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Absence of Bilateral Vision Loss from Amiodarone: A Randomized Trial

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Abstract

Background—Amiodarone's role as a cause of toxic optic neuropathy is based on case reports. Annual frequency estimates, 0.36 to 2.0%, which have been made without reference to the dose or duration of treatment, are 12 to 200 times higher than those for idiopathic nonarteritic anterior ischemic neuropathy. The object of this study was to determine the incidence, dose, and time-until-onset of bilateral vision loss from amiodarone as a secondary end-point in an investigation of amiodarone's role in preventing sudden death.

Methods—Randomized subjects received body-weight determined doses of closed-label amiodarone (837) or placebo (832) in a prospective, double-masked manner. Closed-label amiodarone subjects were followed, unless death occurred, a minimum of 27 months. Median follow-up in survivors was 45.5 months. The end point was removal from the study because of bilateral vision loss.

Results—No subject was removed from the study because of bilateral vision loss. Subjects receiving continuous amiodarone for 4 to >60 months at daily doses of >2.0 (N=696), >3.0 (N=559), or >4.0 (N=219) mg/kg, had maximum possible (95% confidence) annual incidences of bilateral toxic vision loss of 0.23%, 0.29% or 0.74%, respectively. The maximum possible annual incidence rate of bilateral vision loss from amiodarone in all 837 subjects, medium age 60 years, receiving a mean daily dose of 3.7 mg/kg (300 mg) was 0.13%.

Conclusions—At the doses commonly used clinically, bilateral vision loss from amiodarone toxic optic neuropathy occurs infrequently, if at all.

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Introduction

An argument for the existence of amiodarone toxic optic neuropathy (ON) is its higher frequency in those taking the drug than can be attributed to idiopathic nonarteritic anterior ischemic optic neuropathy (NAION). However, frequency estimates of both conditions have been based solely on retrospective analyses. Idiopathic-NAION annual estimates range from 0.01% to 0.03% (a 10-year incidence of 0.3%) (1,2). Annual incidence estimates of amiodarone toxic ON have been 12 to 200 times higher, i.e., 0.36% (a 5-year incidence of 1.79%), approximately 2% (unstated time interval), and 2% (2,3,4). These estimates have not been correlated with either the dose or duration of treatment. Even if correct, these higher incidences of amiodarone associated ON could be the result of an increased prevalence in cardiac patients of idiopathic-NAION risk factors, such as diabetes and hypertension, rather than drug toxicity (5,6).

Obstacles to performing a prospective, double-masked, randomized, placebo-controlled study of the incidence of amiodarone toxic ON include the ethical dilemma of enrolling a matched placebo control group, the large number of subjects required, the unmasking effect of amiodarone corneal deposits, and the lack of drug company interest.

With regard to study size, an initial enrollment of 668 subjects would be needed to determine with 95% confidence that amiodarone toxic-ON occurred assuming: a 1.5% annual incidence, a 42 month study, an annual death rate of 8% and a 0.03% annual incidence of idiopathic NAION. The second obstacle is the unmasking effect caused by amiodarone corneal deposits, present in more than 97% of patients receiving 200 to 300 mg amiodarone daily and 99% of patients receiving 200 to 1200 mg amiodarone, 5 days per week (7,8). Techniques that might reveal corneal deposits such as slit lamp, funduscopic, and retinoscopic examinations would have to be excluded. However, the largest obstacle may be drug company disinterest in funding such a study. After a 1997 $22.8 million judgment against Wyeth-Ayerst Pharmaceuticals, labeling was changed to emphasize the possible occurrence of amiodarone associated ON. This shifted a pharmaceutical product liability issue to a physician malpractice problem.

The present study was part of a placebo controlled long-term trial designed to compare amiodarone and defibrillators in the prevention of sudden death (9). Described is the failure of amiodarone toxic ON to manifest itself as bilateral vision loss in 837 subjects followed at three month intervals for a median duration of 45.5 months and unless death occurred, a minimum duration of 27 months.

