The evolving role of the cardiac inotrope, enoximone, in heart failure

LIAM J CORMICAN, A CRAIG DAVIDSON

Abstract

Chronic heart failure is a progressive syndrome which continues to have high rates of morbidity and mortality. Heart failure rates are increasing in parallel with the ageing population, as are rates of hospitalisation for acute episodes of decompensated failure. Little progress has been made in the medical management of such episodes. Positive inotropes, including selective phosphodiesterase III inhibitors, are associated with increased mortality when administered over the long term. Now newer approaches, using selective agents such as enoximone orally at lower doses alone or in combination with carefully titrated beta$_1$-selective adrenergic blockade, may provide a more favourable outcome in terms of symptom management, functional status and improved survival. Trials are underway to determine whether this is the case. Published trials with enoximone and protocols for forthcoming trials are reviewed.

Key words: decompensated heart failure, phosphodiesterase inhibitors, enoximone, phase III trials.

Br J Cardiol (Acute Interv Cardiol) 2002;**9**(1):AIC 26–AIC 31

Introduction

Heart failure is a debilitating condition resulting from left ventricular dysfunction, which can be ischaemic or non-ischaemic in aetiology. Non-ischaemic causes include hypertension, valvular heart disease, thyroid disease, alcohol misuse, congenital heart disease and cardiomyopathy. The clinical syndrome is complex and includes fatigue, shortness of breath on exertion or at rest, orthopnoea, paroxysmal nocturnal dyspnoea, nocturia, changes in mental health status and anorexia.

Quality of life may be severely impaired in cardiac failure patients. Their functional status can be assessed using the New York Heart Association (NYHA) functional classification (table 1).[1] Decompensated heart failure has been defined as sustained deterioration of at least one functional class, with objective evidence of volume overload such as crepitations or oedema.[2] Prognosis is poor, and 75% of patients hospitalised with heart failure for the first time will die within five years.[3] A Canadian study of 153 consecutive patients hospitalised with acute decompensated heart failure reported a one-year mortality of 33%.[4]

Table 1. New York Heart Association classification of heart failure

Class I.	No limitation. Ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations
Class II.	Slight limitation of physical activity. Comfortable at rest but ordinary activity results in fatigue, palpitations or dyspnoea
Class III.	Marked limitation of physical exercise. Comfortable at rest but less than ordinary activity results in symptoms
Class IV.	Unable to carry out any physical activity without discomfort. Symptoms of heart failure are present even at rest, with increased discomfort with any physical activity

The population prevalence of heart failure is estimated to be 3–20 per 1,000 population, affecting around 1–3% of the general population and rising to 30–130 per 1,000 in those aged over 65 years.[5] The prevalence of heart failure increases in direct relation to age. Heart failure is the most common cause of hospital admission in the elderly, and the elderly comprise the majority of patients admitted to hospital for heart failure.[6] Within Guy's and St Thomas' NHS Hospitals Trust, patients with decompensated heart failure comprised 1.4% of all hospital admissions over the three years from June 1999 to May 2002. The proportions of these patients requiring an intensive care or coronary care unit admission range from 2.5% to 6.7% each year.[7]

The annual rate of hospitalisation for heart failure is around 30%; there is wide variation between adjusted death rates and readmission rates within the UK.[8] Heart failure is a costly disease, estimated to consume about 2.0% of healthcare expenditure in developed countries.[9] More than two thirds of treatment costs relate to hospitalisations and in the UK these hospitalisation costs exceeded 2.5% of all healthcare expenditure in the year 2000. Such costs are set to escalate in parallel with the ageing population. By the end of this decade more than 16% of the population will be over 65 years of age; and current estimates indicate that the number of people aged 85 plus in the UK will double from 1.9% of the total population in 1999 to nearly two million by the year 2031.[10]

Lane Fox Unit, St Thomas' Hospital, Lambeth Palace Road, London, SE1 7EH.
Liam J Cormican, Specialist Registrar
A Craig Davidson, Consultant Physician/Intensivist
Correspondence to: Dr Liam J Cormican
(email: cormitron@yahoo.com)

Table 2. Factors which may precipitate acute decompensation of chronic congestive heart failure

- Non-compliance with therapy
- Arrhythmias
- Pulmonary embolism
- Hypertension
- Ischaemia
- High-output states e.g. anaemia, pregnancy
- Systemic infection
- Renal, pulmonary or gastrointestinal illness
- Inappropriate drug therapy

Adapted from: Redfield MM. *Diagnosis and evaluation of congestive heart failure.* In: Mayo Clinic Cardiology Review (ed Murphy JG). Futura Publishing Company: Armonk, NY, 1997; pages 597-622.

