How Toxic is Amiodarone to the Liver?

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Every clinician "knows" that amiodarone causes hepatotoxicity, but exactly how toxic is it? If left too long on amiodarone, will your patient die, as one of the first published cases of amiodarone hepatotoxicity did? [1] There are now dozens of other case reports in the literature, but how clearly was the causality proven in all these patients who were sick enough to be receiving amiodarone, a drug that was in the past often reserved for the sickest of the sick? Is there a denominator that can be used to calculate an incidence from these cases? If the more than 60 million people exposed to amiodarone worldwide were used, would that not make the incidence of amiodarone hepatotoxicity exceedingly small?

No prospective follow-up or retrospective case series has identified a high rate of clinical hepatotoxicity. This begs the question, does clinically asymptomatic elevation of a serum transaminase to twice the upper limit of normal constitute hepatotoxicity? As pointed out by *Mattar et al.* most cases of amiodarone liver injury are limited to an asymptomatic transaminitis that resolves either spontaneously or after dose reduction. They examined the use of amiodarone in a population of 409 patients who might be expected to be at higher risk for toxicity because of pre-existing liver abnormalities from metabolic syndrome, high prevalence of statin use, and in many cases, heart failure. Contrary to expectations, no cases of clinical hepatitis, cirrhosis or death related to the therapeutic use of amiodarone were identified in that population during an average period of observation of over 3 years [2]. Similarly, pre-existing liver dysfunction was not predictive of transaminitis in a population of 720 Chinese patients. Kum et al showed that not only did a large proportion of their population of patients starting amiodarone have ALT abnormalities at baseline (14.3%), but that the incidence of significant liver dysfunction was not statistically different (4.4 vs. 3.7%) in patients with or without elevated baseline ALT [3].

The histological changes that occur in the liver of patients ingesting alcohol are remarkably similar to those in patients receiving amiodarone [1, 4]. Like alcohol, amiodarone, to varying degrees, can produce microsteatosis, apoptosis and necrosis of the hepatocytes. Therefore, it is worth pausing to consider that similar issues surround the intake of alcohol. Low doses can be consumed with impunity by the majority of the population, but as the dose of alcohol increases (implying exposure to high blood concentrations), so does the likelihood of serious hepatic damage [5]. Nonetheless, a significant portion of patients demonstrate resistance to the negative effects of alcohol at high doses. Similarly, amiodarone can be shown to have a concentration-response relationship for its hepatic effects with evidence of differing sensitivities to toxicity within the population [6]. When used at low doses, amiodarone, like alcohol, seems to cause toxicity only under uncommon circumstances.

The difference between alcohol and amiodarone is that the individual titrates their own dosing of alcohol, while it is the physician who controls a patient's exposure to amiodarone. Therefore, the onus is on the physician to find the correct dose of amiodarone for long-term maintenance in each individual patient. However, without widespread clinical measurement of serum amiodarone concentrations, we will never discern if those patients who develop toxicity did so because of abnormally high concentrations produced by atypical pharmacokinetics with normal doses.

Change in serum transaminase level is an indicator of early hepatic inflammation, but the physician is faced with the fact that in the NHANES trial, 8.9% of patients were found to have abnormal alanine aminotransferase (ALT) values [7]. This makes baseline testing indispensable if valid interpretation is to be made of any ALT measurements after exposure to amiodarone. It must also be remembered that by defining normal as a laboratory measurement within two standard deviations of the mean, the 2.5% of the healthy population at the upper tail of the normal distribution will be labeled as abnormally high. More than

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30% of abnormal transaminases readings will then be found to have returned to the normal range with retesting [8]. This makes retesting of asymptomatic individuals with an abnormal transaminase extremely important and diagnosis of amiodarone hepatotoxicity inadvisable on the basis of a single measurement.

