Lee et al., Cardiovasc Pharm Open Access 2018, 7:4
DOI: 10.4172/2329-6607.1000244

Cardiovascular Pharmacology: Open Access

Review Article Open Access

Amiodarone Use in Pre-Heart Transplant Patients and its Effect on Graft Function and Mortality

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Received date: July 20, 2018; **Accepted date:** August 08, 2018; **Published date:** August 15, 2018

Abstract

Amiodarone is a commonly used agent to treat life-threatening cardiac arrhythmias in patients with heart failure. While survival after heart transplantation has improved greatly over the decades, the use of amiodarone prior to transplant is controversial. Some reports describe graft dysfunction and increased risk of mortality post-transplant in patients that are exposed to amiodarone pre-operatively, while others do not. Here, we review and summarize the available literature on this topic.

Keywords: Amiodarone; Heart transplant; Mortality; Heart; Transplant; Primary graft dysfunction;Theophylline

Introduction

Amiodarone an iodinated benzofuran derivative, was first developed in the early 1960s and became widely popular in Europe to treat angina. A few years later, an Argentinian physician, Dr. Mauricio Rosenbaum, discovered that it reduced both supraventricular and ventricular arrhythmias in his patients. Physicians throughout the world subsequently started using amiodarone for cardiac arrhythmias and the drug was finally approved in 1985 for use in the United States for the treatment of ventricular arrhythmias.

Amiodarone is categorized as a class III antiarrhythmic agent as it inhibits both potassium and calcium channels, thereby prolonging action potential repolarization. It also inhibits adrenergic stimulation (alpha- and beta-blocking properties) and modulates sodium channels. Amiodarone decreases AV conduction and sinus node function, as well. Although amiodarone is an effective antiarrhythmic agent, it has numerous serious side effects. Affecting close to 30% of patients over 10 years, these side effects include bradycardia, skin discoloration, hepatotoxicity, neurotoxicity, vision problems, pulmonary toxicity, hyperthyroidism, and hypothyroidism. Amiodarone is extensively metabolized by the liver primarily by cytochrome P450 3A4 and 2C8. The drug is excreted mainly through hepatic metabolism, and very little is excreted renally. The average half-life after a single dose is 58 days (range: 15 to 142 days). After chronic oral therapy, the mean half-life ranges from 40 to 55 days. The metabolite of amiodarone, N-desethylamiodarone, is also an active metabolite with a similarly long half-life. Contributing to the long half-life, amiodarone is lipophilic and has a very large volume of distribution. Following discontinuation, adipose tissue serves as a reservoir (Table 1).

Onset of action	Oral: 2 days to 3 weeks IV: Within hours
Duration after discontinuation of amiodarone	Variable, 2 weeks to months
Bioavailability	Oral: ~50% (range: 35% to 65%)
Volume of distribution	Oral: 66 L/kg (range: 18 to 148 L/kg)
Protein binding	>96%
Metabolism	Hepatic (CYP2C8, CYP3A4)
Terminal Half-life	Single dose: 58 days (range: 15-142 days) Chronic therapy: Mean range: 40-55 days (range: 26-107 days)
Excretion	Feces; urine (<1% as unchanged drug)

Table 1: Pharmacokinetics of Amiodarone.

In a recent ISHLT registry analysis [1], roughly one-third of the patients on the heart transplant waiting list were taking amiodarone for the treatment of arrhythmias. Given the its impact on heart rate, primary graft dysfunction (PGD) post-heart transplant, and mortality, there is considerable interest in understanding the short-,

intermediate-, and long-term impacts of amiodarone use prior to transplantation.

Effect on post-transplantation chronotropy

In 1991, Macdonald et al. [2] noted that patients treated with amiodarone had significantly lower heart rates post-transplant. In 2003, Goldstein et al. [3] reported an association of increased risk of bradycardia and, interestingly, a trend towards delayed median time to first rejection episode in pre-transplant patients treated with amiodarone. This may be related to amiodarone induced alterations in hepatic metabolism of immunosuppressants. In a study by Woo et al. [4] of 292 patients undergoing transplantation, periprocedural amiodarone induced bradycardia did not affect the rate of pacemaker placement in patients after transplant (p=0.08). A potential confounding factor may have been the periprocedural use of theophylline which, in one study, decreased the need for permanent pacemakers from 16.1% to 2.6% [5].

Primary graft dysfunction (PGD)

Primary Graft Dysfunction (PGD), as defined by consensus guidelines as PGD-left ventricle (PGD-LV) (includes left and biventricular dysfunction) and PGD-right ventricle (PGD-RV) (includes right ventricular dysfunction alone), occurs in an estimated 7.4% of transplant patients. Of those with PGD, mortality is as high as 30% at 30-days and 34.6% at 1-year. As such, whether perioperative use of amiodarone impacts the incidence of PGD is of great interest to the transplant community. Yerebakan et al. [6], found that those who were treated with amiodarone prior to transplant had more frequent acute graft dysfunction (14% *vs.* 4.7%, p=0.04). In this report, acute graft dysfunction was defined as the need for MCS within the first 7 days of transplant. Since then, three retrospective single-center studies have been published using the consensus guidelines. Lushaj et al. [7], noted that pre-transplant amiodarone use was associated with PGD (p=0.025). Nicoara et al. [8], found that amiodarone use pre-transplant was associated with a 1.67 time greater odd of developing PGD (p=0.045). In a study of 269 patients by Wright et al. [9], pre-operative amiodarone use was an independent risk factor for severe PGD (OR 6.05; p<0.001). The risk of amiodarone associated PGD was noted to be dose-dependent. In fact, on the day of operation, each 100 mg increase in amiodarone dose and each 18,300 mg increase in the 6-month cumulative dose increased the risk of severe PGD.