Methods

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (9) was multi-centered, prospective, and had three randomized and matched arms. Two arms were double-masked: those receiving amiodarone and placebo. The third arm received an implanted defibrillator. The primary end-point was death from any cause. Vital status was known for all 2,521 subjects at the time of the last scheduled visit.

Each arm had a median age of 60, a median cardiac ejection fraction of 24 to 25%, and a maximum cardiac ejection fraction of 35%. They were matched for prevalences of the idiopathic NAION risk factors, diabetes, 29% to 31%, and hypertension, 55% to 56%. These prevalences were high. For comparison, the US prevalence of diabetes in 50 to 59 year-olds is 8% and in 60 to 74-year-olds is 12.6% (10) The US prevalence of hypertension in 55 to 64 year-olds is 48% (11). Subjects entered the study from September 1997 to July 2001. All surviving patients were followed through October 2003. The minimum follow-up was 27 months unless death occurred.

All patients were treated with open-label conventional drug therapy for heart failure. Patients receiving amiodarone could not enter the study. However, post-randomization, any patient in any of the three arms could have open-label amiodarone, uncontrolled as to source and dose, initiated as a component of conventional therapy. The arm receiving closed-label amiodarone was given Cordarone (Wyeth-Ayerst Pharmaceuticals).

Subjects in the two-masked arms received a one-month loading dose of closed-label amiodarone or placebo consisting of 800 mg daily for one week followed by 400 mg daily for three weeks. Thereafter, the daily maintenance dose depended on the body weight recorded at each visit. Subjects weighing more than 200 pounds received 400 mg daily, those weighing 150 to 200 pounds received 300 mg daily, and those weighing less than 150 pounds received 200 mg daily. If bradycardia occurred, the on-site cardiologist could lower the loading dose and lower or temporarily discontinue the maintenance dose. Non-compliance was defined as discontinuation of either placebo or amiodarone at any time during an interval period. Placebo and amiodarone were identical appearing 200 mg scored tablets provided by Wyeth-Ayerst Pharmaceuticals.

Interval patient reports were filled out at baseline, one week, one month and every three months thereafter by the Nurse Coordinator at each site.

Ophthalmic examinations were not performed because detection of the presence or absence of corneal deposits would compromise the double masking of the arms receiving amiodarone and placebo. However, patients were permitted to have eye examinations outside the study. The reports filled out at each interval visit also recorded the types of physicians seen outside the study.

The outcome measured was the number of subjects with vision loss causing the local site personnel to contact the principal investigator to unmask and discontinue their participation. It was assumed that a progressive bilateral vision loss from long-term toxic exposure to amiodarone would manifest itself to both the patient and the investigators. In order to orient the patient and study personnel toward acquired visual loss, the interval reports contained the query “Optic Neuritis” followed by check boxes “No” or “Yes”. The Nurse Coordinator asked this question at each interval visit and recorded the patient’s answer. The term “Optic Neuritis” was used both because it always appeared with “Optic Neuropathy” in the amiodarone labeling, e.g., “Cases of optic neuropathy and/or optic neuritis, usually resulting in visual impairment have been reported in patients treated with amiodarone”, and was more familiar to the Nurse Coordinators and patients.

A “Yes” checked off in response to the “Optic Neuritis” question did not trigger any alteration in that subject’s status, i.e., no unmasking, no discontinuation from the study, no alteration in treatment and no ophthalmologic examination. It was the local investigator’s responsibility to contact the principal investigator for permission to unmask and remove the subject from the study. Of special concern was the likelihood of false positive “Yes” responses. A total of 148 sites participated in the study. The “Optic Neuritis” question was answered by at least that number of cardiology Nurse Coordinators, increasing the possibilities of either making a marking error or misinterpreting the patient’s visual complaints.

