

Enoximone Therapy as Pharmacological Bridging to Cardiac Transplantation

Jai-Wun Park, Jost H. Wirtz, Erik May, Stephan Mertens
Peter Braun, Rainer Heinzler, Roland Hetzer¹
Chang-Soon Kang² and Karl W. Heinrich

Keeping pre-transplant patients alive while waiting for a suitable donor is still a major challenge. New pharmacological agents which can provide improved hemodynamics are urgently needed in patients with severe heart failure who are on the waiting list for cardiac transplantation. Intravenous enoximone therapy (an initial 0.5 mg/kg bolus, then 1.25-5.0 mcg/kg/min infusion) was administered to 35 transplant candidates with progressive heart failure despite optimal drug regimen including digoxin, diuretics, and ACE-inhibitors. In 18 out of 35 patients complete hemodynamic, echocardiographic, neurohumoral, and Holter-ECG studies were performed before and 24 hours after intravenous enoximone infusion. Patients were then continued on chronic oral therapy of 100 mg twice a day. Enoximone infusion increased the cardiac index (CI) (1.78 ± 0.45 l/min/m² vs 3.04 ± 0.83 l/min/m²; $p < 0.001$) and stroke volume index (SVI) (22.33 ± 9.45 ml/m² vs 32.28 ± 7.29 ml/m²; $p < 0.05$) and decreased wedge pressure (PCP) (24.1 ± 11.98 mmHg vs 17.78 ± 8.76 mmHg; $p < 0.05$) while mean arterial pressure (MAP) was unchanged. Left ventricular ejection time (LVET) (225.1 ± 26.9 ms vs 242.2 ± 25.8 ms; $p < 0.05$) was increased whereas other echocardiographic parameters were unchanged (Left ventricular end-diastolic dimension LVEDD, left ventricular end-systolic dimension LVESD, fractional shortening FS, early diastolic relaxation parameter Te). Plasma neurohumoral parameters did not change (Aldosterone, epinephrine, renin, atrial natriuretic factor) except for a significant drop in norepinephrine (936.7 ± 443.2 pg/ml vs 522.4 ± 287.6 pg/ml; $p < 0.05$). Holter-ECG parameters (ventricular premature beats VPB, couplets, ventricular tachycardia VT) were not influenced by enoximone infusion. During the mean follow-up time of 11.9 weeks 4 out of 35 patients died due to progressive heart failure, 4 patients died of sudden cardiac death, and 6 patients were successfully transplanted. In our study of pre-transplant patients intravenous and oral enoximone therapy improved the acute hemodynamic status, so that transplant surgery could be postponed or performed on an elective basis. Nevertheless the definite role of oral low dose enoximone including its potentially harmful proarrhythmic action remains to be elucidated.

Key Words: Enoximone, cardiac transplantation

The only reliable treatment to definitively influence the natural history of end-stage

congestive heart failure is heart transplantation. In most centers the mortality on the waiting list exceeds the mortality in the first year post transplant due to donor organ shortage. The CONSENSUS-Study (1987) demonstrated that the ACE-inhibitor, enalapril, can significantly reduce mortality in New York Heart Association functional class IV patients (The CONSENSUS Trial Study Group 1987), but even in the enalapril group

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Department of Heart Institute Duisburg KWK, German Heart Institute Berlin¹, FRG and Chung-Ang University², Seoul, Korea

Address reprint requests to J-W Park, Department of Heart Institute Duisburg KWK, FRG

the mortality was more than 30% at one year. Therefore keeping pretransplant patients alive while waiting for a suitable donor is still a major challenge and optimal strategies including new therapeutic alternatives for bridging need to be developed. In severe heart failure refractory to conventional medical therapy including digoxin, diuretics, and ACE-inhibitors enoximone, a phosphodiesterase inhibitor with vasodilator and positive inotropic activities might be of value. Symptomatic and hemodynamic improvement due to short-term intravenous or oral application have been described (Neuzner *et al.* 1991; Friedel *et al.* 1991; Leier *et al.* 1987; Uretsky *et al.* 1983), but the value of long-term use is still controversial (Treese *et al.* 1989; Dubourg *et al.* 1990; Shah *et al.* 1985; Leier *et al.* 1989; Narahara *et al.* 1991; Uretsky *et al.* 1990; Schleman *et al.* 1991). The aim of this prospective trial in pre-transplant patients was to study the short-term effects of intravenous enoximone infusion on hemodynamic, echocardiographic, neurohumoral, and Holter-ECG findings and to assess the benefit in these patients when enoximone therapy was continued orally.

