ABSTRACT. The purpose of this study was to determine the clinical utility of measuring plasma amiodarone levels in patients on chronic amiodarone therapy. Plasma amiodarone and desethylamiodarone (DEA) levels were measured in patients on long-term amiodarone therapy between 2001 and 2003. Of 825 patients taking amiodarone, 77 patients (9%) had therapeutic, 458 patients (56%) had sub-therapeutic, and 290 patients (35%) had trace or undetectable plasma levels. In 535 patients with detectable amiodarone levels, 2% had trace or undetectable DEA levels. In a subgroup of patients with ventricular arrhythmias, the mean plasma DEA level was significantly lower than the mean amiodarone level (0.74 ± 0.46 µg/ml versus 1.43 ± 0.78 µg/ml, p = 0.02). In conclusion, one-third of patients on chronic amiodarone therapy had trace or undetectable plasma levels. Measuring plasma amiodarone levels may be useful in avoiding prematurely changing treatment strategy in patients who fail to respond to amiodarone therapy.

KEYWORDS. amiodarone, desethylamiodarone, plasma amiodarone or desethylamiodarone levels.

Introduction

Amiodarone is a Vaughan Williams class III antiarrhythmic drug with a complex mechanism of action. It is widely used in patients with atrial fibrillation and ventricular arrhythmias. Amiodarone is also used in nearly one-third of patients with automatic implantable cardioverter-defibrillator (AICD) devices who receive AICD shocks for either atrial or ventricular arrhythmias. Many patients develop recurrent paroxysmal atrial fibrillation or receive AICD shocks for ventricular arrhythmias in spite of being on chronic amiodarone therapy. It is not clear whether these patients are non-compliant with medication or are non-responders to amiodarone. The standard loading regimen of amiodarone is 0.8–1.2 g a day up to 10 g, followed by the maintenance dose of 0.2–0.4 g a day for all patients, regardless of their body weight or fat mass. The purpose of this study was to determine the distribution of plasma amiodarone and desethylamiodarone (DEA) levels among patients on chronic amiodarone therapy.

Methods

This study was approved by the research and development committee of Minneapolis Veterans Administration Medical Center (VAMC) and the requirement for individual consent was waived. All patients on chronic amiodarone based on the medication records were identified between March 2001 and March 2003 at VAMC. The standard loading regimen of 0.8–1.2 g a day up to 10 g, followed by the maintenance dose of 0.2–0.4 g a day were used in all patients. Their amiodarone levels were measured within 3 months of the loading and every 6 months while on a maintenance dose. The amiodarone and DEA assays were done by the standard method of high-performance liquid chromatography (HP-Series 1090, Hewlett Packard). We identified 825 patients who had plasma amiodarone and DEA levels.
measured after loading and at every 6 months thereafter. We classified these patients into three groups according to their amiodarone levels, based on the published guideline from North American Society of Pacing and Electrophysiology (NASPE). Therapeutic amiodarone and DEA levels were defined as 1.5–2.5 μg/ml; subtherapeutic levels were defined as 0.5–1.4 μg/ml and trace or undetectable levels were defined as <0.5 μg/ml or zero. Since most of patients had multiple amiodarone assays, we classified patients into therapeutic group if they had achieved therapeutic amiodarone level at least once during the study period. The sub-therapeutic group included patients with mixed levels of sub-therapeutic, trace or undetectable levels in all their assays and without a single therapeutic level. Patients were classified into trace or undetectable group if all of their levels were trace or undetectable during the study period. Among all 825 patients, eight patients were admitted for ventricular arrhythmias and ICD shocks. Their amiodarone and DEA levels were analyzed.

Continuous variables are expressed as mean ± 1 standard deviation and categorical variables as percentage. A paired t-test and the Wilcoxon rank test for small sample size were used to compare DEA and amiodarone levels in patients with AICD shock.

**Results**

Of 825 patients taking amiodarone, 77 (9%), 458 (56%), and 290 (35%) patients had therapeutic, sub-therapeutic and trace/undetectable plasma levels, respectively (Figure 1). The median duration of the amiodarone use was 8 ± 5.9 months. Thus, over 90% of patients on chronic amiodarone therapy had either sub-therapeutic or trace/undetectable amiodarone plasma levels based the NASPE guideline.8

We further examined the plasma levels of DEA, the only active metabolite of amiodarone. In 535 patients with detectable amiodarone levels, 11 (2%) patients had trace/undetectable DEA levels despite that the majority of them had therapeutic amiodarone levels. Among 825 patients with routine amiodarone assays conducted at 6-month intervals, eight consecutive patients developed AICD shock therapy for ventricular arrhythmias within the 2-year period. Their mean plasma DEA level was significantly lower than the mean amiodarone level (0.74 ± 0.46 μg/ml versus 1.43 ± 0.78 μg/ml, respectively, p = 0.02, Figure 2).

**Discussion**

This study showed three important findings: 1) over one-third of patients on chronic amiodarone therapy had only trace or non-detectable plasma amiodarone levels; 2) majority of patients failed to achieve therapeutic plasma amiodarone levels, as suggested by NASPE; and 3) a small group of patients could not metabolize amiodarone into DEA.