A post hoc analysis was performed on all subjects with a “Yes” response. This consisted of the study’s Chief Nurse Coordinator (JA) contacting each site with a “Yes” response. The local Nurse Coordinator conducted an internal review of the subject’s records to determine if an error had been made in marking the answer box. Once it was determined no marking error had been made, the local Nurse Coordinator contacted the patient, if alive, to determine if either of them had misinterpreted the subject’s visual complaints. If there were any doubt, or if optic

neuropathy seemed to have occurred, the local study cardiologist would contact the patient's ophthalmologist or neuro-ophthalmologist for corroboration.

Excluded from analysis were 12 patients claiming "Optic Neuritis" at the time of randomization and 21 subjects for whom there were no post-randomization data. These exclusions reduced the sizes of the three arms to closed-label amiodarone 837, placebo 832 and defibrillator 819.

The study was approved by the human subjects' committee at each of the 148 sites that provided patients. The National Heart, Lung and Blood Institute provided sponsorship and oversight and appointed a safety and data monitoring board to oversee the conduct of the trial. Every patient provided written informed consent. Wyeth-Ayerst provided closed-label amiodarone at no cost, but no other support, and had no role in the design, management, or interpretation of the study and its data.

Results

No subject was removed from the study because the principal investigator was notified of visual loss.

The sizes of the three arms were reduced by death: closed-label amiodarone from 837 to 599, placebo from 832 to 595, and defibrillator 819 to 641. The respective median and minimum follow-up periods in survivors were 45.5 months and 27 months.

The mean daily dose of closed-label amiodarone was 300 mg, or 3.7 mg/kg body weight, at three months and remained at this level thereafter. 41% of the closed-label amiodarone subjects temporarily or permanently discontinued the drug at some point in the study. Most discontinuations were physician directed, transient, and due to bradycardia. As a result, amiodarone was used 87% of the time during the first two years and 81% of the time over the total follow-up period.

The number of subjects in each arm receiving open-label amiodarone at any time in the study was: closed-label amiodarone 44, placebo 81, and defibrillator 113. Of the 44 subjects who received open-label amiodarone in the closed-label amiodarone group: a) only 11 subjects used both closed and open-label amiodarone at the same time and b) in 23 subjects open-label amiodarone was begun just before the last study visit or at the end of life.

There were 39 "Yes" responses to the "Optic Neuritis" query. No subject had more than one interval report with a "Yes" response. The post hoc analysis determined that all 39 were false positives. The local Nurse Coordinator had made 36 of the 39 errors, with the majority being due to inadvertently checking the wrong answer box. Three errors were due to patient misinterpretations. In patients receiving amiodarone, there were misinterpretations by both Nurse Coordinators and subjects caused by the corneal deposits, discovered by out-of-trial visits to ophthalmologists or optometrists, being confused with "Optic Neuritis". The answer to the "Optic Neuritis" question was recorded 25,632 times, giving a false positive rate of 0.0015. There were, respectively, 17, 10 and 12 false positive responses in the closed-label amiodarone, placebo, and defibrillator arms. Logistic regression analyses failed to show significant differences in false positive incidences: closed-label amiodarone vs placebo, $p=0.18$; closed-label amiodarone vs defibrillator, $p=0.39$; and placebo vs defibrillator, $p=0.62$.

The Table shows the distribution, by maximum daily dose, of 735 closed-label amiodarone subjects who had ≥ 4 months of uninterrupted treatment at that dose. The Table was constructed with a higher mg/kg/d dose having precedence over a longer duration of treatment, i.e., the maximum mg/kg/d dose, taken for a minimum uninterrupted four months, determined that subject's location in both the mg/kg/d and the mg/d portions of the Table. The reasons why all

837 closed-label amiodarone subjects did not receive their maximum mg/kg/d dose for at least 24 uninterrupted months were: death, weight change, non-compliance and physician directed dose alteration. Of 735 subjects taking their maximum closed-label amiodarone ≥ 4 months, 335 (46%) were at this maximum dose for uninterrupted periods of more than 24 months and 491 (67%) were at this maximum dose for uninterrupted periods of more than 12 months. For 477 (65%) of subjects, this maximum dosage was between 2.0 and 4.0 mg/kg/d. An additional 192 (26%) received 4.0 to 5.0 mg/kg/day and another 27 (3.6%) received >5.0 mg/kg/day.

