Pharmacokinetic Characteristics of Amiodarone in Long-Term Oral Therapy in Japanese Population

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To evaluate the pharmacokinetic properties and an optimum dose schedule of amiodarone in long-term oral therapy, serum concentrations of amiodarone and its metabolite, desethylamiodarone, were monitored from 345 Japanese inpatients who received amiodarone therapy for a variety of cardiac arrhythmias. Serum amiodarone and desethylamiodarone concentrations were determined by high performance liquid chromatography system. It was observed that the amiodarone and desethylamiodarone concentrations gradually increased with time. The frequency distribution in the amiodarone clearance of 245 subjects, who received fixed maintenance amiodarone therapy for at least 6 months, was nearly a unimodal one. The variation in the ratio of desethylamiodarone to amiodarone concentration in serum was very small. Although no differences in age, dose, dose duration, amiodarone or desethylamiodarone concentration or ratio were observed between men and women; however, the mean amiodarone clearance of women was significantly higher than that of men. The laboratory data were mostly within normal values and no significant relations were observed between serum amiodarone concentration and clinical laboratory data. These results suggest that the individual variation in pharmacokinetics of amiodarone is comparatively small, which might be sufficient to decide that the maintenance dose was the same one (200 mg/d) in long-term oral amiodarone therapy.

Key words amiodarone; long-term therapy; pharmacokinetics; Japanese

Amiodarone is an important antiarrhythmic agent in the prevention of sustained ventricular tachycardia and fibrillation. Until recently, however, concerns about potentially dangerous non-cardiac side effects and its complex pharmacokinetics have limited the use of amiodarone to the most drug-resistant and high risk subjects. Nonetheless, amiodarone appears to significantly improve in patients after myocardial infarction, and amiodarone has begun to be accepted as a first-line therapy as opposed to a last-chance drug. Amiodarone’s increase in popularity is exhibited by its rapidly growing use in the management of refractory atrial arrhythmias.1,2

On the other hand, amiodarone is predominantly metabolized to desethylamiodarone, which is the active metabolite, by cytochrome CYP450(CYP)3A4 and CYP2C8, and desethylamiodarone is further metabolized by CYP3A4.3,4 It has unique pharmacokinetic properties, with 55 d constituting a typical half-life, and pharmacokinetic interactions with various therapeutic agents,5–7 including warfarin,8–10 phenytoin,11–13 flecainide14–16 and cyclosporine.17,18 With the growing number of patients maintained on long-term amiodarone therapy, it is more important to evaluate interindividual variability and characteristics in detail; however, few reports of the pharmacokinetics of amiodarone in long-term therapy have been published,19 especially, no report was published using the Japanese population.

The aim of this study was to evaluate an optimum dose schedule and pharmacokinetic properties of amiodarone in long-term oral therapy in the Japanese population.

Subjects Data were collected from 345 Japanese inpatients who received amiodarone therapy for a variety of cardiac arrhythmias at the National Cardiovascular Center between September 1998 and December 2003. Patients received loading doses from 200 to 400 mg/d for 2 weeks (bid, 0700 and 1900 h), as determined by their cardiologist on the clinical response, without attempts to achieve a specific serum concentration, and received daily maintenance doses from 100 to 200 mg (bid, 0700 and 1900 h). The most common long-term maintenance dose was 200 mg/d. Because all subjects were inpatients, compliance was ensured through administration by a nurse or pharmacist.

Blood Sampling To determine the serum concentration of amiodarone and desethylamiodarone and laboratory examination data, blood samples were drawn at 0700 h from an arm vein. Blood samples were centrifuged at 3000 rpm for 10 min, and serum samples were obtained. Written informed consent was obtained from all subjects before participation in this study.

Assay Serum amiodarone and desethylamiodarone were determined by an HPLC system using amitriptyline as an internal standard (IS).20 In brief, amiodarone and desethylamiodarone were extracted with diethylether followed by evaporation. The residue was reconstituted in methanol before injection into the HPLC system. The HPLC system consisted of a reverse-phase column (Shim-pack, CLC-ODS, Shimadzu Corp., Kyoto, Japan), and an ultraviolet absorbance detector operated at 242 nm. The mobile phase consisted of a mixture of methanol, water, and 28% ammonia water (91:8.8:0.2 by volume), and the flow rate was 1.5 ml/min. Retention times of the IS, desethylamiodarone and amiodarone were 6.6, 11.7, and 19.2 min, respectively. The minimum measurable concentration was 50 ng/ml when 0.5 ml of serum was used. Inter- and intraday variations were less than 5.0%.