Based on the complex pharmacokinetics and the variable bioavailability, a standard loading regimen of 0.8–1.2 g a day up to 10 g, followed by the maintenance dose of 0.2–0.4 g a day is routinely used in clinical practice for amiodarone use.7 The therapeutic plasma

---

**Figure 1**: Distribution of plasma amiodarone levels in patients on long-term amiodarone therapy.

**Figure 2**: Difference between plasma amiodarone and desethylamiodarone levels in patients with ventricular arrhythmias.
Amiodarone levels usually range between 1.5 and 2.5 μg/ml. Measuring tissue levels of amiodarone or DEA is not possible non-invasively. However, plasma amiodarone levels have been proposed as surrogate markers for tissue levels since a linear correlation between tissue and plasma concentrations of amiodarone was demonstrated. Routine monitoring plasma amiodarone level is not recommended due to the lack of large clinical trials in correlating therapeutic effects with amiodarone levels. Nevertheless, measuring amiodarone levels is recommended in patients with recurrent arrhythmias; with new symptoms after change of drug dose or formulation; with possible toxic side-effect; or if the drug dose can be titrated downwards. Our study suggests that checking plasma amiodarone levels during the clinic follow up may be helpful in identifying those individuals with trace or undetectable amiodarone levels.

We speculated that the wide range of amiodarone plasma levels were due to non-compliance, malabsorption, and variable bioavailability. The lack of any amiodarone plasma levels in over one-third of patients was most probably due to non-compliance. In view of the serious nature of amiodarone toxicity, our study does not suggest that we should increase oral amiodarone dosage based on the sub-therapeutic levels. However, in patients with only trace or non-detectable amiodarone levels, a serious discussion about medication compliance may be warranted to avoid premature decision on therapy failure and switching to a different medication. A fat-rich diet is known to aid in amiodarone absorption through the gastrointestinal tract, enhancing the absorption by 2.4- to 3.8-fold compared with the fasting state. Owing to the retrospective nature of the study, we could not control for the diet effect on the plasma amiodarone levels. Amiodarone is a highly lipophilic drug with a 1000-fold higher concentration in fat tissue than in the plasma and a prolonged elimination half time. High lipophilic drugs like amiodarone tend to have complex pharmacokinetics in obese people. Patients with high body mass index (BMI) taking tacrolimus, a lipophilic immunosuppressive drug, require a lower daily dose per kilogram of body weight. A positive correlation between BMI and pulmonary toxicity in patients taking amiodarone has been reported. In a comprehensive review of effect of obesity on pharmacokinetics by Cheyomol et al., it was recommended that dosing of lipophilic drugs in obese population should be based on calculation of total body water. Despite the complex pharmacokinetic nature, amiodarone does not appear to have excessive or unexpected accumulation in fat tissue on long-term administration. In addition, the longer exposure time, not the higher concentrations of amiodarone in the plasma or fat tissue, seems to be associated with its late adverse effects. The marked variable range of plasma amiodarone levels based on the current standard dosing regimen confirms the complex pharmacokinetics and the need for further study in this area.

Amiodarone is metabolized into DEA through cytochrome P450 enzyme CYP3A4 in the liver. With chronic oral amiodarone therapy, the DEA concentration gradually increases to about 80% that of amiodarone concentration over several months, and reaches a level either comparable to or in excess of that of amiodarone. In vitro nuclear binding studies suggest that DEA, but not amiodarone, binds the nuclear thyroid hormone receptor T3R alpha 1 to exert its antiarrhythmic effect through K channels. Whether amiodarone or DEA plays the key antiarrhythmic role is unclear. However, the plasma DEA levels >1.3 μg/ml has been one of the strongest predictors of successful pharmacological conversion of atrial fibrillation. In a post myocardial infarction dog model, both amiodarone and DEA were effective in suppressing ventricular arrhythmia in a dose-dependent fashion, although DEA was approximately three times more potent than amiodarone for the same plasma concentration. It has been shown in dogs that 50% suppression of ventricular ectopy required DEA concentration of ≥1.4 μg/ml. In our study, majority of the eight consecutive patients with ICD therapy had ischemic cardiomyopathy. However, none of them had DEA levels >1.4 μg/ml, even though most of them had therapeutic amiodarone. This suggests that DEA may be related to the antiarrhythmic effect for ventricular arrhythmia.

Limitations

This is a retrospective analysis from a single center in a predominantly white, male, and older patient population. Owing to the retrospective nature of the study, we could not verify for drug compliance and for determining the diet effect on amiodarone and DEA levels. The subgroup analysis on patients with ICD shock therapy for ventricular arrhythmias was based on a small sample size, thus limiting our ability to make any conclusion about the antiarrhythmic effect of DEA. In addition, due to the retrospective nature, we did not have clinical information about the effectiveness of therapy in those patients with sub-therapeutic amiodarone levels.

Conclusion

One-third of patients on chronic amiodarone therapy had trace or undetectable plasma levels. Measuring plasma amiodarone levels may be useful in avoiding prematurely changing treatment strategy in patients who fail to respond to amiodarone therapy.

References