Pathophysiology of heart failure

Ischaemic cardiomyopathy frequently occurs secondary to acute myocardial infarction and the subsequent remodelling and dilatation of the left ventricle. The fundamental defect in heart failure is decreased myocardial contractility. This progressive remodelling occurs as an adaptive response in order to stabilise cardiac output and to maintain pump function, through activation of the renin-angiotensin and adrenergic nervous systems. The precipitating factors which may cause acute decompensation of chronic congestive heart failure are shown in table 2. Approximately 10% of patients with heart failure have advanced disease and some confusion exists in the terminology of this condition[11] – the terms 'advanced', 'severe', 'refractory' and 'end-stage' heart failure are used interchangeably. While the last term reflects the poor prognosis associated with pump failure, 'advanced heart failure' may embrace the concept of partial reversibility of the heart failure remodelling process.

Treatment strategies in the UK

Treatment strategies have been developed for both chronic stable and acute decompensated heart failure. The aims of treatment in chronic failure are to enhance survival and to minimise symptoms; the challenge with decompensated failure is to stabilise the patient clinically, to restore organ perfusion, to optimise filling pressures and to begin the conversion to chronic therapy.[12,13] In the stable patient with heart failure, evidence has shown that diuretics, vasodilators and inotropes reduce morbidity whereas beta blockade and ACE inhibition improve survival.

Because the natural history of heart failure remains progressive, standard anti-failure therapy becomes ineffective and patients require hospitalisation and parenteral treatment with positive inotropic agents. Dobutamine, milrinone or enoximone are typically used for this purpose, and patients with advanced heart failure may need these to be administered by either continuous or intermittent infusion. This may be accomplished in an outpatient setting, with the use of central venous access, which is both costly and unwieldy.[14] In addition, this approach has not been systematically evaluated and it is essentially unproven therapy. European guidelines point out that the IV use of positive inotropes is insufficiently documented in clinical trials and the effect on prognosis is unknown.[13]

In the acute setting positive inotropes are introduced in order to improve performance by augmenting cardiac contractility, often at an advanced stage of the disease in very sick patients. Frequently such short-term benefits are gained at a price. They can cause tachyphylaxis and increased heart rate and oxygen demand, which may be associated with a high incidence of treatment-related complications, and in some cases with a negative trend in survival.[15]

Newer strategies are under investigation, including the use of enoximone, a selective phosphodiesterase III inhibitor (PDEI), alone or concurrently with beta adrenergic blocking agents (beta blockers). Positive inotropes predominantly or partly increase the level of the second messenger cyclic adenosine monophosphate (cAMP) in the cardiomyocyte. This occurs through activation of the beta receptor complex (dobutamine, isoprenaline) or through inhibition of phosphodiesterase, the enzyme which breaks down cAMP (milrinone, enoximone). cAMP has numerous cellular effects through activation of several protein kinases. It leads to an increase in calcium flux through the L-type calcium channels and an increase in the uptake of calcium in the sarcoplasmic reticulum (SR). (Subsequent release of calcium in the SR may lead to arrhythmias.) cAMP also increases ATPase activity of the contractile protein, which results in increased energy consumption and oxygen demand.[16]

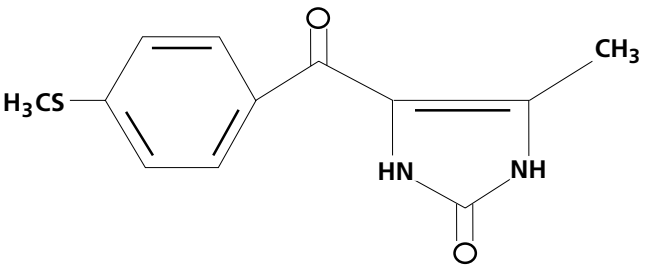
PDEIs as a class possess many pharmacological properties which are potentially beneficial in advanced heart failure. They can improve both systolic and diastolic function, and at lower doses may have favourable myocardial energetic effects and improve exercise tolerance without the development of pharmacological tolerance.[17] They are also effective venodilators and pulmonary vasodilators, they inhibit platelet aggregation, dilate epicardial coronary arteries and bypass grafts, have potent anti-ischaemic effects,[18] may inhibit neointimal formation after vascular injury and may inhibit proinflammatory cytokine formation and the effects of endotoxin.[19] At higher doses, PDEIs are arrhythmogenic and/or may be energetically unfavourable by increasing heart rate. These effects are likely to have been responsible for the increased mortality seen with higher doses used in clinical trials to treat heart failure.[20-22]

