

Amiodarone Toxicity Screening: What are the Clinicians Supposed to Tell Patients

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Abstract

The use of amiodarone in clinical practice continues to be widespread in the setting of nonvalvular atrial fibrillation (NVAF). Use of amiodarone continues especially in the elderly where the drug's favorable characteristics and outcomes in the setting of chronic kidney disease coupled to its low inherent proarrhythmic profile has ensured its continued use. The present work focuses on the information that clinicians should tell their patients regarding requisite toxicity screening during daily treatment with amiodarone when it is maintained at a low dose of 200 mgs per day or less. Several questions need be answered in pursuit of the fundamental query as to whether routine testing for toxicity should still be advised. Most importantly, has ongoing screening shown to be of any proven value?

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Introduction

The use of amiodarone in clinical practice continues to be widespread related to several factors including the general efficacy of the drug in the setting of nonvalvular atrial fibrillation (NVAF) [1]. Practitioners commonly encounter circumstances when other drugs have failed, are contraindicated and ablation has either not provided optimal results or is not appropriate for the specific clinical setting. The result is that the widespread use of amiodarone continues especially in the elderly where the drug's favorable characteristics and outcomes in the setting of chronic kidney disease coupled to its low inherent proarrhythmic profile has maintained its

popularity [2, 3]. The present work focuses on the information that clinicians should tell their patients regarding requisite toxicity screening during prolonged interval treatment with amiodarone using low dose oral amounts of 200 mgs per day. Short intervals of amiodarone after surgery especially protocols that call for the routine limited duration of amiodarone use, such as in the post-aortocoronary bypass setting infrequently if not rarely result in the potential cumulative dose exposure found in chronic utilization for NVAF. Several questions need be answered in pursuit of the fundamental query as to whether routine testing for toxicity should still be advised. Most importantly, has ongoing screening shown to be of any proven value?

How to Judge Amiodarone Use: then and now?

But before we can begin to address the purported value of screening for the toxicity associated with amiodarone, we must establish how the drug was used when first evaluated in the 1960-70's in comparison to its use in 2020. Differences in both indications and its practical applications will impact the likelihood of associated toxicity. Other important questions will of course be how frequent is amiodarone used for the treatment of NVAF in the current outpatient setting. Such use has decreased potentially in frequency and deserves reanalysis given that NVAF ablation is often being considered earlier in the course of NVAF and is being utilized in ever-older patients as experience and success is gained [4]. Further, how often do patients actually develop amiodarone toxicity at the dosage of 200 mgs per day for NVAF? [5]. This concern needs revisiting since much of the literature published regarding toxicity related to the drug is now 30 or more years old encompassing dosages that were on average much higher than the current trends of using only 200 mgs/day.

The above noted disparity between historic and current dosing is closely related to descriptions of who is currently more likely to receive amiodarone chronically for NVAF? Is the 'typical patient' in general similar to patients exposed to the drug in the 1990's or are they older, but healthier even though they have more cumulative but less significant co-morbidities? And now another concern is whether they have failed prior ablative strategies? This brings us to the final set of questions which is the actual focus of the current investigative effort. Is screening for amiodarone toxicity, as it is proposed, currently justified and if not what composes adequate and effective screening? The current effort will begin to address these questions and where possible bring the discussion up to date.

History as a Guide

Early reports from Argentina noted that the pharmacology of a new anti-anginal drug with a novel biological profile, amiodarone, was successful in controlling tachyarrhythmias associated with WPW [6, 7]. They noted that tolerance to the drug was excellent but that there were corneal micro-deposits of the drug as the 'only' important undesirable effect [7]. By 1979 reports noted that recurrent ventricular tachycardia and fibrillation could be controlled [8]. Early reports suggested that atrial fibrillation was not well controlled with amiodarone yet these same authors suggested that with fur-

ther experience they were able to provide control of atrial fibrillation 86% of the time for an average of 36 months [9]. Yet as shared experience was gained demonstrating a remarkable efficacy in treating dysrhythmias, there was recognition and then growing concern over the frequency of amiodarone-related side effects or what has become more commonly called its adverse drug-effect profile [5].

Leak and Edyt noted in a reported 10-year experience that 34% of their patients representing 44 individuals had side effect and that 24 patients (18%) were consequently withdrawn from treatment with the drug.⁹ Several points need to be emphasized that are typical for use of amiodarone during this timeframe. First the daily dose was at a minimum 400 mg/day but many of the patients were routinely treated with 600-800 mg/day. Patients were nearly always treated simultaneously with digoxin, associated with the P-glycoprotein mediated efflux transporter [9]. This is located on the apical surface of the intestinal enterocyte biliary canalicular membrane and the renal tubular cells and has been shown to reduce elimination of digoxin from the body in the presence of amiodarone [10]. This was not understood during the timeframe of this early reporting. The result is that digoxin levels rise and not infrequently elevate to potentially toxic levels. Thus, much of the nausea attributed to amiodarone may be related to the interaction of these two agents but excess amiodarone dosing undoubtedly led to toxicity [1].

