Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis
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CRD summary
This well reported review compared amiodarone with placebo or class Ic drugs for the cardioversion of recent-onset atrial fibrillation (AF). Even though the onset of conversion was delayed, the efficacy of amiodarone was similar at 24 hours compared with class Ic drugs. The conclusions reached by the authors seem valid and the limited generalisability of the findings was acknowledged.

Authors' objectives
To conduct a meta-analysis comparing amiodarone with placebo or class Ic drugs for the cardioversion of recent-onset atrial fibrillation (AF).

Searching
MEDLINE and EMBASE (both from 1967 to October 18, 2001) and the Cochrane Controlled Trials Register were searched for publications in any language. In addition, references from identified trials and from related review articles or editorials were examined for additional studies. Abstracts from the annual scientific meetings of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology were checked from 1990 to 2001. The manufacturers of the included drugs were also contacted.

Study selection
Study designs of evaluations included in the review
Prospective, randomised controlled trials (RCTs) were eligible for inclusion. Both blinded and open-label trials were included. The follow-up ranged from 8 to 48 hours.

Specific interventions included in the review
Comparisons of amiodarone versus placebo, or a class Ic drug administered for cardioversion of recent-onset (less than or equal to 1 week) AF, were included. Trials in the setting of atrial flutter or post-operative AF were excluded, as were those with active control groups. However, trials that used drugs such as digoxin for rate control only in both groups were included. The doses and routes of administration of both amiodarone and the comparative class Ic drug varied. However, most trials reported intravenous administration of a loading dose followed by continuous infusion; oral doses were most often single. Full details of the doses were given in the full paper.

Participants included in the review
The participants had recent-onset (less than or equal to 1 week) AF. The exclusion criteria were similar across all the studies and generally concerned severe heart failure, recent myocardial infarction, unstable angina, use of other anti-arrhythmic drugs, severe conduction disturbances, thyroid dysfunction, hyperkalemia, and severe renal or hepatic insufficiency. The mean age of the patients ranged from 57 to 66. The proportion of males in each trial (where given) ranged from 22 to 73%.

Concomitant medication in some trials included beta-blockers, calcium-channel antagonists and digoxin.

Outcomes assessed in the review
The primary end point was the rate of cardioversion of AF to sinus rhythm within the first 24 hours. The secondary end points were the rates of cardioversion at 1 to 2 hours, 3 to 5 hours, and 6 to 8 hours, mortality, proarrhythmia, and other adverse events such as bradycardia, hypotension, and heart failure.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the
Assessment of study quality
The authors do not report a method for assessing validity, apart from rejecting studies with no control group, those that were not randomised and one that randomised patients according to their date of birth.

Data extraction
All of the data were extracted by one author and checked by at least one other independent author. The authors resolved any disagreements by discussion. The following information was abstracted: patient characteristics, details of administration, treatment crossover, efficacy in converting to sinus rhythm, adverse drug reaction, level of blinding within the trial, and length of follow-up. The relative risks (RRs) and 95% confidence intervals (CIs) were calculated for each included study; the analysis was conducted on an intention-to-treat basis.

Methods of synthesis
How were the studies combined?
The pooled RR and 95% CIs were calculated using either fixed-effect or random-effects (DerSimonian and Laird) models, as appropriate. Methods based on odds ratios (Mantel-Haenszel and Peto methods) were also used and gave similar results. Significance was inferred at a p-value of less than 0.05.

How were differences between studies investigated?
The Cochran Q test was used to assess heterogeneity. Sensitivity analyses were also performed.

Results of the review
Ten RCTs studies were included. Three studies were overlapping in that they compared amiodarone with class Ic drugs as well as with placebo. Six studies (595 patients) compared amiodarone with placebo. Three of these were single-blind, two were double-blind, and the status of the sixth was not stated. Seven studies (807 patients) compared amiodarone with a class Ic drug. With the exception of two studies (one double-blind, the other not stated), all of these were single-blind. Of the 807 patients, 579 were analysed; the 228 patients excluded were from two studies that compared several protocols for the administration of Ic drugs. It was unclear, however, exactly which patients were excluded.

