Conversion of recent-onset atrial fibrillation with intravenous amiodarone: a meta-analysis of randomized controlled trials

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Authors' objectives
To evaluate the efficacy and safety of intravenous amiodarone for conversion of recent-onset atrial fibrillation (AF).

Searching
MEDLINE was searched from January 1975 to March 2001 for studies published in the English language. The search terms were 'atrial fibrillation', 'amiodarone' and 'cardioversion'. Pertinent review articles and the reference lists in the identified studies were examined for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible.

Specific interventions included in the review
Comparisons of intravenous amiodarone with either placebo or other anti-arrhythmic agents were eligible. The only other acceptable anti-arrhythmic agent administered simultaneously with the study drugs was digoxin. Amiodarone was administered as a bolus, a bolus followed by an infusion over the following approximately 24 hours, and an infusion without a preceding bolus. The bolus doses ranged from 2.5 to 7 mg/kg and were administered over times varying from 30 seconds to 30 minutes. The infusion doses ranged from 10 to 20 mg/kg, from 25 to 125 mg/hour, and from 900 to 1,800 mg over the 24-hour period. The active controls were intravenous propafenone, intravenous digoxin, oral quinidine, intravenous flecainide, intravenous procainamide and intravenous verapamil.

Participants included in the review
Patients with recent-onset (less than 7 days) AF were eligible.

AF occurred either spontaneously (most studies) or after cardiac surgery.

Outcomes assessed in the review
Studies that reported the number and percentages of conversions to sinus rhythm, and the number and type of adverse reactions after treatment began, were eligible. The outcomes were determined from 2 to 48 hours after treatment began.

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 selection.

Assessment of study quality
Only RCTs were eligible.

The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following information were tabulated: dosage of intravenous amiodarone; comparative treatment; type of AF;
timing of efficacy and safety outcomes; and conversion rates. The rate differences for conversion to sinus rhythm and adverse events were estimated for each study.

**Methods of synthesis**

**How were the studies combined?**

The pooled rates of cardioversion and adverse reactions were estimated (see Other Publications of Related Interest). The weighted pooled percentage of patients who were cardioverted and the pooled percentage developing adverse reactions were calculated separately for intravenous amiodarone, for active controls, and for placebo. A weighted average rate difference was estimated for the rates of cardioversion and adverse events for amiodarone versus active control, and for amiodarone versus placebo. The results were weighted using the inverse of the variance for each study.

**How were differences between studies investigated?**

The studies were grouped according to the comparison (other anti-arrhythmic agent or placebo). Within the amiodarone and other anti-arrhythmic comparisons, studies that used drugs considered to be of questionable effectiveness in cardioversion (oral amiodarone, intravenous digoxin and intravenous verapamil) were pooled separately.

**Results of the review**

Eighteen RCTs were included; 550 patients received amiodarone, 451 patients received another anti-arrhythmic agent, and 202 patients received placebo.

Overall, 76% of patients receiving amiodarone were cardioverted, compared with 72% of those receiving active anti-arrhythmic therapy and 60% receiving placebo.

**Amiodarone versus other anti-arrhythmic agents (16 RCTs).**

There was no statistically-significant difference in the pooled estimates for conversion rates from 16 cohorts comparing amiodarone and active anti-arrhythmic agents. The pooled estimates were 72.1 and 71.9%, respectively (p=0.84). The cardioversion rate differences between amiodarone and other anti-arrhythmic agents ranged from -56.25 to 74.83. The pooled average rate difference was 0.31 (95% confidence interval: -11.13, 13.91, p=0.84).

**Amiodarone versus drugs of questionable effectiveness (6 RCTs).**

The unadjusted average cardioversion rates were 78% for amiodarone and 59% for the other drugs. Amiodarone was statistically significantly more effective than the other drugs; the pooled rates were 78.3 and 58.7%, respectively (p=0.03).

**Amiodarone versus placebo (5 RCTs).**

Amiodarone was associated with a significantly higher rate of cardioversion than placebo in cohorts comparing the two interventions. The pooled rates were 82.4 and 59.7% for amiodarone and placebo, respectively (p=0.03).

The cardioversion rate differences between amiodarone and placebo ranged from -9.43 to 50.11.

**Adverse events.**

The most commonly reported adverse events with intravenous amiodarone were infusion phlebitis (8%), bradycardia (4%) and hypotension (2%).

Overall, adverse events were reported in 17% of the patients receiving amiodarone, in 14% of those receiving other anti-arrhythmic drugs, and in 11% receiving placebo.

There was no statistically-significant difference in the pooled adverse event rates between amiodarone and other active anti-arrhythmic agents in the cohort comparison studies. The pooled rates were 12.2 and 14.0%, respectively (p=0.64).
Amiodarone was associated with significantly higher rates of adverse event than placebo in the cohort comparison studies; the pooled rates were 26.8 and 10.8%, respectively (p=0.02).

Cost information
Intravenous amiodarone would cost $609 on the basis of a 150 mg loading infusion and a 900 mg infusion over 24 hours. Ibutilide (an FDA approved therapy for cardioversion of AF) costs $464.

Authors’ conclusions
The efficacy and safety profile of intravenous amiodarone is similar to that of other anti-arrhythmics for cardioversions of recent-onset AF. Intravenous amiodarone was significantly more effective than placebo but it was associated with a significantly higher frequency of adverse events, although most were not considered to be dose limiting.

CRD commentary
The study aims were stated, and the inclusion criteria were defined in terms of the study design, intervention, participants and outcomes. Eligible studies were restricted to those listed in one database and published in the English language; this may have resulted in the omission of relevant publications. The lack of an attempt to locate unpublished material raises the possibility of publication bias. No details were given of the methods used to select the studies for inclusion in the review. Eligible studies were restricted to RCTs but no formal validity assessment was undertaken.

The methods used to extract the data were not described and the data tabulated were limited. The rate differences in cardioversion and adverse reactions were tabulated, but the results discussed in the text of the review were predominantly the weighted averages from cohorts within comparisons (amiodarone versus other anti-arrhythmics and amiodarone versus placebo); this ignores the within-RCT comparison. Neither clinical nor statistical heterogeneity were considered. The authors’ conclusions should be interpreted with caution in view of the highlighted limitations of the review.

Implications of the review for practice and research
Practice: The authors state that intravenous amiodarone would be a reasonable alternative to other anti-arrhythmic agents for AF, especially for those patients at high risk of cardiotoxicity.

Research: The authors state that a large, adequately powered randomised comparison of intravenous amiodarone with another effective agent, such as ibutilide, should be designed and conducted. They also state that research is required to ascertain the optimal dosage of intravenous amiodarone for cardioversion.

Bibliographic details

PubMedID
11794432

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Amiodarone /adverse effects /therapeutic use; Anti-Arrhythmia Agents /adverse effects /therapeutic use; Atrial Fibrillation /drug therapy; Bradycardia /chemically induced; Cohort Studies; Humans; Hypotension /chemically induced; Injections, Intravenous; Phlebitis /chemically induced; Randomized Controlled Trials as Topic

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.