But more importantly, the chronic use of 400 mgs/day minimum dosing and up to 800 mgs/day for long term chronic control of dysrhythmias is 2-4 times the normal 200mgs/day dosing provided today. Thus, the first issue is that adverse events or side effects listed from the 1970-80's may be less commonly encountered today simply because the dosing today is a fraction of what was used previously. A closely related issue is that while many of the patients in these trials received high dosages of daily amiodarone, there were in fact two additional factors that potentially predisposed them to toxicity. Many of these same patients simultaneously received exposure to a number of other antiarrhythmics if they could not be controlled on up to 800mgs/day of the amiodarone [9]. Absent the modern employment of AICDs and directed successful ablation, oral antiarrhythmics were the summation of tools existing to combat life-threatening ventricular and supraventricular rhythm disturbances. Very frequently combinations were of these different oral and intravenous agents, posing the question as to toxicity being at least potentially also proportional to these collective exposures.

Thus, the opportunity to develop toxicity was increased by some unknown multiple related to the high levels of amiodarone but also to the presence of other antiarrhythmic agents. The cumulative potentially unpredictable impact on the patient's hepatic or pulmonary system is at least theoretically reasonable if not likely. So, either the second agent, the increased level of amiodarone or the combination of these two drugs altering the kinetics of either or both could underwrite systemic and cellular toxicity of the therapeutic cocktail.

Finally, the vast majority of these patients suffering from dysrhythmias were in the setting of systolic heart failure [9]. Often severe systolic heart failure. This means that circulation times were likely increased or slowed meaning that hepatic, renal and systemic flow rates and clearances were reduced or at least altered often allowing prolongation of exposure in the micro-environment. Could this contribute to increases in adverse outcomes related to prolonged cellular exposure? It is a generally agreed upon principle in pharmacokinetics, that altered clearances, volumes of distribution and direct availability of active metabolites related to reduced hepatic, renal or gastrointestinal function predispose to a spectrum of adverse drug responses [11]. These patient groups could thus be predisposed to heightened drug-related toxicity based on higher dosing, reduced clearances and unaccounted for accentuated impact from competing agents.

One last footnote is that notwithstanding Leak's 10-year experience, many of these encountered complications were after amiodarone use in patients followed for 6 to 12 months or less.⁹ Even this noted 10-year experience of Leak and Eydt, the mean duration of their treatment with amiodarone was 13 months. A second report noted the 600 mg twice daily loading dose followed by 600 mgs per day as the routine only lowered if there were reported side effects [12]. In this report, the mean dose was reduced from 572+ 283 at 45 days to 372 + 174 at 6 months with the mean follow up again of only 11 months.¹² This short follow up similar to the 13 months noted above was in part a representation of the dismal statistics describing the life-expectancy of those afflicted with recurrent life-threatening dysrhythmias in the setting of advanced heart failure. In the pre-AICD and pre-guideline-directed medical management for systolic heart failure development of recurrent dysrhythmias was an ominous occurrence. Very likely such a shortened duration of monitoring artificially decreased the cumulative risk of chronic amiodarone exposure since many of these patients were simply not receiving the drug over months and certainly not for years. The fore-

seeable toxicity in the early years of amiodarone use were thus, if anything underreported. But it is clear that early use of amiodarone was radically different in comparison to its current use.

Current Use

The current use of amiodarone when chronically administered reflects the collective experience and cautious selection of this agent based on the full appreciation of its toxic potential. In the era of AICD deployment and direct ablative intervention for life-threatening dysrhythmias there is limited primary reliance on amiodarone as the final management strategy for dysrhythmia control. Primary prevention of death from ventricular dysrhythmias is successfully addressed with seminal reports noting that AICD use was superior to any pharmacological intervention [13]. There continues to be what amounts to a rescue strategy using amiodarone for patients presenting with recurrent discharge, an 'electrical storm' composed of life-threatening dysrhythmias in those with an AICD [14]. Yet this strategy arguably is also becoming a short term proposition in setting of ablative techniques to sequester or quarantine the dysrhythmia within an anatomic location [15, 16].

