

Interaction of ischaemia and encainide/flecainide treatment: a proposed mechanism for the increased mortality in CAST I

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Abstract

Objective—To determine whether an interaction between encainide or flecainide and intercurrent ischaemia could account for the observed increase in cardiac and sudden deaths in the study group in the Cardiac Arrhythmia Suppression Trial (CAST) I.

Design—CAST I was a randomised, double blind, placebo controlled study in which patients received the drug which suppressed at least 6 premature ventricular contractions per minute by 80% or episodes of non-sustained ventricular tachycardia by 90%. Arrhythmic sudden death or aborted sudden death were the study end points. Measured secondary end points included recurrent myocardial infarction, new or increasing angina pectoris, congestive heart failure, and syncope. The CAST I database was analysed to determine which of three end points occurred first—cardiac death or cardiac arrest, angina pectoris, or non-fatal recurrent infarction. They were regarded as mutually exclusive end points. The triad of cardiac or sudden arrhythmic death plus congestive heart failure and syncope was similarly analysed.

Results—It was assumed that recurrent non-fatal infarction and new or increasing angina pectoris were ischaemic in origin. The sum of these non-fatal ischaemic end points and sudden death were nearly identical in the placebo group (N = 129) and the treatment group (N = 131). The one year event rate in each group was 21%. However, the treatment group had a much greater fatality rate (55 v 17; $P < 0.0001$) than the placebo group. The same relation was found when the data were examined on the basis of drug exposure rather than intention to treat. The temporal and circadian events were similar in each group and were consistent with an ischaemic pattern. No such patterns emerged from analysis of the presumed non-ischaemic end points of congestive heart failure and syncope.

Conclusions—These data suggest that the interaction between active ischaemia and treatment with encainide or flecainide may have been responsible for the increased mortality seen in the treatment group in CAST I. This conversion of a non-fatal to a fatal event emphasises the need for future antiarrhythmic drugs to be screened in ischaemic models.

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Keywords: antiarrhythmic drugs, ischaemia, CAST I, encainide/flecainide

Although ventricular tachycardia/ventricular fibrillation is a dominant mechanism of cardiac death in patients who have had a recent myocardial infarction (< 1 year), and although the density of ventricular ectopy following shortly upon an acute infarction predicts subsequent cardiac mortality, efforts to reduce mortality by suppressing ventricular ectopy have failed.¹⁻³ In the Cardiac Arrhythmia Suppression Trial (CAST I)^{1,2} the active drug groups had a higher cardiac and sudden death mortality than the placebo group.

In an earlier analysis mortality and morbidity in CAST I Echt *et al* presented data suggesting that the increase in mortality for the patients assigned to active drugs was associated with an increase in angina pectoris and non-fatal reinfarction in the placebo group.² Because these end points were not mutually exclusive, no conclusion could be drawn relating these two observations, although Echt *et al* speculated that an interaction might exist. Akiyama *et al*, also in an analysis of CAST I data, showed that the 1 year mortality in patients with a non-Q wave myocardial infarction assigned to the treatment group was markedly increased, with a relative risk of nearly four times that of the placebo group.⁴ Because of the enhanced ischaemic potential in the non-Q wave myocardial infarction, Akiyama *et al* postulated an ischaemia-drug interaction causing an increased mortality in the treatment group. These two observations as well as the earlier suggestions made by the Task Force of the Working Group on Arrhythmias of the European Society of Cardiology,⁵ led us to evaluate the possibility that an interaction between encainide/flecainide treatment and ischaemia accounted for the excess mortality of the treatment group in CAST I.

Patients and methods

The CAST protocol has been described in detail previously.^{1,2} In brief, patients with at least six premature ventricular depolarisations per hour without ventricular tachycardia lasting more than 15 beats at a rate of ≥ 120 per minute were eligible for enrolment after documented myocardial infarction. Based on the results of open label titration which demon-

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strated a predefined, high-level suppression of ventricular ectopy (80% of premature ventricular contractions and 90% of runs of non-sustained ventricular tachycardia) patients were randomly assigned to drug treatment or placebo. Holter electrocardiograms were obtained at 4 months and scheduled for 12 months after the index myocardial infarction.

