Treatment of severe heart failure: quantity or quality of life? A trial of enoximone

A J Cowley and A M Skene on behalf of the Enoximone Investigators

Abstract

Objectives—To determine the effects of enoximone on mortality and quality of life in patients with severe end stage heart failure.

Design—A randomised, double blind, placebo controlled trial of the addition of enoximone to conventional treatment. Planned minimum follow up of one year.

Setting—District general hospitals and cardiological referral centres in the United Kingdom.

Patients—Planned 200 patients with severe, symptomatic heart failure despite treatment with diuretics and where appropriate and tolerated angiotensin converting enzyme inhibitors and digoxin.

Results—The study was ended early by the ethics committee after 151 patients had been recruited because of an excess mortality in the enoximone group: 27 deaths compared with 18 in the placebo group ($P < 0.05$). Quality of life measured with a disease specific questionnaire showed a clinically significant improvement at week 2 with a mean increase score of 0.48 in the enoximone treated patients compared with 0.14 in those receiving placebo ($P = 0.0086$). With the Nottingham health profile questionnaire the physical mobility score was improved after three months in the enoximone group, median 21.3 compared with 41.8 in the placebo group ($P = 0.008$).

Conclusions—In patients with severe heart failure who remain incapacitated despite conventional treatment enoximone reduced survival but had a beneficial effect on the quality of life. Drugs that improve symptoms in severe end stage heart failure should not be discarded lightly.

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Heart failure is common and is probably becoming more common. It imposes a huge burden of morbidity and mortality on patients and an ideal treatment would therefore improve both symptoms and survival. Although angiotensin converting enzyme (ACE) inhibitors reduce symptoms and have a favourable effect on prognosis,¹⁻³ even with this treatment almost all patients continue to have an impaired capability for exercise and many remain severely incapacitated. Cardiac transplantation is effective in improving

symptoms and survival in those who remain severely incapacitated, but this option is only available for a small minority of patients. The treatment of most patients with severe heart failure remains difficult.

Enoximone is an orally active cyclic adenosine monophosphate phosphodiesterase (cAMP PDE) inhibitor and by this mechanism has inotropic and vasodilator properties. It has been shown to improve the symptoms and exercise capability of patients with severe heart failure who remain symptomatic despite optimum treatment with diuretics and ACE inhibitors.⁴ Although retrospective analysis of one exercise study suggested that it may be associated with an adverse effect on survival⁵ no prospective trial has been completed which has specifically attempted to determine the effects of enoximone on mortality.⁵

The Prospective Randomised Milrinone Survival Evaluation (PROMISE) trial clearly showed that milrinone, another cAMP PDE inhibitor, caused a reduced survival, a higher rate of adverse events, and no symptomatic improvement in patients with severe heart failure.⁶ It is not known whether the adverse effect on survival is limited to milrinone or is a class effect, and it is not known whether other cAMP PDE inhibitors may cause an improvement in symptoms. The purpose of this study was to examine the effect of enoximone treatment given by mouth on mortality and quality of life in a group of patients with severe heart failure who remained severely incapacitated despite optimum treatment with diuretics and ACE inhibitors. Recruitment to the study was started a year before the results of the PROMISE trial became known.

Patients and methods

PATIENTS

It was originally planned to recruit a total of 200 patients with severe heart failure from centres in the United Kingdom. The minimum follow up was to be one year. All patients were symptomatic despite optimum treatment with a loop diuretic, at a minimum dose equivalent to 80 mg frusemide daily, and ACE inhibitor or other vasodilator and digoxin. The patients were in New York Heart Association (NYHA) classification III or IV. Patients were included if their heart failure was due to ischaemic heart disease, dilated cardiomyopathy, or primary valvular incompetence with evidence of impaired left ventricular function. All patients had an enlarged heart on chest radiograph.

Enoximone Investigators

JR Hampton (University Hospital, Nottingham), JM Rowley (Mansfield and District Hospital, Mansfield), M Millar-Craig (Derbyshire Royal Infirmary, Derby), SP Hanley (North Manchester General Hospital, Manchester), S Dubrey (Charing Cross and Westminster Hospitals, London), RM Boyle (York District Hospital, York), M Joy (St Peter's Hospital, Chertsey), DB Barnett (Leicester Royal Infirmary, Leicester), A Zaida (Walsgrave Hospital, Coventry), GD Johnston (Belfast City Hospital, Belfast), DP Nicholls, (Royal Victoria Hospital Belfast), J Potter (Leicester General Hospital, Leicester), RH Smith (North Tees General Hospital, Stockton on Tees), EW Barnes (Darlington Memorial Hospital, Darlington), C Ward (Wythenshawe Hospital, Manchester), J McMurray (Western Infirmary, Glasgow)

Cardiovascular Medicine, University Hospital, Nottingham
A J Cowley

British Heart Foundation Statistics Group, University of Nottingham,
A M Skene

Correspondence to:
Dr A J Cowley,
Cardiovascular Medicine,
University Hospital,
Nottingham NG7 2UH.

