Meta-analysis of flecainide safety in patients with supraventricular arrhythmias

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Authors' objectives
To assess the safety of the class Ic anti-arrhythmic flecainide in patients with supraventricular arrhythmias and largely normal left ventricle.

Searching
MEDLINE, BIOSIS Previews, EMBASE and the Cochrane Library were searched from their inception until 30th November 2000, using the terms 'flecainide' and 'human clinical trial'. The reference list of a published meta-analysis was checked and the manufacturer of flecainide was questioned about any unpublished studies. Only papers written in English, German, French or Italian were included; those in other languages (Japanese and Chinese) were excluded.

Study selection
Study designs of evaluations included in the review
Prospective clinical studies were sought. This included controlled and uncontrolled studies.

Specific interventions included in the review
Studies where flecainide was used to treat supraventricular arrhythmias were sought. In the included studies, flecainide was administered either orally (mean dose 216 mg/day; standard deviation, SD=65) or intravenously (i.v.) (mean dose 1.93 mg/kg body weight, SD=0.21; maximum dose per treatment 156 mg). The mean exposure time was 241 days (SD=224) in the oral studies and 4 hours in the i.v. studies. The total documented flecainide exposure time was 2,015 patient years, to which the short-term i.v. studies contributed only 0.5 patient years. The comparators, where used, were placebo or other anti-arrhythmics (propafenone, sotalol, amiodarone, cibenzoline or digoxin).

Participants included in the review
Studies including participants with supraventricular arrhythmias and largely normal left ventricle, or absent structural heart disease, were sought. In the included studies, those receiving flecainide had a mean age of 55 years (SD=13) and 60% were male; in the control groups, the mean age was 54 years (SD=12) and 58% were male. Participants with structural heart disease were excluded, although three studies involving participants with 'heart disease' (mainly coronary heart disease) were included. Studies on children only were excluded.

Outcomes assessed in the review
The primary end point was mortality. The secondary end points were adverse events and drop-out rates. The adverse events in the included studies were grouped according to whether cardiac or noncardiac. The cardiac adverse events were angina, palpitations, hypotension, syncope, heart failure/dyspnoea, sinus node dysfunction, bundle branch block and AV-block. The noncardiac adverse events were gastrointestinal disturbances (diarrhoea, nausea) and central nervous system effects (headache, dizziness, vertigo and visual disturbances). Studies that apparently met the inclusion criteria, but lacked data on side-effects, were excluded.

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The author did not state that they assessed validity.

Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The categories of data extracted included details of the treatment and comparators, the number of
participants (intention-to-treat basis or per protocol), the participants’ characteristics, and adverse effects.

**Methods of synthesis**

How were the studies combined?
The statistical analysis was performed using descriptive methods (mean values weighted by patient numbers plus or minus the SD), and the chi-squared test and Fisher's exact test to compare the flecainide data with the control group (or historical data). A 95% confidence interval (CI) was calculated for the primary end point. A P-value of less than 0.05 was considered statistically significant.

How were differences between studies investigated?
The author did not state a method for assessing any differences between the studies.

**Results of the review**
The included studies comprised 26 double-blind randomised controlled trials (RCTs; 15 were placebo-controlled), 25 RCTs without blinding, and 71 uncontrolled studies. The analyses included 122 studies for the mortality outcomes (4,811 treated with flecainide and 1,986 controls) and 103 for the secondary outcomes (4,375 treated with flecainide and 1,818 controls). Those studies reported in abstract only were excluded from the secondary analyses, but were assumed to have reported any deaths that had occurred.

Eight deaths were reported in the flecainide-treated group (4,811 participants) versus one in the control group (1,986 participants). Total mortality in the flecainide group was 0.166% and the mortality rate per 100 patients years was 0.397 (95% CI: 0.172, 0.781). In relation to exposure time, the difference in deaths between the two groups was not statistically significant (P=0.46).

Proarrhythmic episodes were significantly rarer in the flecainide group (2.7%) than in the controls (4.8%), (P=0.001). Details of other cardiac symptoms and events were given in paper.

Noncardiac side-effects were observed in 16.7% of the flecainide- treated participants and 11.1% of the controls (P=0.06). Among the more frequent effects were dizziness, visual disturbances, other central nervous system effects and gastrointestinal disturbances. Visual and central nervous system disturbances were significantly more frequent in the flecainide-treated groups, while gastrointestinal symptoms were more frequent in the controls.

In total, there were 1,391 (31.8%) adverse events in the flecainide group and 522 (28.7%) in the control group, (P<0.05). Drop-outs related to side-effects numbered 194 (4.4%) in the flecainide group and 100 (5.5%) in the control group (P=0.07).

**Authors’ conclusions**
The use of flecainide to treat supraventricular arrhythmia was safe in patients without structural left ventricular damage. Intense diagnostic efforts should be made to exclude patients with structural left ventricular damage, especially ischaemic heart disease.

**CRD commentary**
This was a well-written paper with clear aims. The literature search was extensive, although the author acknowledged that unpublished studies may have been missed. The author stated that the review was presented in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement, but the methods used in the review (study selection, quality assessment, data extraction, etc.) were not described. There was little information about the included studies, e.g. which studies were RCTs and what proportion of participants were from these types of studies. The author chose to include any prospective study, including RCTs and cohort studies, but in doing data from different types of studies were combined. However, side-effects are relatively rare events and by doing this the author has attempted to assess all available evidence. The author also acknowledged that it is possible that the side-effects were under-reported, as most of the included studies did not focus on safety; it was assumed, however, that deaths would be detailed. The conclusions
would seem to follow from the results.

Implications of the review for practice and research
Practice: The author stated that flecainide is advisable for patients with supraventricular arrhythmias, with the proviso that left ventricular damage is absent.

Research: The author stated that a large safety trial would be desirable, but commented that the cost may make this prohibitive.

Funding
3M Medica, Borken, Germany.

Bibliographic details

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Anti-Arrhythmia Agents /adverse effects /therapeutic use; Arrhythmia /chemically induced; Cardiomegaly /mortality /physiopathology; Flecainide /adverse effects /therapeutic use; Heart Ventricles /physiopathology; Middle Aged; Randomized Controlled Trials as Topic; Tachycardia, Supraventricular /drug therapy /mortality /physiopathology

AccessionNumber
12002004039

Date bibliographic record published
29/02/2004

Date abstract record published
29/02/2004

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.