This review looks at the use of the PDEI, enoximone, and assesses its use orally in different presentations of ventricular dysfunction. Enoximone has been available for clinical use in the UK since April 1988, and there is an extensive number of publications on this compound.

Pharmacology of enoximone

Enoximone is a non-glycoside, non-catecholamine, imidazolone derivative (figure 1), which is a positive inotrope and arteriolar

Figure 1. Molecular structure of enoximone



vasodilator. It selectively inhibits SR-associated type III phosphodiesterase, the membrane-bound enzyme which is expressed at high levels in human ventricular myocardium and vasculature; and it probably also involves cyclic guanosine monophosphate, cGMP.[23] PDEIs are known to hydrolyse cGMP, which may explain regulation of vascular tone by enoximone and may be the underlying mechanism of its vasodilatory and cardiotonic activity. It was synthesised for the purpose of finding a cardiotonic agent with a wider therapeutic index than that exhibited by the digitalis glycosides.[24]

Intravenous enoximone is indicated for the treatment of acute congestive heart failure, typically when cardiac output is reduced and filling pressures are increased, in patients requiring IV therapy who can be closely monitored. The initial haemodynamic response to enoximone will determine the subsequent rate of administration and duration of treatment. In typical clinical doses, the majority of patients will exhibit a 30% or greater increase in cardiac output and a decrease in mean pulmonary arterial wedge pressure of approximately 40%. Onset of action is prompt after intravenous administration, with peak response in cardiac index occurring in 10–30 minutes.[25]

Enoximone is available for IV use in several European countries (Perfan®) and is under development for oral use, both as monotherapy and in combination with beta blockade.[13] Intravenous therapy should be initiated with a dose of 0.25–0.75 mg/kg as a slow injection.[12] Further doses of 0.25–0.5 mg/kg can be given every 30 minutes until there is a satisfactory response or until a total initial dose of 3.0 mg/kg is achieved. For maintenance the initial dose (not more than 3.0 mg/kg) can be repeated as required every 3–6 hours or a continuous IV infusion at a rate of 1.25–7.5 mcg/kg/min can be instituted.[12] The total dose should not exceed 24.0 mg/kg/24 hours.

Enoximone is about one tenth as potent as milrinone for inhibiting type III PDE, so oral and IV doses of enoximone are about 10 times those of milrinone. The mean half-life of enoximone is 4.2 hours in normal volunteers and 6.2 hours in heart failure patients. With continuous infusions at higher doses, the median clearance is 6.3 ml/min/kg and the median elimination half-life is approximately eight hours. In heart failure patients, a loading dose of 90 mcg/kg/min over 20–60 minutes followed by an average maintenance infusion of 1.0 mg/min over 48 hours maintained mean plasma levels at 3.6 mcg/ml and 9.7 mcg/ml for the parent compound and the active sulphoxide metabolite, respectively.[26,27]

Enoximone is extensively metabolised in the liver to sulphoxide derivatives, including at least one active derivative. These derivatives are renally excreted and dose reduction is recommended (as with milrinone) in patients with renal and/or hepatic failure.[28] While the safety and effectiveness in children remain to be established, enoximone is used in lower doses in children and infants recovering from cardiac surgery and the pharmacokinetics in infants are similar to those in adults.[29] Contraindications in patients with known hypersensitivity to enoximone, and special warnings and precautions, are detailed in the SPC. Although enoximone has not been shown to be arrhythmogenic in electrophysiological studies,[18,30] premature ventricular contractions have been observed in some patients. Less frequently, ventricular and supraventricular arrhythmias have been observed, but these are more likely in patients with pre-existing arrhythmias. Other possible adverse reactions include thrombocytopenia, gastrointestinal side effects and increases in hepatic enzyme levels.[27]