The absence of reported bilateral vision loss led to the following exact binomial 95% confidence interval calculations:

1. The maximum possible annual incidence of bilateral vision loss from amiodarone toxic ON in a population, median age 60, receiving a mean daily dose of 3.7 mg/kg (300 mg) amiodarone for a median duration of 45.5 months, and a minimum duration of 27 months, unless death occurred, was 0.13%.
2. In subjects receiving amiodarone for a median duration of 45.5 months and a minimum duration of 27 months, unless death occurred (Table):
    - **a)** In mg/kg/d –
        - **a.** 696 received >2.0 mg/kg/d for uninterrupted periods of four months to >60 months. Their maximum possible annual incidence of bilateral vision loss from amiodarone toxic ON at a dose of 2.0 mg/kg/d was ≤0.23%.
        - **b.** 559 received >3.0 mg/kg/d for uninterrupted periods of four months to >60 months. Their maximum possible annual incidence of bilateral vision loss from amiodarone toxic ON at a dose of 3.0 mg/kg/d was ≤0.29%.
        - **c.** 219 received >4.0 mg/kg/d for uninterrupted periods of four months to >60 months. Their maximum possible annual incidence of bilateral vision loss from amiodarone toxic ON at a dose of 4.0 mg/kg/d was ≤0.74%.
    - **b)** In mg/d –
        - **a.** 719 received 200 mg or more daily for uninterrupted periods of four months to >60 months. Their maximum possible annual incidence of bilateral vision loss from amiodarone toxic ON at a dose of 200 mg/d was ≤0.23%.
        - **b.** 515 received 300 mg or more daily for uninterrupted periods of four months to >60 months. Their maximum possible annual incidence of bilateral vision loss from amiodarone toxic ON at a dose of 300 mg/d was ≤0.32%.
        - **c.** 260 received 400 mg or more daily for uninterrupted periods of four months to >60 months. Their maximum possible annual incidence of bilateral vision loss from amiodarone toxic ON at a dose of 400 mg/d was ≤0.63%.

Discussion

The strengths of this study were the long duration of amiodarone treatment, the completeness of the follow-up data and the large number of subjects. When dealing with optic nerve toxicities from systemically administered drugs, bilaterality is a hallmark. As stated in Grant and

Schuman's text, Toxicology of the Eye, "Simultaneous involvement of the two eyes is particularly characteristic" (12). If a toxic ON had occurred in the present study, and the patient were not initially aware of it, the long follow-up period on amiodarone would have resulted in a progressive, devastating bilateral loss of vision. This did not occur. There was no patient terminated from the study because the principal investigator was notified of loss of vision.

Review of 52 English-language case reports of optic neuropathy associated with (2,3,13-21), or believed probably due to (22), amiodarone use, found that the duration of treatment until onset of vision loss was stated in 50 cases and the median was four months. Vision loss occurred after 24 months of treatment in only one case. In the present study, the median follow-up in the group administered closed-label amiodarone was 45.5 months and all subjects who lived long enough were followed a minimum of 27 months. If amiodarone toxic ON were missed, it was because either the subject died shortly after its onset, i.e., before it could progress to a bilateral functional deficit, or the onset of toxicity occurred close to October 31, 2003, the termination date for the study. If this latter situation had occurred, the subject would have been on the drug a minimum of 27 months without the toxicity manifesting itself.

The maximum possible annual incidences of bilateral vision loss from amiodarone toxic ON stated in this study are qualified by duration of treatment and dose. Qualifications are necessary because the longer the duration of exposure and the higher the dose, the greater the frequency, incidence and severity of toxicity and the more rapid its onset and rate of progression. The influence of these factors can, in turn, be altered by a number of variables such as age, genetic make-up, diet and drug interactions; investigations of amiodarone have examined some of these (23-25).

