Predictors of Intravenous Amiodarone Induced Liver Injury

Thesis

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Abstract

We concluded that Parenteral amiodarone induced liver injury (AILI) and its severity could be predicted by underlying heart disease (cardiomyopathy, low EF), liver disease (congestive hepatomegally, elevated bilirubin and aminotransferases), hemodynamic instability (DC cardioversion, inotropic support), and increasing dose of amiodarone.

In high risk patients, we recommend that benefit of IV amiodarone should be weighed against its possible hazard, especially in non life threatening conditions such as atrial fibrillation.

Key words: Desethylamiodarone - Drug induced liver injury - Cardiopulmonary resuscitation - Amiodarone induced cirrhosis

INTRODUCTION

Amiodarone is a highly effective antiarrhythmic agent for the treatment and prevention of various tachyarrhythmias. There are multiple reported and well-established side effects of amiodarone therapy such as effects on the thyroid, skin, lungs, nerves, and cornea. The effect of amiodarone on the liver resulting in hepatotoxicity is a recognized complication of amiodarone.[1]

Drug induced liver injury (DILI) due to oral amiodarone was extensively studied. However, the available data regarding acute hepatotoxicity form intravenous (IV) amiodarone are not far beyond case reports.[1-16] The mechanisms of liver injury with IV amiodarone is controversial. Ischemic injury due to compromised hemodynamic conditions may have a role.[5] Solubilizers in the IV amiodarone preparation such as polysorbate 80 were reported to be responsible for hepatotoxicity, possibly due to immune-mediated alteration of hepatocellular membrane.[6,16] Importantly, the mechanism of injury with IV amiodarone is different from that in chronic exposure to oral therapy, therefore, acute hepatic injury following IV amiodarone does not preclude subsequent oral therapy.[6,17]

Acute elevation of liver enzymes following IV amiodarone use ranged from mild asymptomatic to severe life threatening, and frequently necessitates drug discontinuation. In most of the reported cases, the liver injury occurred within 24-

48 hours of therapy and reversed within 2-3 weeks of discontinuation.

Parenteral amiodarone is commonly used in critically ill and hemodynamically unstable intensive care unit patients. Therefore, multiple factors may predispose patients to IV amiodarone induced liver injury (AILI). Possible predisposing factors for AILI were variably reported in different case studies. Underlying liver injury from heart failure, high dose of IV amiodarone, hypotension from ventricular arrhythmias (VAs), and postoperative therapy following coronary artery bypass grafting (CABG) were observed in case reports.[4,8,18,19] Up to our knowledge, there are no prospective clinical studies that addressed the predictors of AILI.

The prediction of amiodarone induced liver injury (AILI) and its severity may help careful patient monitoring or the choice of other measures alternative to amiodarone in high risk patients. Little is known regarding predictors of AILI.

Aim of the Work

The aim of work is to address the predictors of AILI and its severity.

Chapter 1
INTRAVENOUS AMIODARONE

Introduction

Amiodarone is a benzofuran that was synthesized and utilized as an antianginal agent in the 1960s, [20] however was later found to have antiarrhythmic properties. [21] The oral preparation was affirmed by the FDA for use in the USA in 1985, and I.V structure was endorsed by the FDA in 1995. Both were shown for grown-ups with life-debilitating ventricular arrhythmias when different medications are insufficient or can't go on without serious consequences. Amiodarone is the most generally recommended antiarrhythmic pharmaceutical in the US, to a great extent because of its adequacy in the administration of both supraventricular and ventricular arrhythmias. [22] What's more, amiodarone has almost no negative inotropic action, and a low rate of ventricular proarrhythmia, making it worthwhile for use in patients with heart disappointment. [23] In spite of these favorable circumstances, the utilization of amiodarone is connected with a generally high occurrence of symptoms, making it a confused medication to utilize securely.

Pharmacokinetics

I.V amiodarone has a complex pharmacology that starts with its formulation. [24] Amiodarone is not water soluble, thus a solvent, polysorbate-80 was included. This dissolvable is by all

accounts in charge of the hypotensive impact of the I.V amiodarone. [25] Likewise, polysorbate-80 has additionally been appeared to decrease heart rate, depress AV node conduction and increase atrial and ventricular refractory periods. [26] Once infused, a large percentage of amiodarone is bounded mainly to albumin and also to beta lipoprotein and alpha-1 acid glycoprotein, an acute-phase reactant. [27] Being exceptionally lipophilic, [28] amiodarone and its metabolite, DEA, have an extensive volume of distribution and variable uptake into various tissues. IV amiodarone starts to act inside 60 minutes, with quick onset of activity inside minutes taking after an IV bolus.

