Patterns of Response to Intravenous Enoximone

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SUMMARY: The cases of four male patients with severe cardiac failure due to ischaemic heart disease are presented. They were selected on the basis of their wide variation in response to the intravenous administration of enoximone, an haemodynamic stimulant licensed recently. They serve to emphasize the need for close haemodynamic and electrocardiographic monitoring in a unit with appropriate facilities for remedial action if adverse responses occur when this drug is employed.

Introduction

Enoximone is a drug with inotropic and vasodilating properties. Available evidence suggests that these effects result from increased intracellular cyclic adenosine monophosphate (cAMP) concentration which is produced by inhibition of a specific isoenzyme of phosphodiesterase(1). It has been licensed recently solely for intravenous use. The cardiovascular effects of this drug when administered both intravenously and orally have been the subject of two symposia(2,3). In these publications and in the literature of the manufacturer, it is the mean cardiovascular response that is emphasized. This is reported to be an increase in cardiac index due to an increased stroke index associated with a balanced decrease in systemic vascular resistance. In consequence, no statistically significant changes in mean heart rate or systemic blood pressure are said to occur. However, recent personal experience suggests that a cautious approach is fully vindicated when enoximone is used. The purpose of this paper is to report the wide variation in the responses of individual patients to this drug so that its intravenous administration is monitored carefully and that appropriate facilities for remedial action are available if an aberrant response should occur.

Patients and Methods

All four male patients who are the subject of this report had cardiac failure (cardiac index < 3.0 L/min/m²) due to ischaemic heart disease. Each had additional complicating conditions the details of which are shown in Table 1. For three of these patients (cases 1, 2 and 4), cardiac failure was chronic, advanced and impossible to improve further with diuretics and vasodilators without precipitating pre-renal failure. In the remaining patient (case 3), a mild degree of impaired cardiac reserve was worsened acutely by a myocardial infarction and was not improved by thrombolytic therapy with streptokinase. Antecedent renal disease, possibly hypertensive nephropathy, lowered the threshold for development of pre-renal failure in this case which it was not possible to improve with diuretics and vasodilators.

Each of these patients was refractory to standard

treatment for cardiac failure and it was felt that a trial of treatment with enoximone could be appropriate provided haemodynamic monitoring was undertaken before, during and after administration of this drug.

Haemodynamic Monitoring Methods

With the exception of the first patient (case 1), right heart catheterization via a central vein was undertaken using a pulmonary artery flotation catheter which was inserted in standard fashion and advanced to the wedged position so that the adequacy of left ventricular filling pressure could be assessed before administering enoximone. Cardiac index was estimated by thermodilution (TD) using an American Edwards COM-2 cardiac output computer. The mean of six measurements with a coefficient of variation of less than 10% was employed on each occasion and from this value mean systemic vascular resistance index was derived (see below). Systemic arterial blood pressure was monitored by a teflon cannula inserted into the radial or brachial artery. Central venous pressure was monitored employing a saline manometer and pressure values were converted to mm Hg.

Haemodynamic monitoring of the first patient (case 1) was non-invasive. Cardiac index was estimated by thoracic electrical bioimpedance (TEB) employing a NCCOM3 monitor (BoMed Medical Manufacturing Ltd., Irvine, California). Systemic arterial blood pressure was estimated employing a semi-automated, calibrated sphygmomanometer (COPAL UA-251). Clinical observation of jugular venous pressure showed this remained unchanged. Several reports have indicated that when cardiac index is estimated simultaneously by TEB and TD in the same patients, similar values are obtained(4-9). Moreover, a recent critical and authoritative review of all the clinical methods available to estimate cardiac output suggested that the general opinion was that TEB may be a better indicator of change in cardiac index than of absolute values(10). This capability was ideal for the present monitoring purposes.

Table 1
Case details of four male patients treated with enoximone

Case No.	Initials	Age (Yrs)	Race	Cardiac Diagnosis	NYHA Class	Other Diagnoses	Cardiac Rhythm	Pre-Renal Failure	Additional Medication	Enoximone dosage between 1st & 2nd Haemodynamic Assessment	Duration of Enoximone Therapy before 2nd Haemodynamic Assessment
1	GS	71	C	IHD (MI- 11 Yrs CHF- 6½ Yrs)	IV	HT- 20 Yrs	AF	+	Frusemide 120 mg o.m. Digoxin 0.125 mg o.m. Captopril 12.5 mg o.m. Spironolactone 25 mg t.d.s. Isoprenaline 45 mg t.d.s.	6 ug/kg/min for 24 hours	24 hrs
2	BT	62	C	IHD- 9 Yrs (MI- 5 Yrs CABG- 4 Yrs CHF- 1Yr)	IV	HT- 9 Yrs PVD- 9 Yrs ASTHMA- 60 Yrs	AF & occasional VE's	+	Frusemide 40 mg + Amiloride 5 mg, 3 tabs o.m. Digoxin 0.125 mg o.m. Prednisolone 20 mg o.m. Aspirin 75 mg o.m. Lactulose 10 ml b.d.	3 x 0.5 mg/kg bolus IV. + 7.5 ug/kg/min for 24 hrs + 5 ug/kg/min for 41 hrs	72 hours
3	AD	65	N	IHD- 9 Yrs (AMI- 8 Days LVF- 8 Days)	II (marked worsening 2° to Acute LVF)	HT- 13 Yrs CB Yaws UTI Gout - 8 Yrs CRF- 13 Yrs	SR	+	Allopurinol 100 mg o.m. Heparin 5000u s.c. b.d. Nifedipine SR 40 mg b.d. Temazepam 20 mg nocte Trimethoprim 200 mg b.d. Lactulose 15 mls b.d.	1 x 0.5 mg/kg bolus IV.	0.5 hr
4	RS	58	C	IHD- 3 Yrs (MI- 3Yrs CHF- 3 Yrs)	III	MVD (Mild) T.HYPOT 6 Yrs	AF	-	Frusemide 40 mg + Amiloride 5 mg, 1 tab o.m. Digoxin 0.25 mg o.m. Captopril 25 mg b.d. Thyroxine 250 mcg o.m. Isosorbide Mono-nitrate SR 50 mg o.m. Temazepam 10 mg nocte	1 x 0.5 mg/kg bolus IV. + 1 x 1.0 mg/kg bolus IV.	2.5 hrs