METHODS

Patients

Patients older than 18 years of age and listed as candidates for heart transplantation were considered for enoximone therapy if progression of congestive heart failure was evident despite optimal conventional drug regimen including digoxin, diuretics and an ACE-inhibitor. Patients with a left ventricular ejection fraction of less than 25% were hospitalized and kept in bed for several days. After this period a hemodynamic evaluation was performed. In cases with a cardiac index below 2.5, l/min/qm intravenous enoximone therapy was started. If the cardiac index increased at least 30% after 24 hours of enoximone infusion, enoximone therapy was continued orally. In these patients digoxin therapy was stopped except in cases of tachyarrhythmia.

Hemodynamic study

Hemodynamic measurements were performed before and during intravenous enoximone infusion. A Swan-Ganz-thermodilution balloon catheter 7F was used for registration of wedge pressure. The cardiac output was measured by the thermodilution method by bolus injection of 10 ml cold saline. Heart rate was registered by continuous ECG-monitoring, arterial blood pressure by pressure-sensor in the radial artery. Mean arterial pressure (MAP), the cardiac index (CI), the stroke volume index (SVI), and systemic vascular resistance (SVR) were calculated.

Echocardiographic study

Echocardiographic examination was performed before and 24 hours after the beginning of intravenous enoximone infusion by one experienced observer with a Toshiba Sonolayer SSH 160A and a 2.5 MHz probe. The M-mode output was displayed on a strip chart recorder at a paper speed of 100 mm/sec along with an electrocardiogram. The subjects were studied in the left lateral position. Left ventricular echocardiograms were recorded at the level of the free edges of the mitral valve leaflets. The echocardiograms were digitized by two observers with a hand-controlled crosswire cursor according to a computerized method. These data were processed by a computer (IBM AT 02) (Park *et al.* 1988). Left ventricular end-diastolic (LV-EDD) and end-systolic (LVESD) dimensions were measured according to the recommendations of the American Society of Echocardiography (Sahn *et al.* 1972), and the fractional shortening was calculated by following the formula:

$$\frac{\text{LVEDD} - \text{LVESD}}{\text{LVEDD}} \times 100 \%$$

Left ventricular ejection time (LVET) was measured as the time interval between aortic valve opening and closure. The early diastolic relaxation parameter (Te) was derived from the posterior wall endocardium line. Te is the time interval between maximal posterior wall contraction and maximal posterior wall endocardium backward movement velocity. Te is described in detail elsewhere (Park *et*

al. 1988; Park *et al.* 1989). Te was calculated as the mean of 3 consecutive heart cycles.

Neurohumoral study

The blood samples for neurohumoral studies were taken one hour after Swan-Ganz-catheter placement and at the end of 24 hours enoximone infusion. Collection time was 8 a.m. Radioimmunoassays were used for measurements of aldosterone (Aldosteron-RIA, Biermann GmbH, Bad Nauheim), epinephrine (Adrenalin 125-J RIA, DRG Instruments GmbH, Marburg), norepinephrine (Noradrenalin 125-J RIA, DRG Instruments GmbH, Marburg), renin (Renin IRMA Pasteur, Laboserv, Gie en), and atrial natriuretic factor (125-J ANP, IBL, Hamburg)(Manz *et al.* 1990). The reference range of healthy volunteers are given by the producers as follow: aldosterone 12-150 pg/ml, epinephrine 15-70 pg/ml, norepinephrine 150-450 pg/ml, renin 5-29 pg/ml, ANF 25-111 pg/ml.