The primary end point of the trial was arrhythmic death or cardiac arrest with resuscitation, where these were presumed to be due to ventricular arrhythmia. The site principal investigator classified each death and provided a summary of the circumstances surrounding the death. An events committee reviewed each death and differences were resolved by consensus.⁶ There was an initial 86% concurrence between the events committee and the site investigator.

In addition to the primary end point, all cardiac deaths and secondary end points were prospectively defined and tabulated.² The secondary end points included new or worsened angina pectoris; recurrent non-fatal myocardial infarction; syncope, defined as unexpected, transient loss of consciousness not explained by physical trauma; and new or worsened congestive heart failure. Angina pectoris was regarded as new if it was not present at baseline and as worsened if the patient deteriorated by at least one Canadian Cardiovascular Society functional class. Congestive failure was regarded as new if the findings were not present at baseline and worsened if the patient's symptoms worsened by at least one New York Heart Association functional class.

We analysed the CAST I database to determine which of three end points occurred first, either cardiac death or cardiac arrest, or angina pectoris, or non-fatal recurrent infarction. These were regarded as mutually exclusive end points. For this study patients were censored when they reached the first end point. Death which followed quickly upon a reinfarction or change in the angina pattern was regarded as a fatal end point; by definition a patient who did not survive an admission to hospital for angina pectoris or recurrent myocardial infarction was considered to have reached a fatal end point. We performed a similar analysis for non-fatal syncope and congestive heart failure, assuming that these end points were non-ischaemic in origin.

Actuarial curves for this study were calculated by the Kaplan-Meier method.⁷ Analysis groups were initially determined by assignment at randomisation, according to the principle of intention to treat. Kaplan-Meier curves were calculated for the encainide/flecainide treatment group and from the placebo group for the combined end points and separately, for the non-fatal end points and the cardiac death end point. Because the hypothesis of this retrospective study is specifically predicated upon exposure to drug and not treatment class, we reanalysed the data after censoring patients (N = 120) three days after they had stopped taking the study drug. The log rank statistic was used to determine

the significance of differences between the curves.

Results

We created two sets of data. One set used the intention-to-treat data and the other the exposure-to-drug data censored three days after the start of individualised treatment. Figure 1A–C shows the intention to treat data. In each figure the placebo and treatment groups are compared. When cardiac death and non-fatal, ischaemic end points of new/worsening angina or non-fatal reinfarction were mutually exclusive end points, the estimated one year event rate was 21% in both treatment and placebo groups (fig 1A). Mortality was higher in the encainide/flecainide treatment group ($P < 0.001$) whereas non-fatal ischaemic end points were more frequent in the placebo group ($P < 0.006$) (figure 1B & C). The bar graph shows numerical data for the intention to treat groups (fig 2). Increased mortality in the treatment group is balanced by the increased non-fatal ischaemic end points in the placebo group.

When patients were censored three days after individualised treatment started, the results were no different from the intention to treat data. The censored data curves are almost identical to the intention to treat curves (not shown). One reason for the similarity of the two analyses may be that 34 of the 120 patients in whom encainide/flecainide treatment (28%) was stopped were given another primary antiarrhythmic drug. Nineteen of these 34 patients were given open label encainide or flecainide.

We assumed that non-fatal syncope and congestive heart failure were non-ischaemic clinical end points. The estimated survival to these end points combined with the mortality end point showed a higher mortality for the treatment group, reflecting that group's higher mortality. However, unlike the presumed ischaemic end points (when the data were censored for cardiac death), there was no difference between the placebo and drug groups. There was no evidence of an interaction between drug assignment and these non-ischaemic end points. While congestive heart failure can certainly be part of the ischaemic syndromes, the CAST I definition is centered on chronic deterioration of pump function, which is probably caused by a late remodelling phenomenon or non-coronary mechanism. Ischaemia-mediated ventricular arrhythmias severe enough to cause syncope were a central concern in CAST I. However, the CAST I definition of syncope as a transient loss of consciousness excluded as much as possible ongoing ischaemic triggers and sustained ventricular arrhythmias, a study end point in its own right.