A three-compartment model can clarifiy the kinetics of this drug. After absorption, serum levels in the central or plasma compartment at first increase quickly. After the initial distribution phase, amiodarone and DEA are found extensively in the deep compartment, which consists of adipose tissue, lung, liver and lymph nodes. [29] Most minimal levels are found in the peripheral compartment, being composed of brain, muscles and thyroid. Drug levels in the peripheral and deep compartments rise at a much lower rate because of the large volumes of distribution. This model likewise clarifies the different phases of elimination of amiodarone after drug discontinuation. The relatively short half-life for disappearance of amiodarone from plasma after a single-dose or short-term I.V administration is likely a measure of drug redistribution from vascular space into tissue and not true body elimination.

This is followed by a much longer terminal elimination period as amiodarone redistributes from deep stores. [30]

The significance of this deep compartment is that; the longer period of the infusion, the greater the amount of parent and metabolite that is deposited in the deep compartment. There is deferral in the onset of antiarrhythmic activity when smaller loading doses are used; a higher dose is important to accomplish a myocardial and plasma concentration during the time that the deep compartment is being filled. [31]

The drug is metabolized primarily by a P450 cytochrome oxidase (CYP3A4)-dependent oxidative deethylation. The main metabolite is DEA, which is active and has an electrophysiologic impact similar to the parent compound. [30] A much littler amount of metabolite is produced when the drug is given intravenously rather than orally unless the drug is infused for several days. [32] Drug elimination is through the biliary system. There is insignificant role of the kidneys in elimination of both amiodarone and DEA due to their large volume of distribution and extensive protein binding; the last effect additionally minimizes drug removal by dialysis. [33] Thus there is no compelling reason to alter the dosage in renal failure. [34] With the possible exception of massive hepatic failure, systemic diseases, including congestive heart failure, do not mandate I.V amiodarone dose reduction, nor is there any need to utilize lower dosages in the elderly. [28]

Like I.V structure, oral amiodarone is uniquely lipophilic, resulting in a very large volume of distribution and a prolonged time to reach stable plasma levels. [23] It is incompletely absorbed and its bioavailability is around 30 to 70 percent. [24,30] After absorption, the medication undergoes extensive enterohepatic circulation. An expansive first pass effect (hepatic P450 cytochrome oxidase-dependent oxidative de-ethylation) results in mono-N-desethyl amiodarone (desethylamiodarone). Peak amiodarone serum levels, after oral dosing, are accomplished within 3–7 hours. After long-term oral therapy, amiodarone has a true elimination half-life somewhere around 60 and 142 days. [35] Like I.V structure, oral form is excreted through biliary system. Likewise renal clearance is negligible, in this way the dose of the drug does not need to be diminished in patients with renal failure, including dialysis-dependent patients.

Electrophysiologic actions

Amiodarone is classified as a Vaughan-Williams class III antiarrhythmic agent due to its inhibition of outward potassium channels, the drug also has class I sodium channel blocking effects, class II antiadrenergic effects, and class IV calcium channel blocking effects. It is a broad spectrum anti-arrhythmic drug. I.V amiodarone act on specialized and nonspecialized atrial and ventricular tissue and thus it has numerous electrophysiologic effects. [36]

Through blocking beta-adrenergic receptors and slow calcium channels (L-type), amiodarone slows the heart rate and depresses AV node conduction. Either or both of which suppress triggered activity and thus may explain the low proarrhythmia potential of amiodarone, [37] and make it successful in abating the ventricular rate in critically ill patients with atrial tachyarrhythmias. [38]

It slows intraventricular conduction by blocking the inactivated sodium channel in phase 0. This property may explain the efficacy of the agent in the suppression of ventricular tachyarrhythmias. [39]

It prolongs atrial and ventricular repolarization by inhibiting potassium channels (inward potassium channel rectifier (IKr). [40] A potassium channel blocking action may be more relevant and important during long-term therapy. [41] According to this action, it prolongs the duration of the action potential and the refractory period of both atrial and ventricular tissue.

The antisympathetic effect is brought by a noncompetitive alpha- and beta-blockade. [42] Despite the fact that this impact may not be identified by a decline in heart rate, it might be a vital component in the suppression of acute electrical instability.