Holter-ECG study

A 24 hour holter-ECG recording was performed before enoximone therapy and during enoximone infusion using an Oxford Medilog 4500 System. Only tapes with a recording length of 22±2 hours were used for further analysis. Ventricular premature beats (VPB/24 hours), ventricular pairs (couplets/24 hours), and ventricular tachycardia events (VT/24 hours) were counted. Ventricular tachycardia was defined as 3 or more consecutive complexes with a rate >100 beats/min.

Statistical analysis

The results are presented as mean±1 standard deviation. Paired Student's t-test was used to evaluate the difference. Differences were considered significant at p<0.05.

RESULTS

Study patients

35 patients met the above criteria for congestive heart failure refractory to optimal conventional drug regimen. These 35 patients consisted of 32 men and 3 women, whose ages ranged from 38 to 63 years (mean 51±6

years). Of the 35 patients, 24 had ischemic cardiomyopathy, 8 had idiopathic cardiomyopathy, and 3 had developed pump failure many years after valve replacement. The mean ejection fraction in these patients was 19%±6%, with a range of ejection fraction from 8% to 25%. The medication at the beginning of the study was as follows: All 35 patients were treated with furosemide, captopril, and digoxin. The mean furosemide dose was 215 mg (80-1500 mg) per day, captopril doses ranged from 3×6.25 mg to 3×25 mg per day. After initiation of enoximone therapy, digoxin therapy was discontinued in 27 patients. In 8 patients (23%) further digoxin therapy was necessary due to atrial fibrillations with tachyarrhythmia.

Enoximone doses

Intravenous enoximone therapy was started with a 0.5 mg/kg bolus given over 10 minutes followed by an infusion dose of 1.25-5.0 mcg/kg/min depending on cardiac index increase (mean 3.36 mcg/kg/min). The oral dose of enoximone was 100mg twice a day.

Hemodynamic, echocardiographic, neurohumoral, and holter-ECG findings

In 18 out of 35 patients complete hemodynamic, echocardiographic, neurohumoral, and Holter-ECG studies were performed before and 24 hours after intravenous enoximone therapy. The data are outlined in tables 1, 2, 3

Table 1. Hemodynamic findings

	Control	Enoximone	
HR (l/min)	87.1±18.5	96.3±21.6	n.s.
MAP (mmHg)	79.4 ±14.97	71.28±12.63	n.s.
CI (l/min/m ²)	1.78±0.45	3.04±0.83	**
SVI (ml/m ²)	22.33±9.45	32.28±7.29	*
PCP (mmHg)	24.1±11.98	17.78±8.76	*
SVR (dynxsecxcm ⁻⁵)	1700.8±555.8	952.8±384.0	**

*p<0.05 **p<0.001

HR=heart rate, MAP=mean arterial pressure
CI=cardiac index, SVI=stroke volume index,
PCP=wedge pressure

SVR=systemic vascular resistance

Enoximone : measurements 24 hours after continuous enoximone infusion

Table 2. Echocardiographic findings

	Control	Enoximone	
LVEDD (mm)	69.5±11.5	68.6±10.9	n.s.
LVESD (mm)	61.3±10.7	59.6±10.2	n.s.
FS (%)	12.1±3.6	13.1±3.9	n.s.
LVET (ms)	225.1±26.9	242.2±25.8	*
Te (ms)	79.4±14.6	72.7±14.3	n.s.

p<0.05

LVEDD=left ventricular end-diastolic dimension

LVESD=left ventricular end-systolic dimension

FS=fractional shortening

LVET=left ventricular ejection time

Te=early diastolic relaxation parameter

Enoximone: measurements 24 hours after continuous enoximone infusion

Table 3. Neurohumoral findings

	Control	Enoximone	
Aldosterone (pg/ml)	300.6±449.2	126.9±156.9	n.s.
Epinephrine (pg/ml)	111.2±54.4	84.1±38.9	n.s.
Norepinephrine (pg/ml)	936.7±443.2	522.4±287.6	*
Renin (pg/ml)	612.9±905.6	663.7±1284.3	n.s.
ANF (pg/ml)	751.5±365.3	670.7±263.8	n.s.

