hepatic extraction ratio (ERh) (<0.3) than that for lidocaine (>0.7). Further, the interindividual variation of mexiletine clearance is low. Therefore, changes in hepatic blood flow may produce considerable differences in mexiletine metabolism. Another possibility is that CHF affects mexiletine metabolism via changes in drug-metabolizing enzyme activity in the microsomes. Therefore, further studies to characterize the mechanism(s) whereby CHF affects mexiletine metabolism would be of benefit.

In conclusion, CHF status significantly affects mexiletine clearance. Therefore, dose adjustments and careful monitoring are likely required in CHF patients receiving mexiletine.

REFERENCES