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TRIAL DRUGS

Suitable patients were randomly allocated in a double blind trial to the addition of enoximone or matching placebo. The starting dose of enoximone was 50 mg three times a day, which could be increased at the discretion of the investigator to 100 mg three times a day after two weeks of drug treatment.

All patients were evaluated after two, four, and six weeks, three months, and then every three months after randomisation.

QUALITY OF LIFE QUESTIONNAIRES

Two different types of quality of life questionnaire were used. The first was a disease specific questionnaire which asked 30 questions about six different areas of the potential impact of heart failure on mobility, emotional state, home management, social activities, and general symptoms. The answers were graded from 1 to 7, the higher number signifying the greater wellbeing. The other questionnaire was not disease specific—the Nottingham health profile questionnaire assesses the impact on energy, pain, emotional reactions, sleep, social isolation, and physical mobility.^{7,8} Both questionnaires were completed by the patients before randomisation and after two weeks, three months, and one year of the trial drug regimen.

STATISTICAL METHODS

Sample size

One hundred patients in each group would have at least 80% power to detect a reduction in the one year mortality from 50 to 30%.

Endpoints

The primary endpoint of the study was the number of days to death for each patient, assessed on an intention to treat basis. Survival times were censored for patients alive at the end of the study at the date last seen and for the patients lost to follow up at the date last known to be alive. All deaths were treated equally in the intention to treat analysis irrespective of previous withdrawal and whatever the cause of death. Survival curves for the two groups were estimated using the Kaplan-Meier procedure and compared using a log rank test. Analysis using a proportional hazards model was also performed to estimate the

magnitude of the increase in risk after correction for prognostic variables.

Secondary endpoints

Efficacy of treatment was assessed by the quality of life questionnaires, the frequency of hospital admissions, by the NYHA classification, and by changes in concomitant drug treatment. Overall mean scores were calculated from the 30 questions on the quality of life questionnaire, a higher numerical response indicating better wellbeing. Differences between treatments were assessed using *t* tests. The Nottingham health profile was analysed according to the user's manual with a Mann-Whitney rank sum test.

Ethical considerations

The study protocol was approved by the ethical committees of all the participating centres. Its running was also supervised by an independent safety committee. Because relatively few patients were to be included in the trial no interim analyses were planned. After the publication of the PROMISE trial the chairman of the safety committee asked for a formal framework to be established to assess quantitatively adverse mortality, which in fact became apparent as the trial progressed. It was decided to use the significance of any interim analysis by the procedure of Lan and DeMets.⁹ The spending rule was chosen to be the so-called Pocock boundary with an overall significance level of 0.025 for harm only.

The safety committee actually undertook interim analyses at 10, 20, and 30% of the total months of recruitment. At the third interim analysis the observed significance level for the log rank comparison of the survival curves was required to be < 0.003 for early stopping to be indicated.

Results

The trial was ended early on the advice of the safety committee when a total of 151 of the planned 200 patients had been randomised because of an excess mortality in the patients treated with enoximone.

BASELINE CHARACTERISTICS

Table 1 shows the baseline demography for the patients at randomisation. For all major variables the groups were well matched. All but eight patients were being treated with ACE inhibitors and in these an ACE inhibitor had been tried but had not been tolerated. A total of 23% were in NYHA class IV and consistent with this the median dose of frusemide was 160 mg daily. The mean cardiothoracic ratio was 60%. These characteristics indicate that the trial achieved its objectives of including very ill patients.

TRIAL DRUGS

One hundred and three patients were titrated to 100 mg three times a day after two weeks and were maintained on this dose. In 27 patients the dose was not increased above 50

Table 1 Baseline demography

	Enoximone (n = 75)	Placebo (n = 76)
Sex ratio (male: female)	59:16	63:13
Age (mean)(y)	66.4	66.8
Race (No white)	74	75
Aetiology		
Ischaemic heart disease	57	61
Dilated cardiomyopathy	13	13
Primary valvar	9	8
Mean duration of CHF	43	38
NYHA grade		
III	57	59
IV	18	17
Mean diuretic dose (mg frusemide)	165.6	163.6
ACE I	70	73
Mean CTR (%)	60.45	59.73

In some patients there was more than one cause. CHF congestive heart failure; CTR, cardiothoracic ratio; NYHA; New York Heart Association; ACEI angiotensin converting enzyme inhibition

Figure 1 Kaplan-Meier survival curves for those patients receiving placebo (broken line) and those receiving enoximone (solid line) ($P < 0.05$).