In those 52 English language case reports reviewed, the daily dose at the time of vision loss was stated in 43 cases and the mean was 358 mg. This was a higher mean daily dose than that in the present study, 300 mg. In the literature case reports, 19, 1, 2, 1 and 1 subject received, respectively, daily doses of 400 mg, 500 mg, 600 mg, 800 mg and 1200 mg. While the relative number of subjects, 44% (19 of the 43) at the 400 mg daily dose level is high in the case report literature, the absolute number of subjects receiving this dose for at least 4 months in the present study, 255, is far larger (Table); none, 172 of whom were at this dose for more than a year, developed bilateral vision loss from amiodarone associated ON.

Amiodarone is widely distributed in the body; data providing maintenance daily doses in either mg per kg body weight or meter square body surface, and amiodarone blood levels at the time of ON onset, would be much more meaningful than daily mg maintenance doses. Unfortunately, the case literature does not provide either type of information with one exception, a single amiodarone blood level (3). The present study emphasizes daily maintenance doses in mg/kg body weight. It is of interest to see how the relative distribution of patients in the Table changes when dose calculation changes from mg/day to mg/kg/day.

The final comparison with the case literature is with regard to age. The median age in the present study was 60 years (range 22 to 88). The median age in the amiodarone associated ON case report literature was 66 years (range 32 to 83). Age differences do not appear to explain this study's absence of bilateral vision loss.

The literature's retrospectively derived annual incidence estimates of amiodarone toxic ON, 0.36% to 2%, appear too high. At the doses commonly in use, the annual incidence, if the condition exists at all, is less than 0.13%.

Limitations of the Present Study

The major weakness of this study was the absence of ophthalmologic examinations at each visit. These were not part of the protocol because detection of the presence or absence of corneal deposits would have compromised the double-masking of amiodarone vs placebo groups for both the sudden death and optic neuropathy end points. An alternative evaluation was possible, consisting of: 1. visual acuities, to assess central (macular) function, obtained by the nurse coordinator; 2. automated visual fields, to assess peripheral visual function, obtained by a technician; and 3. fundus photographs, obtained by an ophthalmic photographer, to confirm optic neuropathy and not some other cause of vision loss, e.g., cataracts, diabetic retinopathy, vitreous bleeds or occipital lobe infarcts. However, such an approach would have added more expense, personnel, and time than a routine ophthalmologic examination, creating an unacceptable commitment for a study which had as its primary goal, the evaluation of defibrillators in preventing sudden death.

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Table

Closed-Label Amiodarone Subjects Treated ≥ 27 Months Unless Death Occurred: Distribution by Uninterrupted Treatment Duration at Maximum Dose

Maximum		Uninterrupted Months								
Mg/kg/day	**4-6**	**>6-9**	**>9-12**	**>12-18**	**>18-24**	**>24-36**	**>36-48**	**>48-60**	**>60**	**Total**
≤2.0	4	2	6	7	5	7	6	2	0	**39**
>2.0-3.0	14	10	14	18	14	36	15	15	1	**137**
>3.0-4.0	24	37	29	31	30	89	50	38	12	**340**
>4.0-5.0	28	33	29	26	20	25	16	10	5	**192**
>5.0-6.0	6	3	1	0	1	3	4	0	0	**18**
>6.0-7.0	0	1	0	1	1	0	0	0	0	**3**
>7.0	1	2	0	1	1	1	0	0	0	**6**
Total	**77**	**88**	**79**	**84**	**72**	**161**	**91**	**65**	**18**	**735**
Mg/day	**4-6**	**>6-9**	**>9-12**	**>12-18**	**>18-24**	**>24-36**	**>36-48**	**>48-60**	**>60**	**Total**
100	2	2	2	0	2	5	2	1	0	**16**
200	18	23	20	30	24	46	27	13	3	**204**
300	30	32	29	31	30	49	28	21	5	**255**
400	26	29	28	23	15	60	34	30	10	**255**
600	1	2	0	0	0	1	0	0	0	**4**
800	0	0	0	0	1	0	0	0	0	**1**
Total	**77**	**88**	**79**	**84**	**72**	**161**	**91**	**65**	**18**	**735**