*p<0.05

Enoximone: measurements 24 hours after continuous enoximone infusion

and 4. There were no statistically significant changes observed for heart rate (87.1±18.5 per min vs 96.3±21.6 per min; n.s.) or mean arterial pressure (79.4±14.97 mmHg vs 71.28±12.63 mmHg; n.s.). The cardiac index significantly increased from 1.78±0.45 l/min/m² to 3.04±0.83 l/min/m² (p<0.001) and the stroke volume index increased from 22.33±9.45 ml/m² to 32.28±7.29 ml/m² (p<0.05). The pulmonary wedge pressure dropped from 24.1±11.98 mmHg to 17.78±8.76 mmHg (p<0.05) and the systemic vascular resistance from 1700.8±555.8 dynxsecxcm⁻⁵ to 952.8±384.0 dynxsecxcm⁻⁵ (p<0.001).

There were no statistically significant changes in M-mode echocardiographic parameters LVEDD (69.5±11.5 mm vs 68.6±10.9 mm; n.s.),

Table 4. Holter-ECG findings

	Control	Enoximone	
VPB	7372.0±12397.9	4853.5±6512.3	n.s.
Couplets	1007.5±1567.8	577.6±963.7	n.s.
VT	274.5±491.6	202.5±458.9	n.s.

Control: 24 hours registration before enoximone therapy

Enoximone: registration during 24 hours continuous enoximone infusion

VPB=ventricular premature beats

VT=ventricular tachycardia

LVESD (61.3±10.7 mm vs 59.6±10.2 mm;n.s.), FS (12.1±3.6 % vs 13.1±3.9%; n.s.) or early diastolic relaxation parameter Te (79.4±14.6 ms vs 72.7±14.3 ms; n.s.). LVET was significantly increased from 225.1±26.9 ms to 242.2±25.8 ms (p<0.05).

There were no statistically significant changes in plasma aldosterone (300.6±449.2 pg/ml vs 126.9±156.9 pg/ml; n.s.), epinephrine (111.2±54.4 pg/ml vs 84.1±38.9 pg/ml; n.s.), or renin (612.9±905.6 pg/ml vs 663.7±1284.3 pg/ml; n.s.). Norepinephrine significantly decreased from 936.7±443.2 pg/ml to 522.4±287.6 pg/ml (p<0.05).

There were no statistically significant changes for premature ventricular beats (7372.0±12397.9 vs 4853.5±6512.3; n.s.), couplets (1007.5±1567.8 vs 577.6±963.7; n.s.) or ventricular tachycardia events (274.5±491.6 vs 202.5±458.9; n.s.).

Clinical response to enoximone therapy and patients follow-up (mean 11.9 weeks) (fig. 1)

At the beginning of the study 11 patients were NYHA functional class III and 24 patients were NYHA functional class IV. After 24 hours of intravenous enoximone therapy 10 out of 11 NYHA class III patients remained in class III. In the follow-up period on oral enoximone medication 7 out of these 10 patients were alive waiting for transplant surgery, one patient was transplanted successfully and 2 patients died of sudden cardiac death. One patient improved to NYHA class II and remained stable on follow up and was, therefore, removed from the transplant waiting list.