Figure 2 Kaplan-Meier estimates of withdrawal for those patients receiving placebo (broken line) and those receiving enoximone (solid line) ($P = 0.0019$).

Figure 3 Kaplan-Meier estimates of time to first hospital admission for those patients receiving placebo (broken line) and those receiving enoximone (solid line) ($P = 0.044$).

mg three times a day and in the remaining patients the dose varied throughout the study.

MORTALITY

Figure 1 shows the Kaplan-Meier survival curves for the two groups of patients. At the time the safety committee recommended that the trial should be discontinued 23 patients in the enoximone group and nine patients in the placebo group had died ($P < 0.002$). When all outstanding data had been collected at the formal closure of the database the corresponding numbers were 27 and 18 ($P < 0.05$). Sudden death occurred in 11 patients receiving enoximone compared with five receiving placebo, whereas progressive heart failure caused 12 deaths while receiving enoximone and 11 while receiving placebo. Four and two deaths in the enoximone and placebo groups respectively were due to other causes.

Because of the small number of patients included in the trial and the fact that no subgroup was specified in the protocol, the analysis of subgroups can only be thought of as exploratory. There was a significant excess mortality in the enoximone treated patients, however, with a baseline heart rate of greater than 85 beats/minute ($P = 0.0036$) in those with heart failure of less than two years' duration ($P = 0.045$) and those with a diuretic requirement of greater than 120 mg frusemide daily ($P = 0.040$). Conversely, the only subgroup with a lower but non-significant observed mortality in patients receiving enoximone were those with a heart rate of less than 85 beats/minute ($P = 0.79$).

WITHDRAWAL

Figure 2 shows Kaplan-Meier estimates of withdrawal rate, including death, in the two groups. A total of 62 patients was withdrawn from the study, 40 while receiving enoximone and 22 while receiving placebo ($P = 0.0019$). The median time to withdrawal was 98 days for enoximone and 206 days for placebo. The three most common reasons for withdrawal were death, patient request, and adverse events. Adverse events led to withdrawal in 13 patients receiving enoximone and 10 receiving placebo.

ADMISSION TO HOSPITAL

Figure 3 shows the Kaplan-Meier estimates of time to first admission to hospital. The median time to first admission was 86 days for those patients receiving enoximone and 149 days for those receiving placebo ($p = 0.044$). In total there were 156 admissions to hospital and of these 67 were due to worsening heart failure (37 enoximone and 30 placebo) and 10 due to a dysrhythmia (four enoximone and six placebo).

QUALITY OF LIFE

Table 2 shows the changes in the disease specific questionnaire over the study period. There was no difference in mean baseline scores, 3.44 for enoximone and 3.63 for placebo. By week 2 mean levels had increased by 0.48 in the enoximone group ($P =$

Table 2 Disease specific questionnaire

	Means value		Change from baseline		P value
	Enoximone	Placebo	Enoximone	Placebo	
Baseline	3.44	3.63			
Week 2	4.01	3.79	0.48	0.14	0.0086
Three months	4.33	4.18	0.70	0.62	0.6631
One year	4.28	4.25	0.66	0.65	0.9748

Table 3 Nottingham health profile. Median physical mobility score

	Enoximone (n)	Placebo (n)
Baseline	42.03 (64)	34.5 (67)
Week 2	31.9 (56)	41.8 (59)
Three months*	21.3 (37)	41.8 (47)
One year	21.99 (12)	34.68 (17)

*When change from baseline to three months is examined, difference between enoximone and placebo $P = 0.008$.

0.0086), indicating an improved quality of life, whereas there was no statistically significant change for the placebo group, 0.14. There was no other significant difference thereafter, probably because of the reduced numbers of patients continuing in the trial, although the mean values for the enoximone treated patients were always higher.

Table 3 gives the median physical mobility scores from the Nottingham health profile questionnaire. Measured with this questionnaire a reduction in score indicates an improved quality of life. With the Nottingham health profile, as with the disease specific questionnaire, the enoximone group was more severely symptomatic than the placebo group. Once treatment began, however, there were fewer problems with physical mobility in the enoximone group throughout the study. This difference reached statistical significance at month 3 with respect to change from baseline ($P = 0.008$).

There was no difference in NYHA classification between the groups at any time during the study.

Discussion

This trial has shown an excess mortality with a cAMP PDE inhibitor in patients with severe heart failure, but it raises the much wider question of what we are trying to achieve in treating these patients. In patients with mild symptoms improvement in survival is obviously the prime objective. In more severely ill patients with distressing if not disabling symptoms, this may no longer be so and an improvement in their quality of life may be more important. These severely symptomatic patients may even be prepared to risk a reduced life expectancy for an improvement in their quality of life. In this situation the results of this study suggest that enoximone may be a useful drug for the treatment of heart failure.

