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Editorial Comment

Adverse Effects of Amiodarone at Low Dose: Plus Ça Change*

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In this issue of the Journal, Vorperian et al. (1) present a statistically rigorous meta-analysis of the adverse effects of low dose amiodarone (maintenance dose ≤400 mg/day) reported in four trials of its use in patients at risk of arrhythmic death. As the authors observe, only trials with this randomized, double-blind, placebo-controlled design can allow an accurate description of the nature and frequency of adverse effects attributable to a therapy. Adverse effects are a critical issue in determining the appropriate use of amiodarone, which is widely perceived to be the most effective antiarrhythmic drug for almost all tachyarrhythmias. To date, other antiarrhythmic drugs with class III activity have failed to fulfill hopes that they might share the efficacy of amiodarone without the toxicity (2). Indeed, the perception of the efficacy of amiodarone is reflected in its use as the most commonly used antiarrhythmic agent in large-scale trials of therapies in patients deemed to be at risk of arrhythmic death. Racemic sotalol, which shares the class III antiarrhythmic activity of amiodarone, in addition to possessing marked class II activity, currently appears to be its major rival in this context (3). However, the potential of amiodarone to cause serious and irreversible organ damage and its unusual pharmacokinetics, whereby even reversible effects persist for many weeks after withdrawal, have made many physicians fearful of its use. The unique set of circumstances under which amiodarone entered the pharmacopoeia in the United States may also have contributed to the degree of fear regarding its use: Food and Drug Administration (FDA) approval was given in 1985 for it to be used in the treatment of life-threatening ventricular arrhythmias on compassionate grounds, without the normal process of review. Most reports by U.S. investigators in the 1980s used maintenance doses of 400 to 800 mg/day. In contrast, "low dose" amiodarone (maintenance dose ≤400 mg/day) has been widely used in Europe for many years in the treatment of supraventricular and ventricular arrhythmias. The experience in the United States has now evolved, and low maintenance doses have been used in all recent large-scale trials involving long-term therapy with amiodarone. Some adverse effects of amiodarone have been known to be influenced by dose for many years, but there has been no previous analysis specifically of the adverse effects of low dose amiodarone in published reports. The presentation of the present meta-analysis (1) should therefore enhance our understanding of the use of this unusual drug.

Criteria for the inclusion of a trial in this meta-analysis included a minimal mean follow-up period of 12 months and a clear description of adverse effects in both the amiodarone and placebo groups. All four trials that were included concern patients deemed to be at high risk of arrhythmic death: two studied post myocardial infarction (MI) patients (4,5), and two studied patients with symptomatic heart failure and asymptomatic ventricular arrhythmia (6,7). These four trials recruited a total of 1,465 patients, of whom 738 were randomized to receive amiodarone, allowing reasonable estimates of the incidence of adverse effects with an incidence of around ≥0.5%/year. The meta-analysis demonstrates a high degree of cohesion in the reporting of adverse effects between the four trials, thus increasing the confidence in its conclusions. However, the pace of the field is reflected in the fact that this meta-analysis is already out of date. Earlier this year, two studies were reported on that fulfill the criteria for inclusion in it (8,9). The pilot study of one of these (the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial [CAMIAT] [4]) enrolled only 77 patients and is included in the meta-analysis, but the completed study (8) enrolled 1,202 patients with frequent or repetitive ventricular depolarizations after MI, and the mean follow-up period was 20 months. The other recently reported study (the European Myocardial Infarct Trial [EMIAT] [9]) used amiodarone at a maintenance dose of 200 mg/day in patients with a post-MI left ventricular ejection fraction of ≤40%. EMIAT alone enrolled more patients (n = 1,486) than are represented in the meta-analysis published here, and the mean follow-up period was 21 months. It is therefore instructive to analyze the results of this meta-analysis in light of these two newly published trials.