Discussion

Earlier analyses of the CAST database showed that the treatment and placebo groups could not be distinguished by numerous baseline

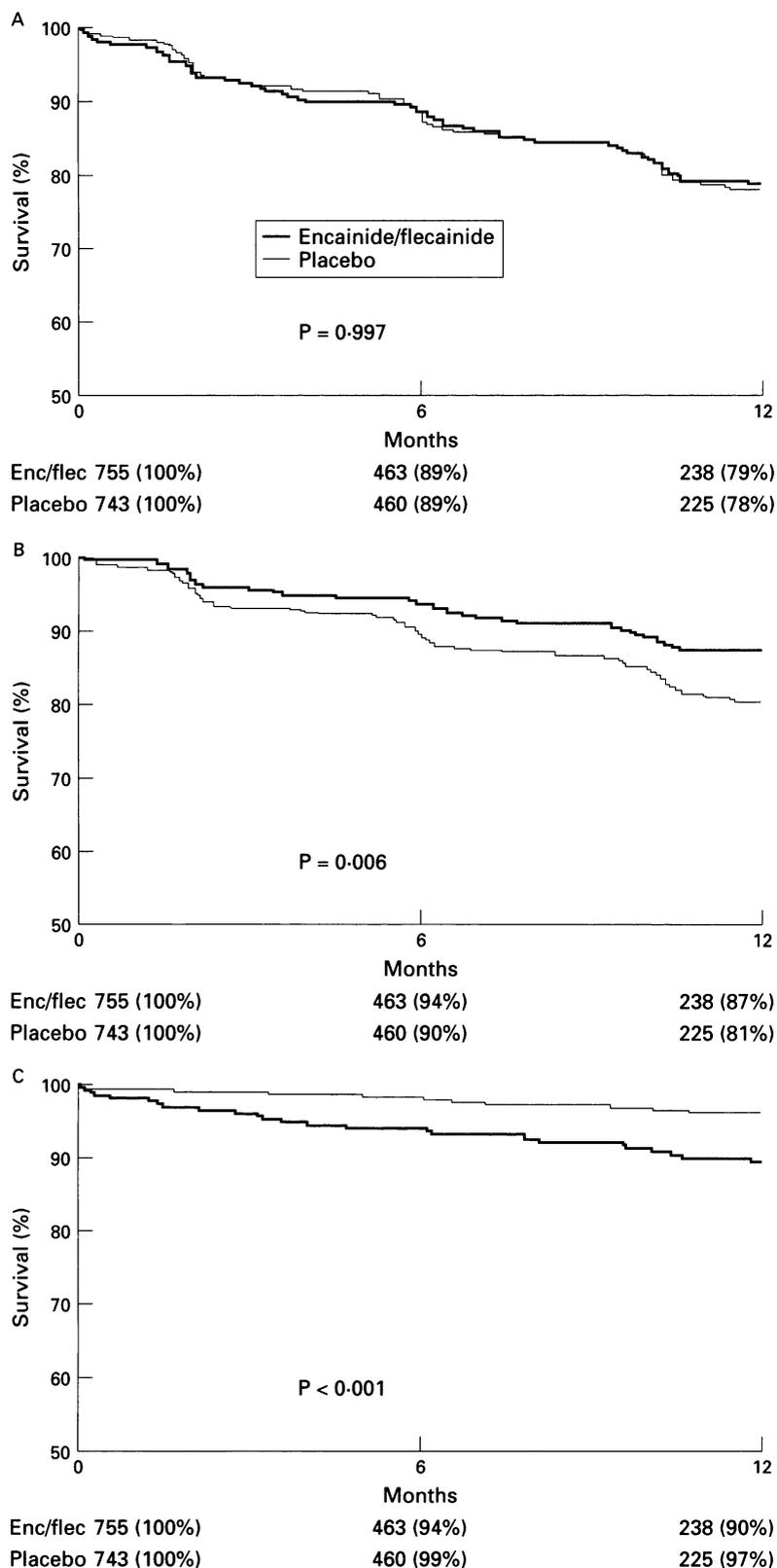


Figure 1 (A) CAST I survival to new/worsened angina or recurrent, non-fatal myocardial infarction or cardiac death/arrest. (B) Survival data to new/worsened angina or recurrent non-fatal myocardial infarction. These data are censored for death/cardiac arrest. (C) Survival data to cardiac death/arrest. These data are censored for new/worsened angina or recurrent, non-fatal myocardial infarction. A–C are censored for non-cardiac death and are based on the intention to treat.

clinical, historical, electrocardiographic, mechanical, and concurrent pharmacological characteristics.^{1–2} Thus differences in the baseline risk profiles of the two groups at entry to the study cannot account for the observed differences in non-fatal ischaemic events.