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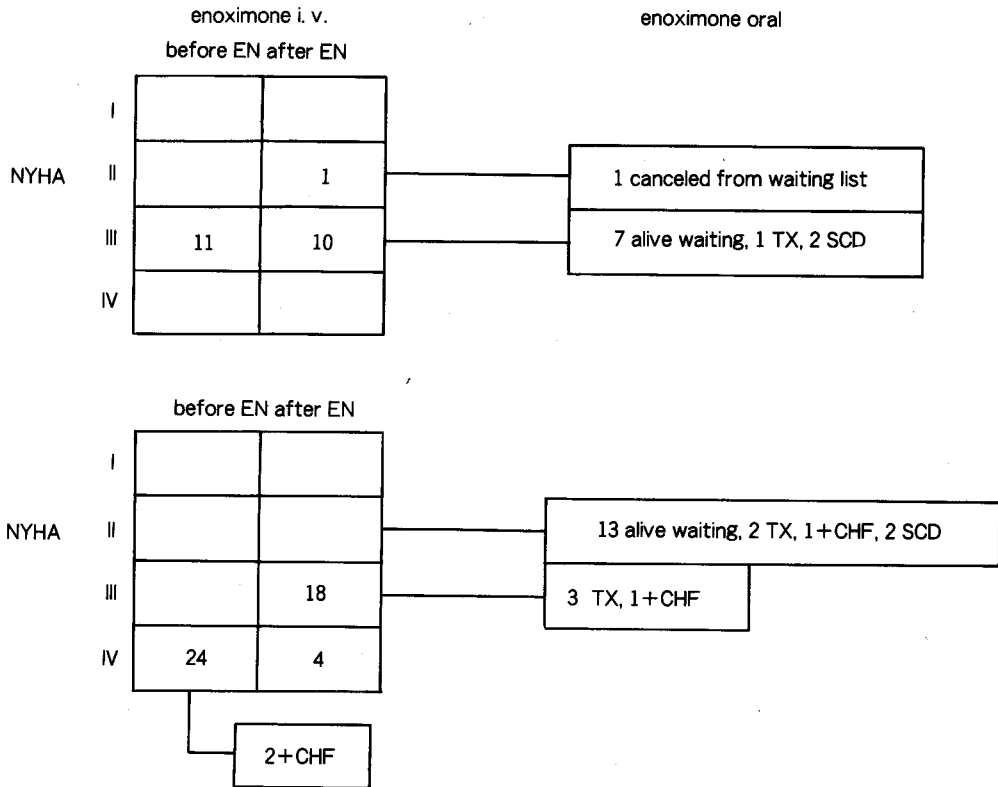


Fig. 1. Clinical response to enoximone therapy and patients follow-up (mean 11.9 weeks) EN=enoximone, CHF=congestive heart failure, SCD=sudden cardiac death, TX=transplantation

Two out of the 24 patients in NYHA class IV died during enoximone infusion due to progressive heart failure. Eighteen patients improved to NYHA class III, and 4 patients remained in NYHA class IV. In the follow-up period on oral enoximone, 13 out of these patients remained alive waiting for a donor organ, 2 patients were successfully transplanted, 1 patient died due to progressive heart failure, and 2 patients died of sudden cardiac death. Out of 4 patients remaining in NYHA class IV, 3 were successfully transplanted and 1 patient died due to progressive heart failure. While 11 of the 24 (46%) patients in NYHA class IV have died or were transplanted during the study period, only 3 out of 11 (27%) patients in NYHA class III have died or required transplantation.

DISCUSSION

This study shows that intravenous and oral enoximone achieves clinical improvement and hemodynamic stability in pre-transplant patients with progressive heart failure refractory to digoxin, diuretics, and ACE-inhibitors. Although 2 patients died despite intravenous enoximone infusion due to progressive heart failure, the remaining 33 patients (94%) could be hemodynamically stabilized. Six patients (17%) were successfully transplanted. The overall survival rate during the mean follow-up time of 11.9 weeks was 77%. Hemodynamic stability enabled patients to be discharged from the hospital and to be transplanted without the increased risk of unstable hemodynamics.

Short-term effects of intravenous enoximone infusion

We found a similar improvement in hemodynamic parameters as described by several previous groups (Neuzner *et al.* 1991; Friedel *et al.* 1991; Uretsky *et al.* 1983; Kereiakes *et al.* 1984; Martin *et al.* 1984; Amin *et al.* 1984; Weber *et al.* 1986): The cardiac index and systemic vascular resistance were decreased. No significant influence on arterial blood pressure or heart rate was noted. In this study, improvement was achieved with a low loading dose of 0.5 mg/kg enoximone followed by a low maintenance dose of 1.25-5.0 mcg/kg/minute. These doses are lower than those quoted in the literature. In our experience lower doses were well tolerated and did not produce arrhythmias. At higher doses such as 2 mg/kg arrhythmias have been noted (Bristow *et al.* 1990; Bristow *et al.* 1988).