Enoximone is approximately 85% plasma protein-bound and clinically significant drug interactions are unlikely to occur as a result of displacement from protein binding. The drug does not interact significantly with widely used diuretics, potassium supplements, antiarrhythmics (diltiazem, propranolol, lignocaine or procainamide), anticoagulants, sedatives or positive inotropes (dobutamine or dopamine).[27]

Haemodynamic effects

A potent inotrope, enoximone improves systemic haemodynamics in patients with severe chronic heart failure.[31] A typical starting dose of 0.5 mg/kg provides a 30% increase in cardiac index and a 20% increase in pulmonary artery diastolic pressure over 1.5–4.0 hours.[32] The drug causes a significant decrease in pulmonary capillary wedge pressure (PCWP), while left ventricular dP/dt increases despite a decrease in arterial pressure and systemic vascular resistance, all without significant heart rate change. Such changes indicate improvement in left ventricular function.

The inotropic and vasodilatory properties of enoximone were initially shown in a study of 10 patients with severe heart failure, in whom nitroprusside, dobutamine (in doses of 10 mcg/kg/min) and enoximone (at 2 mg/kg) were administered sequentially.[33] All agents increased stroke volume index to a similar extent, but enoximone produced less tachycardia than dobutamine, and consequently a smaller improvement in cardiac index. Mean arterial pressure was not changed by dobutamine but was reduced by 9% with enoximone. All three agents significantly reduced systemic vascular resistance and improved cardiac pump function, when assessed by the increase in stroke index, to a similar extent. Enoximone resulted in less hypotension than nitroprusside (mean arterial pressures -9% and -22%, respectively). Thus,

enoximone showed a clinically significant increase in cardiac index with only minor changes in rate pressure product.

A further study comparing dobutamine and enoximone showed that enoximone is effective in acutely improving central haemodynamics, such as reducing systemic vascular resistance, pulmonary artery wedge pressure (significantly more than dobutamine) and systemic arterial pressure, but is a less potent stimulant of renin secretion than dobutamine.[34]

There is also some evidence that phosphodiesterase inhibition may have a role in the treatment of diastolic dysfunction associated with heart failure,[35] but there are insufficient clinical data to support enoximone specifically in this role.

Clinical trials

Clinical experience has been gained with oral enoximone in the short- and long-term management of heart failure of differing severities and aetiologies. In an open study of 69 patients with chronic heart failure of moderate to advanced severity, oral enoximone (1.8 $\pm$ 0.5 mg/kg every 6–8 hours) was given for an average of 35 weeks.[36] Within 12 weeks the majority of surviving patients were improved by at least one NYHA functional class. In a subset of patients who were able to perform reproducible treadmill exercise before entry, average maximal oxygen uptake increased significantly ($p<0.05$) at 2–4 weeks and remained increased at 12 weeks. Eleven patients experienced (generally mild) gastrointestinal effects. The overall 12-month survival in this population was 44%, and no deaths occurred in class II patients. Hospitalised, clinically unstable class IV patients accounted for more than half of all deaths; 17 patients died of cardiogenic shock and 10 died suddenly at home. The high mortality rate was consistent with mortality rates reported on similar patient groups.

The clinical effects of low dose enoximone (25 mg and 50 mg tds) were compared against placebo in a randomised, double-blind study in 105 patients with NYHA class II to III heart failure of ischaemic or non-ischaemic aetiology. After a 12-week treatment period both treatment groups had a significantly improved exercise tolerance in comparison to placebo. There was no significant difference between the two treatment groups. The treatment groups did not have a higher incidence of arrhythmias and actually had a lower mortality rate than the placebo group.[17]

Enoximone 150 mg tds and captopril 25 mg tds (in addition to diuretics) were compared in a double-blind, randomised, crossover trial of one month's duration in 13 patients with severe heart failure.[37] The cardiac index at rest did not change with either drug but both drugs caused an increase in cardiac index at peak exercise ($p<0.05$). Systemic vascular resistance (SVR) at rest decreased with enoximone ($p<0.5$) and was unchanged with captopril; SVR at peak exercise was not lowered by either drug. No difference was detected between the haemodynamic response to the two drugs after one month's treatment, either at rest or during exercise.