When we combined the non-fatal ischaemic end points, (reinfarction and unstable angina) with cardiac mortality as mutually exclusive end points there was no significant difference in end point incidence between the encainide/flecainide treatment group and the placebo group (fig 1A). The higher incidence of fatal cardiac events was counterbalanced by a reduction in the incidence of non-fatal ischaemic events (fig 2) in the encainide/flecainide treatment group. This suggested the possibility that the excess mortality in the encainide/flecainide treatment group may reflect a conversion of a non-fatal ischaemic event to a fatal event by the treatment drugs. The observation strengthens the suspicion suggested by the earlier analysis of CAST I deaths² in which we first observed higher non-fatal ischaemic end points in the placebo group and higher mortality end points in the active treatment group. It also extends the observation and enhances the validity of the report by Akiyama *et al* that showed a higher than anticipated mortality in patients with non-Q wave myocardial infarction assigned to active drug.⁴

In an elegant dog model developed by their group,⁸ in which the combination of ischaemia and alterations in the autonomic milieu can be studied, Schwartz *et al* showed that flecainide, though anti-fibrillatory, favoured the occurrence of sustained ventricular tachycardia during acute myocardial ischaemia.⁹ In an earlier animal study with the antiarrhythmic agent, aprindine, Nattel *et al* noted an increase in serious ventricular arrhythmias, including ventricular fibrillation, if the antiarrhythmic agent was present before the onset of ischaemia.¹⁰

Ischaemia has long been known to initiate ventricular arrhythmias, including ventricular fibrillation.^{8,9,11,12} Ischaemia can initiate ventricular rhythm disorders at the onset of flow deprivation, even when this is only transient, or during the different recovery phases from myocardial infarction.^{13,14} Two canine models using conscious animals have been used to show this. In one model the circumflex artery was occluded in an animal 4–7 days after an anterior myocardial infarction with preserved flow was created.¹¹ The prior infarct, not

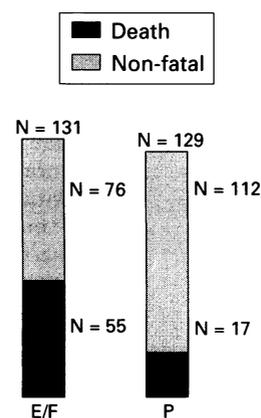


Figure 2 Total number of ischaemic endpoints for active treatment and placebo separated into fatal and non-fatal components. E/F, encainide/flecainide; P, placebo.

merely the reduction in flow, dramatically enhanced the likelihood of a fatal ventricular arrhythmia with the onset of an acute ischaemic insult.¹¹ In a second model Schwartz *et al* showed that in the presence of a healed (one month) myocardial infarction, acute ischaemia and enhanced sympathetic tone reproducibly induced malignant ventricular arrhythmias.¹²

Since no evidence exists nor is there a basis for conjecture that antiarrhythmic treatment will alter the natural course of the atherosclerotic process or be prothrombotic, it seems likely that the treatment drugs themselves are responsible for the changes in outcome coincident upon an ischaemic event. The shape of the Kaplan-Meier curve for the combined end points (fig 1A) suggests that the underlying atherosclerotic disease process progressed with equal vigour in both the drug and placebo groups. The mortality events are distributed evenly over time. They occur with the same temporal pattern as the non-fatal ischaemic events. There were no temporal outcroppings in the event curve for the treatment group to suggest that another mechanism was operating. The recent analysis of the circadian pattern of arrhythmic deaths in CAST¹⁵ found that the peak incidences were within two hours of awakening or in the late afternoon; this is consistent with the pattern of ischaemic events found in an untreated population.¹⁶ This is further supported by the observation that more than half of the fatal events were accompanied by angina-like symptoms. The 21% ischaemic event rate for this combined end point is consistent with other recent results in post-infarction cohorts.^{17 18}

Though antiarrhythmic drugs seem to exert their beneficial effects by depressing or blocking conduction in reentrant circuits, proarrhythmic aggravation of reentrant circuits by antiarrhythmic agents is well known.¹⁹ Encainide and flecainide reduce ventricular ectopy and arrhythmia, but they have also been associated with an increased rate of proarrhythmia in patients with compromised ventricular function.^{20 21} Both encainide and flecainide have been shown to reduce the fibrillation threshold or to increase the likelihood of ventricular fibrillation when blood flow is compromised.^{9 22 23}