The PROMISE trial was unable to show any symptomatic improvement with milrinone⁶ and a large multicentre trial did not show any improvement in exercise tolerance with enoximone.⁵ Measuring symptomatic improvement in large trials is difficult,¹⁰ however, and other studies with enoximone⁴ and milrinone¹¹ have shown a beneficial effect on symptoms. How best to measure symptomatic impairment is not clear, although exercise tolerance is often used. The patients included in this trial were usually incapable of formal, laboratory based exercise tests because of the severity of their heart failure and we were therefore left with some form of questionnaire

to assess changes in symptoms and quality of life. We deliberately chose two different questionnaires for measuring the quality of life: a disease specific questionnaire and a general questionnaire. Both questionnaires showed symptomatic improvement with enoximone and although the analysis was exploratory the positive findings are consistent with what might be expected with a drug with beneficial effects. The improvement in the Nottingham health profile questionnaire was seen, not surprisingly, in that category which relates to physical mobility. The improvement seen in the enoximone group with the disease specific questionnaire was substantial, particularly in response to questions about improvement in activities and the need for less rest. This, we believe, reflects a clinically useful improvement.

The excess mortality in the enoximone treated patients occurred early and after 100 days the survival curves seem to be parallel. This suggests that any harmful effects of enoximone, either on mortality or morbidity, occur early after the start of treatment. Enoximone also appeared to worsen survival in those patients who had had heart failure for comparatively shorter periods of time, whereas in those with heart failure of longer duration there was no adverse effect. Admission to hospital also occurred sooner in the patients treated with enoximone. The numbers included in the trial do not allow reliable analysis of different mechanisms of death, but there was a twofold increase in sudden death in the patients treated with enoximone compared with those receiving placebo, whereas there was a similar risk of death due to progressive heart failure. An excess of sudden death was also seen in the PROMISE trial. In those patients with a tachycardia before randomisation enoximone caused a considerable excess risk of death, whereas the only patients in whom there was no evidence of a deleterious effect were those with a comparatively slow heart rate. The excess mortality in this study in patients with a tachycardia may also be because these patients had more severe heart failure and this is supported by the fact that the risk of death was higher in those patients receiving larger doses of diuretics. In the PROMISE trial it was also the more severely ill patients who seemed to be harmed by milrinone.

Although the results of this study are in agreement with the PROMISE trial and therefore suggest that the adverse effect on survival is a class effect of cAMP PDE inhibitors, the important difference is that enoximone in this trial caused an improvement in symptomatic wellbeing. In severely symptomatic patients this should not be dismissed lightly. In patients who are less symptomatic an improvement in survival is the primary aim of treatment, but in more severely ill patients the same may not apply. In such patients increased survival may be a secondary concern and it is likely that the patients themselves would prefer an improved quality of life at the expense of reduced sur-

vival. This may not result only from treatment with cAMP PDE inhibitors and we must be careful not to discard drugs which may be of considerable symptomatic benefit in patients with severe heart failure.

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- 1 Cowley AJ, Rowley JM, Stainer K, Hampton JR. Captopril for heart failure: a placebo controlled trial. *Lancet* 1982;II:730-2.
- 2 CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;316:1429-35.
- 3 SOLVD Investigators. Effects of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; 325:293-302.
- 4 Cowley AJ, Stainer K, Fullwood L, Muller AF, Hampton JR. The effects of enoximone in patients with heart failure which is uncontrolled by captopril and diuretics. *International Journal of Cardiology* 1990;28:45-53.
- 5 Uretsky BF, Jessup M, Konstam MA, *et al.* Multicenter trial of oral enoximone in patients with moderate to moderately severe heart failure: lack of benefit compared with placebo. *Circulation* 1990;82:774-80.
- 6 Packer M, Carver JR, Rodeheffer RJ, *et al.* Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991;325:1468-75.
- 7 Hunt SM, McKenna SP. *The Nottingham health profile user manual*. Manchester: Galen Research, 1991.
- 8 Hunt SM, McKenna SP, McEwen J, Backett EM, Williams J, Papp E. A quantitative approach to perceived health status: a validation study. *J Epidemiol Community Health* 1980;34:281-6.
- 9 Lan KKG, DeMets DL. Group sequential procedures: calender vs information time. *Stat Med* 1989;8: 1191-8.
- 10 Cowley AJ, McEntegart DJ. Placebo-controlled trial of flosequinan in moderate heart failure. The possible importance of aetiology and method of analysis in the interpretation of the results of heart failure trials. *Int J Cardiol* 1993;38:167-75.
- 11 Colucci WS, Sonnenblick EH, Adams KF, *et al.* Chronic efficacy trials of oral milrinone in combination with converting enzyme inhibitors in patients with moderate congestive heart failure. *J Am Coll Cardiol* 1993;22(Suppl); 113-8.