Echocardiographic findings

The M-mode echocardiographic parameters used in this study show good reproducibility (Park *et al.* 1988; Park *et al.* 1989). After 24 hours of enoximone infusion left ventricular dimension, fractional shortening and the early diastolic relaxation parameter T_e were unchanged. Left ventricular ejection time was significantly increased due to stroke volume increases.

Neurohumoral findings

In this study the hemodynamic improvement was paralleled by a decrease in norepinephrine. The high baseline plasma levels of norepinephrine reflected an advanced state of heart failure. This was similar to the results of Cohn and coworkers (1984) who found plasma-norepinephrine concentration to be an independent predictor of mortality in patients with severe heart failure. There were no statistically significant changes observed in other neurohormones due to very high measurement mean variations. It should be mentioned that, in these very sick patients the sodium intake was not standardized and the amount and duration of diuretic therapy was variable. Therefore the renin and aldosterone results should be reviewed with caution.

Holter-ECG findings

Malignant arrhythmias are a common problem in end-stage congestive heart failure. Any judgement about the proarrhythmic effect of enoximone in this patient group should be made cautiously, because in severe congestive heart failure there are many factors contributing to arrhythmia. We were concerned about a potential drug interaction between enoximone and digoxin.

For this reason we discontinued digoxin therapy in most cases. In the remaining 8 patients digoxin was continued to control pre-existing atrial fibrillations with tachyarrhythmia. In this study, the amount of ventricular arrhythmia was statistically unchanged during 24 hours of intravenous enoximone infusion, but in several patients we had strong evidence that clinical improvement was paralleled by a decrease in arrhythmia quantity. Conditions of cardiogenic shock in itself is associated with malignant arrhythmias. Achieving hemodynamic stability can reduce malignant arrhythmias in this setting. Arrhythmias associated with hemodynamic instability have to be differentiated from arrhythmias occurring during hemodynamically stable phases. In this study 4 patients died of sudden cardiac death during the follow-up on oral enoximone therapy. Two of these patients were also treated with amiodarone because of a previous history of symptomatic arrhythmias.

Several studies (Likhoff *et al.* 1985; Massie *et al.* 1985; Packer *et al.* 1984; Packer *et al.* 1991) have reported that long-term therapy with phosphodiesterase inhibitors like milrinone or amrinone can enhance the frequency and complexity of ventricular arrhythmias, provoke myocardial ischemia, and accelerate progression of the underlying disease. One possible explanation to explain the harmfulness of milrinone therapy is that the decline in myocardial cyclic AMP has an adaptive role in chronic heart failure. Therefore the enhancement of myocardial cyclic AMP in the failing heart by phosphodiesterase inhibitors may accelerate the progression of the heart disease (Packer *et al.* 1991; Packer *et al.* 1990; Packer *et al.* 1990). In a multicenter double-blind trial of oral eno-

ximone by Uretsky and coworkers (1990), a higher mortality was unexpectedly found in the enoximone group at the end of 16 weeks. However the study was not designed as a mortality trial and the differences may have occurred solely by chance. Furthermore, the study was carried out in patients with mild-to-moderate heart failure who were not on ACE-inhibitors. The patients who are most likely to require this type of drug are those with severe heart failure (Packer *et al.* 1991; Packer *et al.* 1989), not mild to moderate congestive heart failure. A critical point regarding the safety outcome in this study is the dose of enoximone used. Uretsky and coworkers used 300-450 mg per day. In contrast, our patients were treated with 200 mg per day. If we generalize the negative results of the milrinone trial (Packer *et al.* 1991) to other phosphodiesterase inhibitors, long-term therapy with oral enoximone will increase the mortality of patients with severe end-stage congestive heart failure. In the short-term management of patients awaiting cardiac transplantation, oral low dose enoximone may be a useful adjunct and may reduce episodes of hemodynamic destabilization requiring intravenous inotropic therapy. Nevertheless the definite role of oral low dose enoximone including its potentially harmful proarrhythmic action remains to be elucidated.

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