Other workers have assessed the oral use of enoximone with long-term use. In one study, the long-term safety and efficacy of enoximone 50–100 mg tds were evaluated in 30 patients with chronic heart failure (NYHA class II-IV) against background therapy of digoxin and diuretics.[38] During a mean follow-up of 40 weeks, six patients died, four from cardiac causes. In the remaining patients NYHA class improved in 18, was unchanged in five patients and deteriorated in one. Exercise capacity improved during the initial 26 weeks of treatment and was maintained; clinical improvement was also maintained over the study period. There were no changes in heart rate, blood pressure or cardiothoracic ratio or left ventricular dimensions on echocardiography. Improvements were observed in fractional shortening and ejection fraction (though they were insignificant). Cardiac output increased from 2.4 to 3.6 L/min/m^2 ($p<0.001$) in six haemodynamically monitored patients after 52 weeks of drug treatment, while PCWP decreased from 25.8 to 16.6 mmHg ($p<0.001$). The drug was well tolerated, and Holter monitoring did not reveal any change in arrhythmia profile.

Encouraging results have been shown using oral enoximone (100 mg tds) as a substitute for intravenous dobutamine support in end-stage heart failure. A study in 24 patients showed that it can be used effectively in weaning dobutamine-dependent patients, with lower relapse rates than with placebo, over a treatment period of 28 days.[39]

Oral enoximone has also been successfully employed in the management of patients with NYHA class IV heart failure awaiting cardiac transplantation, resulting in an improved pre-transplant six-month survival rate. Though the enoximone-treated patients had a more advanced state of heart failure, the pre-transplant and post-transplantation survival of enoximone-treated patients was similar to that of the control group and gave proof that enoximone treatment was of benefit in this patient population.[40]

Combined oral inotrope and beta blockade

In CHF patients, beta blockers have been shown to reduce mortality significantly. It is postulated that enoximone may facilitate the initiation and up titration of beta blockers since PDEIs retain their haemodynamic action, both the positive inotropic action and the vasodilating properties, in the face of beta blockade. Shakar and colleagues[41] studied 30 patients with class IV heart failure (left ventricular ejection fraction [LVEF]) 17.2 $\pm$ 1.2%, cardiac index 1.6 $\pm$ 0.1 L/min/m^2) who were treated with the combination of oral enoximone < 1 mg/kg tds and (after stabilisation) oral metoprolol, 6.25 mg, slowly titrated up to a dose of 100–200 mg/day. These agents were tolerated by 96% and 80% of patients, respectively. The mean duration of combination therapy was 9.4 months and the mean length of follow-up was 20.9 months. Of the 23 patients on the combination, 48% could be weaned off enoximone therapy in the long term. The LVEF increased significantly from 17.7% to 27.6% ($p=0.01$) and NYHA functional class improved from 4 $\pm$ 0 to 2.8 $\pm$ 0.1 ($p=0.0001$). There was also a trend towards fewer hospitalisations during treatment ($p=0.06$). The estimated probability of survival at one year was 81$\pm$ 9%. Heart transplantation was performed successfully in nine patients (30%). These authors suggested that combina-

Key messages

- The prevalence of chronic heart failure is increasing
- Hospitalisations for severe decompensated heart failure are also increasing
- Treatment of these episodes with positive cardiac inotropes has been associated with increased mortality
- Use of low-dose, oral enoximone alone or combined with selective beta blockade is currently being assessed as a life-saving positive inotropic support

tion therapy was useful in the treatment of severe heart failure and that it might be used as a palliative measure when transplantation was not an option or as a bridge to cardiac transplantation. They recommended that further study (phase III trials) of combined therapy was warranted.

Three stratified clinical trials will assess the efficacy and safety of low-dose enoximone (25 or 50 mg tds depending on a weight cutoff point of 75 kg) for three primary end points. The ability to wean the patient from dependence on IV inotropic therapy will be assessed in EMOTE; the ability to lower the hospitalisation rate will be assessed in EXTEND; and the ability to do both in a population that includes patients with pulmonary hypertension will be assessed in ENOXIE. February 2002 saw the half-way recruitment point for EMOTE, in patients with ultra-advanced heart failure. In ESSENTIAL, the effects of enoximone on survival will be assessed in a mortality tracking protocol that has sufficient power to exclude an increase in mortality. Similarly, in a population of advanced heart failure patients, who have previously failed initiation or uptitration of a beta blocker for haemodynamic reasons, EMPOWER will test the ability of low-dose enoximone to increase metoprolol acceptability and to lower the combined end point of mortality plus hospitalisation.

