Editors

Hypertrophic cardiomyopathy: is there a role for amiodarone?

The usual mechanism of sudden death in various forms of heart disease is thought to be ventricular arrhythmia. However, antiarrhythmic drugs have not been shown conclusively to prevent sudden death, except in the case of β blockers, which improve survival in patients with heart failure and after myocardial infarction (MI), although this may or may not relate to their antiarrhythmic properties. Indeed, class I antiarrhythmic agents and sotalol have been reported to increase mortality because of their proarrhythmic properties. Amiodarone is attractive because it is a potent antiarrhythmic that does not have significant negative inotropic properties, and has fewer proarrhythmic properties than class I agents. Studies in patients with heart failure have demonstrated conflicting results indicating that there may be a survival benefit with amiodarone in non-ischaemic but not ischaemic heart failure. In post-MI patients, reductions in arrhythmic death, but not total mortality, have been reported in the CAMIAT and EMIAT studies.

Potential role for amiodarone in hypertrophic cardiomyopathy

Although the major incidence of sudden death occurs in older people, sudden death does occur in adolescents and young adults. Hypertrophic cardiomyopathy is a common cause of sudden death in these younger patients and prevention of this complication is a major challenge. Risk factors for sudden death in patients with hypertrophic cardiomyopathy include family history of sudden death (especially if in more than one family member), recurrent syncope, abnormal exercise blood pressure response (hypotension or failure of blood pressure to rise), and episodes of non-sustained ventricular tachycardia on Holter monitoring. The last association, reported independently by two groups in the early 1980s, led to the hypothesis that amiodarone might reduce sudden death in high risk individuals with hypertrophic cardiomyopathy. In 1985 McKenna et al reported their experience with amiodarone treatment of high risk patients with hypertrophic cardiomyopathy. This was a non-randomised but well controlled study in which a later high risk cohort (defined as non-sustained ventricular tachycardia on ambulatory ECG monitoring) treated with amiodarone was compared with an earlier high risk cohort receiving a class I agent, usually disopyramide with or without a β blocker. The earlier cohort had a 7% annual mortality, but there were no deaths in the amiodarone treated group over a mean follow up period of 2.6 years.

The study has several limitations. First, it was not randomised or placebo controlled but a comparison of consecutive, well matched patient groups. Second, the earlier cohort had received agents that we now believe may have increased the risk of sudden death. Third, the study was small, and absolute event rates were low. Nevertheless, it offered some evidence that amiodarone might reduce the incidence of sudden death in high risk patients with hypertrophic cardiomyopathy. On the basis of this study, amiodarone was used by a number of groups for the prevention of sudden death in patients with hypertrophic cardiomyopathy and non-sustained ventricular tachycardia on ambulatory ECG monitoring.

Difficulties in identifying high risk individuals

In addition to the of lack randomised trial data, several other factors have limited the widespread use of amiodarone in patients with hypertrophic cardiomyopathy, particularly given its relatively toxic side effect profile. First, the definition of high risk patients based on non-sustained ventricular tachycardia has a positive predictive accuracy of approximately 20%—that is, many patients will be treated unnecessarily using this criterion. Third, concerns have developed regarding the extrapolation of results from highly specialised tertiary referral centres to all patients with hypertrophic cardiomyopathy.

In Maron et al and McKenna et al's original series the annual mortality rates for patients with non-sustained ventricular tachycardia (not treated with amiodarone) were 8% and 7%, respectively. More recent data from non-tertiary referral centres suggest a lower risk of sudden death. Spirito et al found a sudden death rate of 1.4% per year in patients with non-sustained ventricular tachycardia compared with 0.9% in those without this arrhythmia. In most of these patients the episodes of non-sustained ventricular tachycardia were relatively brief and infrequent, and it has been argued that this may explain the lower event rate; however, this question remains unanswered.

Is amiodarone proarrhythmic?