Oral amiodarone is similar to I.V form in all the effects mentioned above; however, IV amiodarone has a number of important electrophysiologic differences from chronic oral amiodarone. [43]

- It delivers a much smaller increase in the action potential duration (APD) in atrial and ventricular myocardium, and a minimal increase in the atrial and ventricular refractory periods. As a result, there is little or no increase in QRS duration or the QT interval, respectively. Additionally, acute amiodarone therapy has no consistent effects on the repolarization phase of action potentials. On the opposite side, the major effect of *chronic amiodarone therapy* is an inhibition of outward potassium currents leading to a prolongation of the APD, and like the other class III agents, amiodarone prolongs the QT interval. However, in contrast to most other class III agents, amiodarone has very little proarrhythmic activity. [36, 44]
- It has little impact on sinus cycle length. It has vasodilator activity that triggers an increase in sympathetic activity, and as a result, there is little or no slowing of the sinus rate.
- It may have more potent and more rapid antiadrenergic activity.
- IV amiodarone inhibits inactivated sodium channels, however to a lesser degree than the oral structure. [43]

The numerous actions of chronic oral amiodarone therapy can produce a variety of changes in the electrocardiogram. These include: [45]

- Both calcium channel blockade and beta blockade may contribute to sinus bradycardia.

- Prolongation of the PR interval and the atrioventricular (AV) nodal refractory period. Thus, AV conduction block may occur, an effect that may also be related to calcium channel blockade since the AV node is a "slow response" tissue that relies on an inward calcium current for depolarization.
- Widening of the QRS complex, as conduction is slowed in ventricular muscle by the blocking effect on the inactivated sodium channel.
- Prolongation of the QT interval due to blockade of IKr, the delayed rectifier potassium current that is responsible for phase 3 depolarization of the action potential.

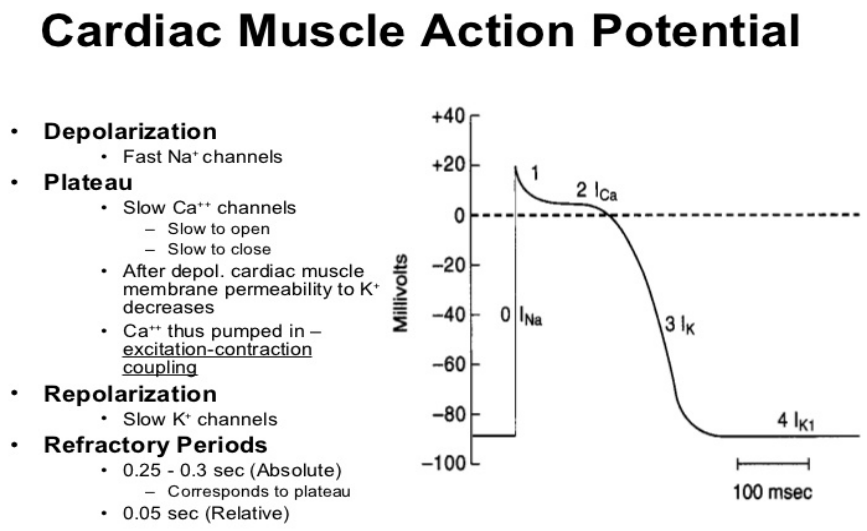

Figure (1): Cardiac muscle action potential. Available at: https:// www. slideshare. net/mobile/physiologylectures/heart-physiology-7424034.

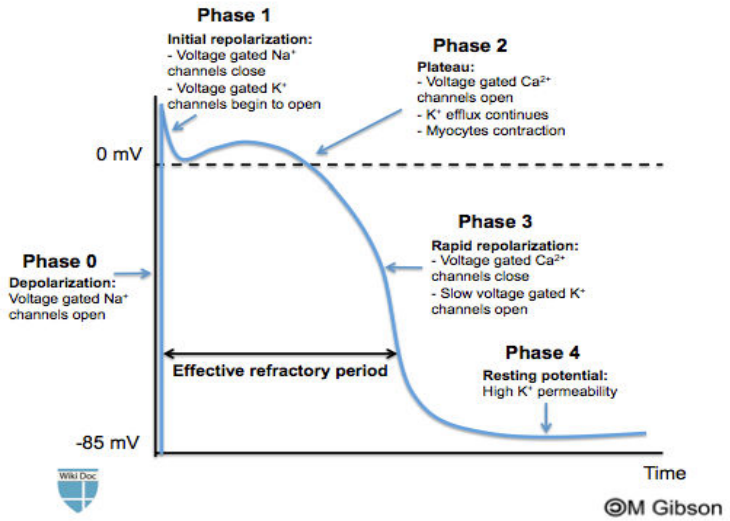

Figure (2): Phases of cardiac action potential. Available at: https:// www. slideshare. net/mobile/physiologylectures/heart-physiology-7424034.