Effect on mortality

The impact of pre-transplant amiodarone use and mortality has yet to be fully defined. Macdonald et al. and Chelimsky-Fallick et al. [10], first reported mortality data in the early 1990s. They observed no difference in 30-day mortality rates between patients who had, and who had not, received amiodarone therapy prior to transplantation. Unfortunately, no data regarding longer-term follow-up was presented. The first association between pre-transplant amiodarone use and long term post-transplant mortality was reported by Chin et al. [11], in 1999, when they reported that > 4 weeks of amiodarone use prior to transplant was associated with increased mortality. In 2004, Blomberg et al. [12], similarly found that patients who received amiodarone for an extended period of time prior to their heart transplantation had decreased 1-year survival. These patients had longer time on ventilator support, increased likelihood of developing acute respiratory distress syndrome, and bleeding complications after heart transplantation. In support of these observational studies on the effect of the dangers of long term amiodarone use as compared to short term use, Sánchez-Lázaro et al. [13], did not observe any significant differences in 30-day mortality in patients who received amiodarone within 1 month pre-transplant versus those who were not treated with it.

Several contemporary studies have also looked at the relationship between pre-transplant use of amiodarone and mortality which have demonstrated conflicting results. In 2014, Yerebakan et al. [6], found that patients treated with amiodarone prior to transplant had a higher rate of in-hospital mortality. Although in-hospital mortality was higher, long-term survival was similar.

In 2015 Baker et al. [14], published a meta-analysis of 869 subjects reporting that the use of amiodarone was associated with a 2-fold increase in post-transplant mortality versus controls.

Subsequent studies, however, have come to the opposite conclusion. First, Rivinius et al. [15] published in 2016 their center's experience after analyzing 530 patients with ≥ 1 year of amiodarone use before transplant compared to those with none or <1 year of amiodarone use. In this study, there was no significant difference between the groups in 1-year, 2-year, 5-year, and overall follow-up mortality after heart transplantation. Second, In 2017 Lushaj et al. [7] published their single-center retrospective study of 220 patients. In their analysis, pre-operative amiodarone use resulted in no significant difference in 30-day or 1-year mortality, but the 5-year survival was significantly lower (p=0.03). Patients exposed to amiodarone also had fewer cellular rejections but higher primary graft dysfunction. Patients were considered in the amiodarone group if they were treated with it within 120 days prior to transplant. Third, in the same year, Rivinius et al. [16]. reported in their retrospective single-center study of 530 patients. Patients were divided into three groups: no continuous amiodarone use group (≤90 days before transplant), acute amiodarone use group (≤ 90 days before transplant), and chronic amiodarone use group (>90 days before transplant). No significant differences in mortality was found between the groups at 30 days, 1-year, 2-year, 5-year, or overall post-transplant follow-up. A significant decrease in early atrial fibrillation among those who use amiodarone chronically was noted. Fourth, Jennings et al. [17,18]. followed up their initial study by updating their meta-analysis to include nine studies with a total of 16,509 patients. In contrast to their initial findings, pre-transplant amiodarone use was not associated with an increased risk of mortality post-transplant versus control. Additionally, the authors performed a sub-group analysis and noted no 30 days or 1 year mortality difference.

In contrast, the most recent study by Cooper et al. using the ISHLT registry database to analyze data on 14,944 transplant patients, of which 4,752 patients received pre-transplant amiodarone, found an increase in mortality in amiodarone treated patients. While limited by the binary nature of whether a patient had received amiodarone pre-transplant (e.g. yes/no, duration unspecified), the study found that amiodarone treated patients had higher one year mortality (HR 1.15, 95% CI 1.02 to 1.30). Further, in propensity-matched analyses, amiodarone-treated patients had higher rates of cardiac reoperation (15% *vs.* 13%) and permanent pacemakers (5% *vs.* 3%).

Discussion

Amiodarone is a very potent and effective antiarrhythmic to treat atrial and ventricular dysrhythmias. Its use has been on the rise especially in patients awaiting heart transplant. This is of a concern for the heart transplant community knowing the myriads of studies linking amiodarone use with post-transplant bradycardia, PGD, and

mortality. The possible negative outcomes associated with pre-operative amiodarone use may be related to its large volume of distribution that effectively leaches the drug into circulation post-transplant, long half-life and pharmacodynamics. The effects of therapeutic levels of the drug post discontinuation at the time of transplant include negative chronotropic and inotropic effects on the transplant by blocking calcium channels, α-receptors, and β- receptors, thereby contributing to post-transplant vasoplegia. Unidentified interactions with oxidative stress leading to worsening ischemia-reperfusion injury has also been proposed but is speculative [1].

To date, studies have been inconsistent with regards to outcomes, likely secondary to inconsistent endpoints. The duration of treatment and the cumulative dose appears to affect outcomes. Registry studies, such as the one conducted by Cooper et al., unfortunately do not address the duration of treatment and cumulative dosage. It is also possible that the inconsistency observed in the studies is due to different factors not related to amiodarone use, such as cohort effects reflecting changes in heart transplant techniques, technologies, use of immunosuppressant medications, closer follow-up and surveillance.

Conclusion

The controversy surrounding pre-operative amiodarone use and post-operative outcomes has yet to be settled. The major limitation to the existing data in establishing a causal link is the lack of prospective, randomized trials. Such a trial is unlikely to ever happen. This lack of randomization only allows us to state that there may be some sort of association and, at the very least, is hypothesis generating. Until a firm link is established, caution is probably the better course of prudence. Assuming a causal relationship, every attempt should probably be made to lower the dose of amiodarone pre-transplant and as early as possible. Consideration of alternative antiarrhythmic drugs should also be given in patients who are on the heart transplant waiting list.

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