Conclusions

Previous evidence suggested that, in spite of the haemodynamic benefits of oral enoximone in patients with decompensated heart failure, there was a risk of increased mortality. Newer evidence suggests that, at lower doses, the administration of enoximone may confer its haemodynamic benefits with an improved safety profile. Furthermore, evidence is emerging of the possible advantages of its administration in conjunction with carefully titrated beta-$_1$ blockade, in terms of symptom management, functional status and improved survival. Trials are underway to determine whether this is the case.

References

1. New York Heart Association. Classification. *Arch Intern Med* 1972; **129**(5):836.
2. Mills RM, Hobbs RE. Drug treatment of patients with decompensated heart failure. *Am J Cardiovasc Drugs* 2001;**1**:119-25.
3. McMurray, Stewart S. The burden of heart failure. *Eur Heart J* 2002; **4**(suppl D):D50-D58.
4. Brophy JM, Deslauriers G, Rouleau JL. Long-term prognosis of patients presenting to the emergency room with decompensated heart failure. *Can J Cardiol* 1994;**10**:543-7.
5. Cowie MR, Mosterd A, Wood DA *et al*. The epidemiology of heart failure. *Eur Heart J* 1997;**18**:208-25.
6. Petrie MC, Berry C, Stewart S, McMurray JJV. Failing ageing hearts. *Eur Heart J* 2001;**22**:1978-90.
7. Guy's and St. Thomas' NHS Trust Emergency Admissions Database.
8. Stewart S, Demers C, Murdoch DR *et al*. Substantial between-hospital variation in outcome following first emergency admission for heart failure. *Eur Heart J* 2002;**23**:650-7.
9. Doughty RN. Heart failure in the elderly: more care required. In: Sharpe N (ed). *Heart failure management*. London: Martin Dunitz, 2000;217-31.
10. OHE compendium of health statistics. 13th edition, 2001. London: Office of Health Economics.
11. Deng MC, Ascheim DD, Edwards NM, Naka Y. End-stage heart failure: which options? *Eur Heart J* 2002;**4**(suppl D):D122-30.
12. Bristow MR, Port JD, Kelly RA. Treatment of heart failure: pharmacologic methods. In: Braunwald E, Zipes DP, Libby P (eds). *Heart disease. A text-book of cardiovascular disease,* sixth edition, 2001, 590.
13. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;**22**:1527-60.
14. Bristow MR. New concepts in the use of positive inotropic agents in ultra-advanced heart failure. In: *New approaches to the treatment of late-stage heart failure* satellite symposium. European Society of Cardiology, Amsterdam, 2000.
15. Remme WJ. Positive inotropes – a new horizon or still a dead end? *Cardiovasc Drug Ther* 2001;**15**:375-7.
16. Skoyles JR, Sherry KM. Pharmacology, mechanisms of action and uses of selective phosphodiesterase inhibitors. *Brit J Anaes* 1992;**68**:293-302.
17. Lowes B, Higginbotham M, Petrovich *et al*. Low dose enoximone improves exercise capacity in chronic heart failure. *J Am Coll Cardiol* 2000;**36**:501-8.
18. Mitrovic V, Thormann J, Neuzner J *et al*. Hemodynamic, antiischemic, and neurohumoral effects of enoximone in patients with coronary artery disease. *Am Heart J* 1989;**117**(1):106-11.
19. Weidenbach H, Burger M, Schricker T, Georgieff M, Adler G, Beckh K. Modulation of hormone-induced activation of glycogenolysis by the phosphodiesterase-III-inhibitor enoximone in the perfused rat liver after endotoxin treatment. *Gastroenterology* 1994;**106**(4/2):A 1006.
20. Packer M, Carver JR, Cheseboro JH *et al*. Effect of milrinone on mortality in severe chronic heart failure. The prospective randomised milrinone survival evaluation (PROMISE). *N Engl J Med* 1991;**325**:1468-75.
21. Cohn JN, Goldstein SO, Greenberg BH *et al*. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. *N Engl J Med* 1998;**339**:1810-16.
22. Uretsky BF, Jessup M, Konstam MA *et al*. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure. Lack of benefit with enoximone compared with placebo. Enoximone Multicenter Trial Group. *Circulation* 1990;**82**:774-80.
23. Movsesian MA, Smith CJ, Krall J *et al*. Sarcoplasmin-reticulum associated cyclic adenosine 5'-monophosphate phosphodiesterase activity in normal and failing human hearts. *J Clin Invest* 1991;**88**:15-19.
24. Dage RC, Kariya T, Hsieh CP *et al*. Pharmacology of enoximone. *Am J Cardiol* 1987;**60**:10C-14C.
25. Uretsky B, Generalovich T, Verbalis JG, Valdes A, Sudhakar Reddy P. MDL 17.043 (enoximone) therapy in severe congestive heart failure: Characterisation of the early and late haemodynamic, pharmacokinetic, hormonal and clinical response. *J Am Coll Cardiol* 1985;**5**:1414-21.
26. Perfan (enoximone). Summary of Product Characteristics. Myogen Inc website. http://www.myogen.com
27. Vernon MW, Heel RC, Brogden RN. Enoximone. A review of its pharmacological properties and therapeutic potential. *Drugs* 1991;**42**(6):991-1017.
28. Dage RC, Okerholm RA. Pharmacology and pharmacokinetics of enoximone. *Cardiology* 1990;**77**(suppl 3):2-13 and discussion 27-33.
29. Booker PD, Gibbons S, Stewart JIM, Selby A, Wilson-Smith E, Pozzi M. Enoximone pharmacokinetics in infants. *Br J Anaes* 2000;**85**:205-10.
30. Miles WM, Heger JJ, Minardo JD, Klein LS, Prystowsky EN, Zipes DP. The