Thus, the current long term use of amiodarone is often for patients selecting drug therapy for the prevention or treatment of atrial fibrillation [17, 18]. Often this is in the older patient where ablation for atrial fibrillation may be deemed suboptimal for initial or even subsequent therapy [19]. Amiodarone use may also be preferred over other drug regimens. But its use in this subset, being older with changes to the pharmacokinetics, may increase the risk of adverse events related to the drug or frank development of toxic effects. Vassal et al, like most authorities acknowledge the usefulness of the drug, although reports have historically varied with regard to its specific efficacy, they recommend lowest possible dosing and vigilant monitoring of patients [1,19]. But what is the evidence-based monitoring strategy for amiodarone toxicity?

Recent guideline recommendations have noted that screening for toxicity needs to occur every 6 to 12 months [20]. But the evidence? The committee appropriately noted that this is an "Area for Further Research" as there is little current data to guide the clinician [20]. But where does this leave the practicing cardiologist who is often facing the quite common clinical scenario wherein a "70-ish" otherwise healthy patient needing care for atrial fibrillation? Such patients, healthy and clinically stable but with chronic conditions or illnesses including hypertension, adult onset or type two diabetes, mild

to moderate renal insufficiency and likely left ventricular hypertrophy represent the age-associated growing burden of atrial fibrillation [21]. Co-morbidities may make a strategy of initially employing ablative intervention less attractive, it may also render this therapeutic approach less likely to provide long term optimal efficacy [22-26]. The argument to employ amiodarone versus ablative therapy or another drug for a patient suffering from atrial fibrillation, in its multiple clinical presentations, is often a nuanced and multi-faceted assessment. But it remains a fact that amiodarone is being used commonly for the treatment of atrial fibrillation and the maintenance of sinus rhythm [2].

Further Research

From a practical standpoint explaining to patients that amiodarone has been found to be effective compared with placebo, with some reports noting its enhanced efficacy compared to other antiarrhythmics must also contain a warning [1]. Its potential for a wide-spectrum of toxic effects, some being life-threatening is also widely recognized [1,27]. Therefore, the practical concern is whether clinicians using this agent can prevent its toxicity by effectively screening patients for recognized problems. Historically, and within the guidelines the above noted 6 to 12 month screening protocols have been, and continue to be employed [20]. But here the data becomes very spotty, if not totally absent. Clearly placebo controlled and blinded trials attempting to establish the optimal strategy are non-existent. A prescient editorial from Horowitz in 1988 noted that even in the era of increased and aggressive use of amiodarone pulmonary function studies could not be relied upon to detect early pulmonary toxicity in the asymptomatic patient.²⁸ There was simply too much variability in testing and the associated cost could not be supported. And importantly, this was during the era of high maintenance dosing. If one could not make the case then, how are we to view the continuation of testing when the daily dosages are markedly reduced, patients are likely healthier and asymptomatic.

Conceptually the challenge is to identify the potential for early toxicity to avoid further pulmonary injury and its outcomes. Is there any data to suggest this actually can be done? Or does true pulmonary toxicity overlap enough with changes in diffusing capacities to render this so insensitive a test with such limited specificity as to liken it to performing periodic invasive angiograms in every patient who ever gets a stent regardless of symptomatology? Further, the efficacy, sensitivity and specificity of drug toxicity detection in otherwise asymptomatic patients using current low-level use of

200 mgs/day is at present nearly pure conjecture [28]. Commentaries and studies on detection are largely historic and still include proportions of patients using high maintenance dosing [12,28]. Thus currently, patients who now on average are older, asymptomatic healthy but with multiple co-morbidities, use a drug that is relatively inexpensive but 'demands' periodic blind testing. This testing has unproven sensitivity or specificity and has almost no data to recommend its current temporal application. This is in itself problematic. For those clinicians such periodic testing is expensive, resisted by these otherwise healthier older patients and may not actually detect what we are asking it to detect.

Conclusion

Recommending toxicity screening on a 6 to 12 month interval in otherwise healthy individuals is perhaps underwritten more by legal considerations than science. Thus, a single opinion to reverse what has been now almost three decades of scheduled periodic screening for amiodarone toxicity is not reasonably supportable. But current practice, arguably done for the reassurance of the physician more than meaningful or provable reduction in, or prevention of toxicity for the patient, is a reality. It begs cogent recognition as to the need to either abandon periodic testing in asymptomatic patients receiving low dose amiodarone, or to enhance investigation of the utility of testing predicated on cumulative amounts of the drug received. Ultimately periodic testing for amiodarone toxicity demands proof that it protects patients. Absent this we are exhausting resources without any idea as to their contribution to patient safety or health.

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