A useful measure of the frequency of important adverse effects of a drug is the rate of discontinuation of active therapy compared with the rate of discontinuation of placebo in double-blind trials. The meta-analysis reports an unadjusted total incidence of discontinuation of 22.9% for amiodarone and 15.4% for placebo. However, probably largely due to differences in the reasons for drug discontinuation used in the four trials, and due to their different durations of follow-up (12 to 45 months), these rates represent a wide range of 14% to 35% for amiodarone and 10% to 34% for placebo. CAMIAT and EMIAT reported rates of discontinuation of 36.4% and 38.5% for amiodarone and 25.5% and 21.4% for placebo, respectively. The incidence of discontinuation of both amiodarone and placebo were linearly related to time in EMIAT. Taken together, these results indicate an odds ratio of discontinuation of amiodarone relative to placebo of ~1.3/year,

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Abbreviations and Acronyms

CAMIAT = Canadian Amiodarone Myocardial Infarction Arrhythmia Trial
EMIAT = European Myocardial Infarct Trial

which is comparable to the overall figure of 1.5 reported in the meta-analysis.

Comparison of the odds ratios for the occurrence rates of particular adverse effects reported in each of the four trials included in the meta-analysis reveals a higher degree of cohesion between the trials, and very similar trends were observed in CAMIAT and EMIAT. Notable differences are 1) CAMIAT included sleep disturbance as an adverse effect, and the incidence of this prompting discontinuation of study medication was significantly higher with amiodarone (1.7% vs. 0.3%); and 2) in CAMIAT the increase in the rate of pulmonary adverse effects with amiodarone reached statistical significance (3.8% vs. 1.2%). Overall, it seems that the odds ratios presented in this meta-analysis would be little changed for the inclusion of these two new trials (which would increase the number of included patients by a factor of 2.8), although the range of confidence intervals would clearly be substantially reduced.

The present meta-analysis and comparison of its results with the adverse effects reported in CAMIAT and EMIAT therefore give us a clear indication of the odds ratios of experiencing particular adverse effects with low dose amiodarone therapy for ~2 years compared with placebo in the populations studied. However, it is the absolute frequency of adverse events attributable to a drug that is of concern. Furthermore, not all adverse effects are equal, even when they prompt drug discontinuation: The pulmonary toxicity and proarrhythmia associated with amiodarone are potentially life threatening and are therefore more likely to be absolute deterrents to its use than, say, trivial ocular adverse effects. The nature of these adverse effects and their incidence and relation to dose therefore merit particular scrutiny.

Amiodarone pulmonary toxicity may be diagnosed by symptoms, changes in radiographic appearance, lung function tests, nuclear scans and lung biopsy. Pneumonitis, pulmonary infiltrates, abnormal biopsy results and reductions in total lung and diffusion capacity have all been reported, and death has been noted in up to 20% of cases (10). Some risk factors for the development of pulmonary adverse effects have been identified: Mean daily dose and duration of therapy are consistently positively associated with toxicity, and plasma levels of desethylamiodarone (11), but not amiodarone (12), have been correlated with toxicity. Other risk factors may be age and pretreatment reduction in lung diffusion capacity (11). However, long-term exposure to, and consequent accumulation of, amiodarone is not a prerequisite for serious pulmonary toxicity: Pneumonitis and infiltrates have been reported after 6 days of commencing therapy (11). Low dose amiodarone compared with placebo was associated with a frequency of 5.2% versus 4.0% in EMIAT (but only 0.8% vs. 0.4% prompting drug withdrawal) and 3.8% versus 1.2% in CAMIAT. These figures are comparable to the odds ratio of 2.0 reported in the meta-analysis.