Pharmacokinetic Analysis It is well known that amiodarone has a long half-life as does desethylamiodarone, which is an inhibitor of metabolism of amiodarone through...
CYP3A4. Therefore, the time required to reach a steady state of amiodarone concentration in serum is extraordinarily long. Thus, because blood samples were collected from inpatients who were administered fixed-maintenance dose of amiodarone for at least 180 d after the loading dose for 2 weeks. It was assumed that their serum amiodarone concentrations had reached a steady state. All samples were taken at the same time, 0700 h (12 h after the administration of amiodarone). Therefore, we used $C_{0700}$ instead of $C_{mean}$ (mean concentration); as a result, the oral clearance of amiodarone ($Cl/F$) was calculated according to the following equations:

$$Cl/F = \frac{(Dose/BW)/t}{C_{0700}}$$

$$Cl(BMI)/F = \frac{(Dose/BMI-BW)/t}{C_{0700}}$$

$$Cl(BSA)/F = \frac{(Dose/BW)/t}{C_{0700}}$$

Where Dose is the daily dose of amiodarone, BW is the body weight, BMI-BW is BW corrected by body mass index (BMI) ($BW \times (22.0/BMI)$), BSA is the body surface area, $F$ is bioavailability, $t$ is the dose interval, and $C_{0700}$ is the serum concentration of amiodarone at 0700 h.

**Statistical Analysis** The data are expressed as mean± standard deviation (S.D.). Statistical analysis was performed with the use of the unpaired Student’s $t$-test. The criterion of significance was $p<0.05$.

**RESULTS**

The demographic characteristics of this study population are listed in Table 1. Figure 1 shows the distribution since the beginning to 1500 d after the therapy using serum 1031 amiodarone and desethylamiodarone concentrations versus time observations collected from 345 inpatients (men 274, women 71). The duration of dosing was fixed at 1500 d in the subjects whose observation time exceed 1500 d. It was observed that the amiodarone and desethylamiodarone concentrations gradually increased with time, whereas desethylamiodarone concentrations were below the limit of this measurement in the first and second day after the start of the therapy. Comparison between serum amiodarone and desethylamiodarone concentrations per dose and the duration of dosing is listed in Table 2. Although the ratio of the desethylamiodarone concentration to the amiodarone one was nearly equal among the all durations, the amiodarone and desethyl-amiodarone concentration per dose gradually increased with the period of the duration.

**Comparison of pharmacokinetic parameters of amiodarone** between men and women who received a fix maintenance amiodarone therapy for at least six months was shown in Table 3. Although significant differences were not observed in the dose, duration, amiodarone and desethylamiodarone concentrations, or the ratio between men and women, it was observed that the $Cl/F$, $Cl(BMI)/F$ and $Cl(BSA)/F$ of women were significantly higher than that in men, respectively. The frequency of distribution in $Cl/F$ of 245 subjects who received a fix maintenance amiodarone therapy for at
least six months is shown in Fig. 2. The relationships between age and $\frac{CL}{F}$, between creatinine clearance and $\frac{CL}{F}$ and between blood urea nitrogen (BUN) are shown in Figs. 3—5. It was observed that age, creatinine clearance and BUN did not affect $\frac{CL}{F}$.

The relationships between serum amiodarone concentrations and clinical laboratory data are shown in Fig. 6. No significant relations were observed between serum amiodarone concentrations and clinical data.

**DISCUSSION**

As shown in Fig. 1, it was observed that serum amiodarone and desethylamiodarone concentrations gradually increased with time, and the increase was continued for an extremely long term. It was reported that amiodarone had an extraordinarily long half-life, with 55 d constituting a typical half-life. The result of this study was the same as in previous reports. Desethylamiodarone inhibits various CYP subfamilies and transporters, including CYP3A4 and P-glycoprotein. These reports suggest the metabolite of amiodarone inhibits the metabolism and transport of the parent compound. Therefore, it is difficult to calculate the time to reach a steady state of serum amiodarone concentration.