There have been reports of sudden death in patients with hypertrophic cardiomyopathy despite amiodarone treatment. Fananapazir et al suggested that amiodarone may even increase the risk of sudden death as a result of its proarrhythmic effects. Using an aggressive programmed electrical stimulation protocol, induction of ventricular tachycardia was “easier” or occurred only with amiodarone in 18 of 35 patients studied. In another study from the same group, amiodarone was given to 50 patients for symptoms refractory to conventional treatment (21 of whom had ventricular tachycardia on Holter monitoring). Seven sudden deaths occurred during a mean follow up of 2.2 years, six within five months of initiation of treatment. The dosage of amiodarone used by Fanapazir's group was high (1600 mg/day loading and 400 mg/day

Glossary

CAMIAT: Canadian Amiodarone Myocardial Infarction Arrhythmia Trial
EMIAT: European Myocardial Infarct Amiodarone Trial
GESICA: Grupo de Estudio de la Sobrevida en la Insuficienca Cardiaca en Argentina

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maintenance), and mean amiodarone blood concentrations were > 2 ng/ml — much higher than recommended by McKenna's group. In general, side effects of amiodarone appear to be dose related26 and the results of these two studies may represent proarrhythmia related to high dosage. The GESICA, CAMIAT, and EMIAT studies used lower doses of amiodarone and there was no evidence of major proarrhythmic effects.10,11

In this issue, Cecchi et al report their experience in an unselected, non-tertiary population of 167 consecutive patients with hypertrophic cardiomyopathy.30 Ninety patients did not have non-sustained ventricular tachycardia on Holter monitoring, 38 had isolated, infrequent non-sustained ventricular tachycardia, and 39 had multiple-replicative non-sustained ventricular tachycardia (similar to the prevalence noted by Maron's and McKenna's groups). Cecchi et al made the assumption in their management protocol that infrequent non-sustained ventricular tachycardia was relatively benign, but multiple-replicative non-sustained ventricular tachycardia was malignant, and treated only patients with the latter with low dose (mean 220 mg/day) amiodarone. As with McKenna et al's study, this was not randomised or placebo controlled. No significant differences in overall survival were seen between the three groups during follow up (mean 10 years). Only one sudden death occurred (in the isolated, infrequent non-sustained ventricular tachycardia group). Eight deaths occurred due to heart failure (four in the group without non-sustained ventricular tachycardia, and four in the multiple-replicative non-sustained ventricular tachycardia group). This study does not permit the definite conclusion that amiodarone prevents sudden death, but it is consistent with McKenna et al's overall beneficial experience and (at the dosage used) is at odds with Fanapazir et al's report of serious proarrhythmic effects. Furthermore, it confirms that in this non-tertiary referral population, the risk of sudden death in patients with isolated infrequent non-sustained ventricular tachycardia is low, and these patients may not need treatment with an agent that has a potentially toxic side effect profile.

Is there a consensus?

Thus, major problems remain in therapeutic decision making in hypertrophic cardiomyopathy. We are able to identify accurately individuals at low risk of sudden death (absence of family history of sudden death, of history of recurrent syncope, absence of frequent non-sustained ventricular tachycardia, and importantly in adolescents and young adults, normal exercise blood pressure response). For the individual who has already suffered an episode of out of hospital cardiac arrest, the decision to implant an automatic cardioverter-defibrillator is usually fairly clear. Does the current evidence justify the routine use of amiodarone with its attendant side effect profile to "high risk" patients, many of whom are young? The answer will only be resolved definitively with an appropriately designed, randomised trial of amiodarone vs defibrillator, which is long overdue. This would overcome many of the ethical issues and provide data as to the efficacy of each of these strategies. In the interim, very recent experience of McKenna's group provides further evidence of the beneficial effects of amiodarone in high risk groups.31 They stratified 474 consecutive patients according to presence of ≤ 1 risk factor (low risk, n = 284) or ≥ 2 risk factors (high risk, n = 190). Mean follow up was 1121 days, and 81 patients received amiodarone. In the group not receiving amiodarone the annual rate of sudden death was 2.5% in the high risk and 1.3% in the low risk group; there were no deaths in the treated group. Therefore, although unequivocal evidence in support of amiodarone is lacking, the weight of evidence strongly favours the use of amiodarone in high risk groups.

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