Although cumulative dose is widely cited as an indicator of increased risk of toxicity, Mattar et al [2] correctly conclude that based on their study and others [6, 9], it does not have a major impact on the prevalence of amiodarone hepatotoxicity. This should be apparent when one considers that cumulative dose is only a good surrogate for exposure until steady state is reached. At that point, by definition drug entering the system is equal to the amount being eliminated and therefore exposure remains constant. Because of its 55-day half-life, it takes 6 to 8 months for amiodarone to reach steady state [10], the time frame upon which most studies correlating cumulative dose with toxicity are based. The period of time during which cumulative dose shows some correlation with effects can extend beyond 8 months depending on an individual patient's pharmacokinetics, changes in body mass, drug interactions, or even autoinhibition of metabolism. However, cumulative dose merely summarizes dosing rate and time on drug, while true exposure risk of toxicity is best assessed by monitoring for any significant changes in steady state serum drug concentrations. Physicians do this as a matter of course for anti-epileptic drugs and digoxin, but because of the mystery generated by the exceedingly long time frame imposed by amiodarone's pharmacokinetics, much of the world has been resistant to monitoring amiodarone as a safety measure.

Even in the absence of therapeutic drug monitoring, a simple ALT measure can identify those patients in whom dose adjustment might be called for, before clinical toxicity actually arises. In reviews summarizing all publications mentioning liver toxicity, the estimate of transaminase abnormalities due to amiodarone varies widely between 4 and 50% of patients. However, modern reviews conclude that the rate is much lower than 4% [11] which concurs with the 2% rate of hepatic dysfunction observed by Primeau et al [12] and the 2.5% rate of transaminitis observed by Pollak et al in 117 patients followed prospectively [6]. Lewis et al found only a 0.5% incidence of clinically overt hepatic disease in their 104 patients [9]. Thus, the results of the retrospective trial by Mattar et al, where 2% of their 409 patients developed transaminitis, are squarely in line with expectations for patients receiving amiodarone [2].

Despite its obvious limitations, monitoring for early signs of liver damage in patients taking amiodarone still makes clinical sense. However, one needs to strike a balance. On the one hand, failing to monitor transaminases at all will miss the patient who does develop toxicity. On the other, over reacting to mildly abnormal values will lead to unnecessary discontinuation of drug that hopefully was started because of its strong clinical benefit for that patient. Because of the prevalence of abnormal transaminases in the population, a baseline measurement is key to interpreting whether transaminases have gone up in response to amiodarone. Given the slow change in amiodarone exposure with changing dose and patient environment, checking ALT every three months during the first year should be adequate to identify issues of toxicity. After that, testing every six months should be adequate. Careful downward titration to the lowest effective dose also makes sense for any drug including amiodarone.

So, how toxic is amiodarone to the liver? At normal doses, in normal patients, the answer is probably not very toxic. In an individual patient, amiodarone associated liver changes can be a scary thing. On a population basis, properly managed amiodarone appears to be as safe or safer than alcohol. However, if the information found on the internet is any indication, patients and physicians have been conditioned to believe that amiodarone is a very common cause of hepatotoxicity. This seems linked to reviews summarizing trial data mixed with anecdotal literature that variously defines toxicity as anything from asymptomatic single point elevation of a transaminase to fulminant hepatic failure. Yet, good quality evidence of high rates of toxicity does not exist in the literature, especially when examined in patients given amiodarone at modern doses. When changes in ALT are noted in a patient taking amiodarone, they should be investigated with a second measurement and a broad differential diagnosis in mind [13]. In particular, physicians should be aware that in the population of patients treated with amiodarone, pre-existing "cardiac hepatopathy" or congestive/ischemic liver disease resulting from cardiac dysfunction can be the cause of altered liver chemistry even in the absence of clinically evident heart failure. It should be remembered that at normal amiodarone doses, the a priori probability that amiodarone is the cause of liver toxicity is actually quite low. As Mattar et al point out, discontinuation of amiodarone for liver toxicity should be a rare occurrence [2].

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