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received the therapy for more than 180 d (Table 3).

As shown in Fig. 2, the frequency distribution was nearly unimodal, 13.1% of the distribution was less than mean minus 1SD, and no subjects were observed at less than mean minus 2SD. Fourteen point seven percentage of the distribution was more than mean plus 1SD, and 4.9% was more than mean plus 2SD. Variation in the ratio of the desethylamiodarone to amiodarone concentration in serum was very small. These data suggest that inter individual variation in the clearance in subjects who received a long-term maintenance fixed dose of amiodarone is comparatively small.

Amiodarone is mainly metabolized to desethylamiodarone by CYP3A4 and CYP2C8, desethylamiodarone is further metabolized by CYP3A4, and amiodarone is transported by P-glycoprotein. Various CYP2D6 alleles carrying a point mutation or a combination of mutations on the chromosome have been reported, and there were poor metabolizers for CYP2D6 mediated drugs.21,22) It was reported that there were CYP3A4 gene and MDR1 mutations. However, a remarkable difference in phenotype of CYP3A4 and P-glycoprotein mediated drugs was not observed compared with that in the phenotype of CYP2D6 mediated drugs.23,24) It was reported that there were CYP3A4 gene and MDR1 mutations. However, a remarkable difference in phenotype of CYP3A4 and P-glycoprotein mediated drugs was not observed compared with that in the phenotype of CYP2D6 mediated drugs. It is well known that the activities of CYP3A4 and P-glycoprotein contribute to the bioavailability of drugs, and the bioavailability of amiodarone is low. On the other hand, desethylamiodarone inhibits the activities of both CYP3A4 and P-glycoprotein23,24) thus it is suggested that the bioavailability of amiodarone is gradually increased with time in subjects receiving long-term amiodarone therapy, and individual variation of the clearance decreases in subjects receiving long-term amiodarone therapy.

As shown in Table 3, no differences in age, dose, dose duration, amiodarone or desethylamiodarone concentrations, or ratio were observed between men and women; however, the mean CL/F, CL(BMI)/F and CL(BSA) of women were significantly increased compared with those of men, respectively. Hunt et al. found a 24% higher CYP3A4 activity in female liver microsomes than in male liver microsomes.24)

However, studies by Schmucker et al.,25) Shimada et al.,26) and George et al.,27) which examined CYP3A4 protein content and function from human livers, were not able to show any significant sex-related differences. One proposed explanation for the differences observed in women is the presence of the female sex steroids estrogen and progesterone, which are known substrates of CYP3A4.28,29) In this study, all subjects were elderly. Therefore, it is suggested that the sex-related difference in amiodarone clearance could not be the explanatory link. The distribution volume of amiodarone is extraordinarily large; especially, the distribution to fatty tissue is large due to the extreme affinity of amiodarone for lipids. It was reported that the body fat in women (mean age 72 years) was significantly higher than that of men (mean age 75 years).30) Therefore, it is suggested that the difference in CL/F between men and women is caused by the distribution to fatty tissue. As shown in Figs. 3—5, it was observed that CL/F was not affected by age, creatinine clearance or BUN. Therefore, it is unnecessary to consider age or renal function for an optimum dose schedule in amiodarone therapy.

It is well known that amiodarone has potentially dangerous non-cardiac side-effects, and some of the side-effects are dose dependent.31,32) As shown in Fig. 6, these laboratory data were mostly within the normal value, and no significant relations were observed between serum amiodarone concentrations and clinical laboratory data. Previous reports, used a small number of subjects and the dose was comparatively high. In this study, a total of 345 subjects was used and the most common maintenance dose was 200 mg/d. Therefore, it was suggested that thyroid hormone metabolism and an elevation of aminotransferases was not affected by the amiodarone concentrations in low-dose amiodarone therapy in such a study.

In conclusion, individual variation in the pharmacokinetics of amiodarone was comparatively small, which might be sufficient to conclude that the maintenance dose is the same (200 mg/d) as in long-term oral amiodarone therapy.
REFERENCES