Proarrhythmia attributable to an antiarrhythmic drug is notoriously hard to define. Bradycardia was reported separately in each of the trials included in the meta-analysis and in both CAMIAT and EMIAT, and "proarrhythmia" is generally used to imply ventricular tachyarrhythmia that is not thought to be due to antiarrhythmic inefficacy. Amiodarone markedly prolongs ventricular refractory periods and consequently has the potential of all class III antiarrhythmic drugs to promote the occurrence of torsade des pointes. The new appearance of this arrhythmia in a patient treated with amiodarone is therefore the clearest example of its potential for proarrhythmia. However, it has long been recognized that there is a remarkably low (<1%) incidence of torsade des pointes in patients taking amiodarone (13) compared with those taking other class III agents (14). The reasons for this probably relate to the wide range of electrophysiologic effects of amiodarone. No patient taking amiodarone was known to experience torsade des pointes in any of the four trials included in the meta-analysis reported in the Journal or in EMIAT. CAMIAT reported a 0.3% incidence of ventricular proarrhythmia with amiodarone, but the incidence was 3% in the placebo group, reflecting the inherent difficulty in distinguishing ventricular proarrhythmia from drug inefficacy in patients treated for ventricular arrhythmia. Given this apparently low incidence of ventricular proarrhythmia, there are no data to support the reasonable assumption that this adverse effect is dose related. In 1983, Rosenbaum et al. (15) published an account of a 10-year experience with amiodarone used in >2,000 patients, often at a maintenance dose of >400 mg/day: Torsade des pointes was not observed; the estimated incidence of pulmonary alveolitis was only 1%; and amiodarone was discontinued because of adverse effects in <3%. Their findings suggest that the use of a low dose regime for amiodarone does not have a major influence on the incidence of serious adverse effects, which is consistent with an early extensive review of amiodarone toxicity (16).

The potential for long-term therapy with low dose amiodarone to be fatal can be crudely estimated. Assuming a cumulative frequency of 2% over 2 years of pulmonary adverse events and 0.1% of ventricular proarrhythmia, and that 10% of each type of toxicity is fatal, an estimate of ~0.1%/year can be made. This estimate clearly ignores the potential for bradycardia and hepatic toxicity to be fatal, but the incidence of death due to these adverse events should be extremely low if adequate precautions and monitoring are used. We believe that 0.1%/year is a reasonable upper estimate of the potential lethal toxicity of long-term low dose amiodarone. Whether this risk is acceptable to patients and physicians depends on the perceived benefit attributable to therapy with amiodarone and the available alternative treatments: It may be very acceptable to patients at high risk of arrhythmic death if they are advised

that amiodarone will substantially reduce this risk, but it may be quite unacceptable to those with more benign arrhythmias, such as supraventricular tachycardia occurring in a heart free of structural disease or ischemia.

Patients and their physicians may not share the same opinion of the importance of various adverse effects: A small risk of irreversible organ damage may be acceptable to a patient who finds advice to avoid unprotected sunbathing intolerable. Indeed, this example illustrates a limitation in viewing the adverse effects reported in these trials as the only major disincentives to the use of low dose amiodarone. The low incidence of photosensitive rash in the trials probably indicates that, despite their blinded design, some patients were given and followed advice to reduce exposure of their skin to sunlight: In an early review (17) of 140 patients treated with a mean maintenance dose of 360 mg, 57% responded positively to a question whether they had noticed a change in sensitivity to sunlight. Furthermore, it is difficult to quantify the hardship associated with amiodarone therapy imposed by the requirement for frequent monitoring and occasional further investigation of abnormal test results.

What else do this meta-analysis and a study of the adverse effects reported in CAMIAT and EMIAT *not* tell us? Although adverse effects prompting drug discontinuation are examined, there is no account of the outcome of these effects after discontinuation. However, earlier reviews of published reports (16) and reports of long-term experience (18) indicate that most adverse effects are reversible. The present meta-analysis and CAMIAT and EMIAT relate only to patients with ischemic heart disease or significant ventricular dysfunction. Adverse effects may be different in nature and frequency in other populations. Patients with "lone" paroxysmal tachycardia of supraventricular origin may be expected to experience a lower incidence of ventricular proarrhythmia and pulmonary adverse effects, but other adverse effects might be more common: Some patients with paroxysmal atrial fibrillation have subclinical sinus node disease, and sinus bradycardia may be a particular problem. Finally, the longest median follow-up period in these studies is 45 months, and adverse effects related to drug accumulation or other mechanisms may only develop after this period.

It may be concluded that the present meta-analysis and the adverse effects reported in CAMIAT and EMIAT confirm the impression left by earlier reports: Amiodarone can be used with a very low annual risk of difficult to treat or irreversible serious adverse effects. Nevertheless, the potential of low dose amiodarone taken for many years to be associated with late adverse effects remains uncertain, and trials that have been recently reported (18) or have stopped recruiting (2,19) and future trials comparing the efficacy of low dose amiodarone with other treatment strategies will define its proper place in the prophylaxis of supraventricular and ventricular arrhythmias.

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