For return of sinus rhythm, amiodarone showed greater efficiency compared with placebo at 6 to 8 hours (RR 1.23, 95% CI: 1.03, 1.47, p=0.022), and at 24 hours (RR 1.44, 95% CI: 1.24, 1.66, p<0.001). The drug showed no efficacy at 1 to 2 hours (RR 1.23, 95% CI: 0.77, 1.96, p=0.39). The authors stated that the incidence of spontaneous return of sinus rhythm at 24 hours should be emphasised as it varied between 35 and 64%. Different random-effects models (unspecified) were tested because heterogeneity was detected in the results at 24 hours (Cochran Q test, p=0.068); these models all gave the same results.

Class Ic drugs were more effective than amiodarone at 1 to 2 hours (RR 0.35, 95% CI: 0.24, 0.50, p<0.001), at 3 to 5 hours (RR 0.44, 95% CI: 0.31, 0.61, p<0.001), and at 6 to 8 hours (RR 0.57, 95% CI: 0.57, 0.80, p<0.001). However, both drugs were equally effective at 24 hours. Random-effects methods were used because of heterogeneity in the results at 1 to 2 hours; these gave similar results. A sensitivity analysis for amiodarone versus placebo showed that excluding the study that caused heterogeneity had little effect, except at 6 to 8 hours when the difference between the two groups no longer reached significance (RR 1.14, 95% CI: 0.99, 1.41, p=0.073). For class Ic drugs compared with amiodarone, the results were homogeneous. The exclusion of studies using oral administration of amiodarone had little effect on the results.

A statistical analysis of the side-effects was not possible due to the small numbers. There were no deaths in any trials. Nonsustained ventricular tachycardia was reported in two patients in the amiodarone group and in one patient given propafenone. One episode of sustained ventricular tachycardia was reported in a patient receiving placebo. Four episodes of 1:1 atrial flutter were reported: three in patients receiving flecainide and one in a patient on placebo. Other side-effects, such as hypotension, bradycardia and heart failure were inconsistently defined and reported, and were...
impossible to analyse accurately. However, the authors stated that most of these adverse events were without consequence.

Authors' conclusions
Amiodarone facilitates conversion of recent-onset AF to sinus rhythm (with a 44% superiority compared with placebo), but with a delay of 8 to 24 hours until the onset of anti-arrhythmic activity. This efficacy is comparable to that of class Ic agents at 24 hours after drug administration, although Ic drugs showed a more rapid onset of action, with some effect already apparent one to 2 hours after administration. However, amiodarone should be used with caution in patients with severe underlying myocardial dysfunction or ischaemic heart disease, as profound hypotension may be induced by intravenous or high-dose oral loading.

CRD commentary
In general, this was a clearly written and useful summary. The search strategy seemed reasonable and it appears that trials published in languages other than English were included. However, the limited search period for abstracts may have resulted in the omission of some trials. While all the participant numbers were given, it was unclear which 228 participants were excluded from the analysis comparing class Ic drugs with amiodarone. For the results of the statistical analysis, despite CIs being given, the authors stated that significance was inferred at a p-value of less than 0.05. However, since heterogeneity was detected when Cochran's Q test gave a result of 0.068, it is assumed that a more conservative level (p<0.1) was used for testing heterogeneity. Also, although the authors stated that amiodarone and class Ic drugs were equally effective at 24 hours, this was not a study of equivalence. The conclusion should thus be that there was no difference between the two drugs at 24 hours.

It is reassuring to note that, as a result of acknowledging limitations of the meta-analyses, the authors performed sensitivity analyses. In addition, limitations of generalisation, in terms of patient population, have been acknowledged. In view of these comments and the caution advised in treating certain groups of patients, the conclusions reached by the authors seem valid, despite some lack of clarity in patient numbers.

Implications of the review for practice and research
Practice: The authors state that, in clinical practice, amiodarone is a reasonable alternative to class Ic drugs and may be the drug of choice in the setting of ventricular dysfunction and ischaemic heart disease if rapid cardioversion is not required. However, amiodarone should be used with caution in patients with severe underlying myocardial dysfunction or ischaemic heart disease, as profound hypotension may be induced by intravenous or high-dose oral loading.

Research: The authors state that since most of the data are on intravenous amiodarone, more studies using oral administration are needed. The issues of optimal dosage and of out-patient treatment initiation should also be assessed.

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