Proarrhythmia, which in the CAST I definition included either or both enhanced ventricular ectopy and non-sustained ventricular tachycardia,² was uncommon in CAST I. At four months, proarrhythmia was found in 1% of patients on encainide, 3% of patients on flecainide, and 6% of patients on placebo. In addition, suppression of ventricular ectopy by the study drug was maintained over the first four months of CAST I (Salerno D *et al*, unpublished). Nearly two thirds of patients retained an 80% suppression rate and in three quarters of the patients suppression exceeded a 60% suppression rate. Because of the premature termination of CAST I, insufficient data for analysis are available at one year. However, earlier studies with both encainide and flecainide^{24 25} have shown comparable suppression rates for as long as two years.

Proarrhythmia, therefore, at least as traditionally defined, though present, cannot explain the increased rate of sudden death in the treatment group of CAST I.

It is also well known that antiarrhythmic drugs, and encainide/flecainide in particular, can cause potentially lethal ventricular tachycardia in non-ischaemic settings.^{20 21} With encainide/flecainide there seem to be two distinct mechanisms. In addition to the traditional proarrhythmic increase in the density of ventricular ectopy, even to the point of sustained ventricular tachycardia, class I-C agents, including encainide/flecainide, cause a prolonged, refractory, malignant ventricular tachycardia. Though uncommon, this is a distinct and identifiable entity that occurs shortly after the start of treatment^{19 26}; it was not seen in CAST I.

We believe the increased mortality in the group exposed to drug is, therefore, probably caused by an interaction that develops after ischaemia occurs. Unfortunately, there is no obvious difference in the characteristics of the fatal rhythm disorder between the drug and placebo groups.² We presume that the mechanism of death is a ventricular arrhythmia. Because this is a clinical observational study, we cannot make any assessment of the cellular mechanism involved. As we have indicated, the longitudinal and circadian patterns are consistent with a mechanism of ischaemia triggering an arrhythmia. Strictly speaking, this too, is a form of proarrhythmia. Because we postulate it is secondary to ischaemia and not a primary (or idiopathic) event and because it is, by definition, fatal, we are hesitant to combine it with the traditional categories of proarrhythmia.

LIMITATIONS OF THE STUDY

This study is a retrospective analysis of the data and is weakened by the lack of an a priori hypothesis. However, the primary CAST I results were themselves unexpected and all attempts to explain them will be compromised by retrospective review of the data with new, post-hoc hypotheses. Of more concern is the small degree of uncertainty introduced by the techniques used to collect clinical end point data. The mortality data were handled rigorously by a prespecified set of criteria.² Though prospectively defined, the secondary end points were not collected with the same rigour or review. The temporal distinctions between a non-fatal and a fatal end point were not defined rigidly because the need to separate fatal and non-fatal end points as mutually exclusive events was not anticipated. However, the clinical judgment exercised seems consistent and reasonable, and disparities are likely to be divided equally between treatment and placebo groups.

Conclusions

In the CAST I population of post-myocardial infarction patients the sum of cardiac deaths and non-fatal ischaemic events, either recurrent myocardial infarction or an increase in the

severity of angina pectoris, were nearly identical in those assigned to placebo or to encainide/flecainide. However, the mortality in the treatment group was far higher than in the placebo group whereas non-fatal ischaemic end points were correspondingly more frequent in the placebo group. Neither the temporal or circadian patterns of mortality were altered by drug assignment. The interaction suggests that an ischaemic event is more likely to be fatal in the presence of encainide or flecainide and that this propensity is present throughout the time course of drug administration.

The results of CAST I were a surprise to the investigators and the cardiology community. In part, these results emerged because of characteristics of the earlier studies. Virtually all of the initial studies with class 1-C drugs had small numbers and were not controlled. None had the power to evaluate mortality. In addition, the studies excluded patients who had sustained a recent myocardial infarction and thus could not have identified or even pointed to an interaction with ischemia.^{27 28} The pilot study for CAST I, the Cardiac Arrhythmia Pilot Study,²⁹ did study post-infarction in patients but did not have the power to assess mortality. Future preclinical and clinical studies with antiarrhythmic agents should be carried out in ischaemic models.^{11 12}

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