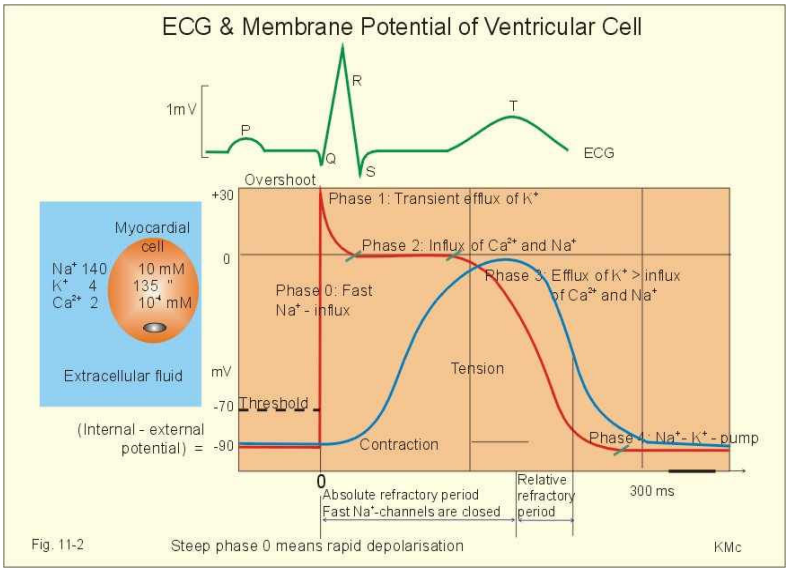

Figure (3): Correlation between the ECG and action potential. Available at: http:// www. zuniv. net/physiology/book/images/11-2.jpg.

Table (1): Comparison of the electropharmacologic effects of oral and intravenous amiodarone

Variable	Oral amiodarone	Intravenous amiodarone
Prolongation of action potential duration in atrial and ventricular myocardium	+++	+
Blockage of inactivated sodium channels	+++	++
Slowing of phase 4 depolarization in the sinus node	+++	+
Calcium channel blockade	+++	+++
Noncompetetive blockade of alpha and beta adrenoreceptors	+	+ (faster)
AV node effective refractory period	↑↑↑	↑↑↑
Ventricular effective refractory period	↑↑↑	↑
Heart rate	↓↓	-/↓
QRS interval	↑↑	↑
QTc duration	↑↑↑	-/↑
A-H interval	↑↑	↑↑↑
H-V interval	↑	-
Block conversion of thyroxine to trilodothyronine	+++	-

A-H interval: time from initial rapid deflection of the atrial wave to the initial rapid deflection of the His bundle potential; H-V interval: time from initial deflection of the His bundle potential to the onset of ventricular activity; +: yes or present; -: no or absent; ↑: increase; ↓: decrease.

Comparison of the electropharmacologic effects of oral and intravenous amiodarone. Compared to oral amiodarone, the intravenous preparation produces a much lesser increase in the action potential duration in atrial and ventricular myocardium and a minimal increase in

the atrial and ventricular refractory periods. As a result, there is little or no increase in QRS duration and the QT interval, respectively. Intravenous amiodarone also has little effect on sinus cycle length and has vasodilator activity that triggers an increase in sympathetic activity; both of these effects results in little or no slowing of the sinus rate. Lastly, the intravenous preparation may have more potent and more rapid antiadrenergic activity Data from: ***Desai AD, Chun S, Sung RJ (1997): Ann Intern Med; 127: 294.***

Hemodynamic effects

The predominant hemodynamic effect of I.V amiodarone is hypotension caused by a combination of arterial vasodilation and negative inotropy. [46] The former may be caused by its solvent polysorbate-80. [25] Blood pressure decreases commonly, even in patients without pre-existing LV dysfunction, but hypotension may be diminished by slowing the rate of infusion. The direct negative inotropic effect of the drug is insignificant and transient, and may be partially caused by its antisympathetic effect and normally does not prompt a diminished cardiac output. To minimize these effects the drug is diluted in 5% dextrose in water and slowly infused.

In patients with LV dysfunction being the standard candidate for amiodarone usage, the net hemodynamic effect is of particular importance. It may be associated with no noteworthy change in hemodynamic profile and no deterioration in functional status. [47]