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

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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).

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

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, peri procedural 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 peri-procedural 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 odds of developing PGD (p=0.045). In a study of 269 patients by Wright et al. [9], pre-operative amiodarone use resulted in no 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, Yerebakan et al. [6], 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 (3% vs 3%).

**Discussion**

Amiodarone is a very potent and effective antiarrhythmic to treat atrial and ventricular dysrythmias. 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. The 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.

References