electrophysiologic effects of enoximone in patients with preexisting ventricular tachyarrhythmias. *Am Heart J* 1989;**117**(1):112-21.
31. Chatterjee K, Kereiakes D, Viquerat C, Podolin R. Potential mechanisms of improved left ventricular function with enoximone in severe congestive heart failure. *Am J Cardiol* 1987;**60**:37C-41C.
32. Erbel R, Meyer J, Diefenbach C *et al*. A dose-response study of intravenous enoximone in congestive heart failure. *Am J Cardiol* 1987;**59**: 31C-36C.
33. Installe E, Gonzalez M, Jacquemart JL *et al*. Comparative effects on hemodynamics of enoximone (MDL 17,043), dobutamine and nitroprusside in severe congestive heart failure. *Am J Cardiol* 1987;**60**:46C-52C.
34. Uretsky BF, Generalovich T, Verbalis JG, Valdes AM, Reddy PS. Comparative hemodynamic and hormonal response of enoximone and dobutamine in severe congestive heart failure. *Am J Cardio*l 1986;**58**: 110-16.
35. Monrad ES, McKay RG, Baim DS *et al*. Improvements in indexes of diastolic performance with phosphodiesterase inhibition in congestive heart failure. *J Lab Clin Med* 1989:**114**;266-71.
36. Maskin CS, Weber KT, Janicki JS. Long-term enoximone therapy in chronic cardiac failure. *Am J Cardiol* 1987;**60**:63C-67C.
37. Scriven AJI, Lipkin DP, Anand IS, Sutton GC, Poole-Wilson PA. Comparison of hemodynamic effects of one-month oral captopril and enoximone treatment for severe congestive heart failure. *Am J Cardiol* 1987;**60**:68C-71C.
38. Treese N, Erbel R, Pilcher J *et al*. Long-term treatment with oral enoximone for chronic congestive heart failure: the European experience. *Am J Cardiol* 1987;**60**(5):85C-90C.
39. Jondeau G, Dubourg O, Delorme G *et al*. Oral enoximone as a substitute for intravenous catecholamine support in end-stage congestive heart failure. *Eur Heart J* 1994;**15**:242-6.
40. Lee HR, Hershberger SRE, Port JD *et al.* Low dose enoximone in subjects awaiting cardiac transplantation: clinical results and effects on beta adrenergic receptors. *J Thorac Cardiovasc Surg* 1991;**102**(2):246-58.
41. Shakar SF, Abraham WT, Gilbert EM *et al*. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure (see comments). *J Am Coll Cardiol* 1998;**31**(6):1336-40.