AF: Atrial fibrillation. AMI: Acute myocardial infarction. C: Caucasian. CABG: Coronary Artery bypass graft. CB: Chronic bronchitis. CHF: Congestive heart failure. HT: Hypertension. IHD: Ischaemic heart disease. MI: Myocardial Infarction (previous). MVD: Mitral valve disease. N: Negro. PVD: Peripheral vascular disease. Pre-renal failure: serum creatinine 180 uM/L or a doubling of admission value associated with worsening cardiac failure. SR: Sinus rhythm. T.HYPOT: Treated hypothyroidism. UTI: Urinary tract infection. VE's: Ventricular ectopic beats.

Calculations

$$\text{MAP} = 1/3 (\text{SBP} - \text{DBP}) + \text{DBP}$$

where, MAP = mean arterial pressure (mm Hg)

SBP = systolic arterial blood pressure (mm Hg)

DBP = diastolic arterial blood pressure (mm Hg)

For TEB (case 1 only)

$$\text{SVRI} = \frac{\text{MAP} \times 80}{\text{CI}}$$

where SVRI = systemic vascular resistance index
(dynes.sec/cm⁵/m²)

CI = cardiac index (l/min/m²)

For TD (cases 2, 3 and 4)

$$\text{SVRI} = \frac{(\text{MAP} - \text{CVP}) \times 80}{\text{CI}}$$

where CVP = central venous pressure (mm Hg)

Timing of Haemodynamic Recording

In each case, an haemodynamic assessment was completed before and after administration of enoximone. The time interval between haemodynamic studies varied from case to case as indicated in the Table. The timing of the second study was dependent mainly on the total dose of enoximone necessary to produce a maximal effect.

Results

The values of haemodynamic variables before and after administration of enoximone are shown in Figure 1. In case 1, the haemodynamic effect was that expected. Cardiac index increased as a result of an increased stroke index whilst systemic vascular resistance index fell. In consequence, systemic arterial blood pressure and heart rate changed little.

In case 2, cardiac index increased primarily as a result of increased heart rate. Although ventricular ectopic beats were present before enoximone was administered, this drug caused a marked increase in frequency of those ectopic beats. However, this arrhythmia did not prevent the increase in cardiac index, fall in central venous pressure and fall in pulmonary artery wedge pressure but a reduction in enoximone infusion rate from 7.5 ug/kg/min to 5 ug/kg/min was necessary to reduce the frequency of ventricular ectopic beats to a safer level. Systemic arterial blood pressure increased indicating that systemic vascular resistance index was unchanged.

Cardiac index did not change in case 3 as a rise in heart rate was exactly balanced by a fall in stroke volume index. However, the vasodilator effect of enoximone was apparent. Systemic arterial blood pressure fell rapidly necessitating prompt infusion of one litre of saline to avert disaster.

Unlike all other patients where clinically significant

change occurred in the value of several haemodynamic variables, the only change which was recorded in the last patient (case 4) was a fall in central venous pressure.

Independent of haemodynamic response, all patients became drowsy during the administration of enoximone. Additionally, the first patient (case 1) became disorientated. There was a marked diuretic response in the case of the second patient (case 2) whose daily urine volume increased three-fold (data not shown). This response was not seen in the other patients.

Discussion

The primary treatment of cardiac failure is elimination of the cause. When this is not possible or does not result in improved cardiac function then non-specific medical treatment is employed. Diuretics and vasodilators both relieve symptoms due to pulmonary congestion; the former by reducing circulating volume and the latter by increasing cardiac output as a result of reducing peripheral resistance. The dosage of both classes of drug is limited by a fall in peripheral circulation, most especially to the kidneys. Both treatment strategies are compensatory as they fail to correct the more fundamental problem of diminished effective cardiac contractility. Until recently, digoxin has been the only oral drug available with activity, albeit weak, to improve impaired myocardial contractility(11,12). This situation could change if the favourable reports concerning new intravenous inotropic drugs, with the potential for oral formulation, are confirmed. However, the present observations cast doubt on the predictability of the response to enoximone when administered intravenously. It is suggested, therefore, that a more cautious approach to the continued use of this drug should be adopted.

As this report is concerned solely with the response to intravenous enoximone, no reference will be made to those studies where the drug has been administered orally. Chatterjee(13) reviewed the results obtained when enoximone was given intravenously to 24 patients with advanced (NYHA Class III-IV) chronic congestive heart failure (CHF). Apart from the variation in change of left ventricular end-diastolic volume observed in this group of patients, no comment was made about variation in patient responsiveness in other haemodynamic respects. Increase in cardiac index, mainly due to increased stroke volume index, with little or no change in heart rate or blood pressure, signifying decreased systemic vascular resistance, is presented as the virtually constant response. No reference was made to adverse effects. By contrast Okerholm *et al*(14), whilst giving no further details, remarked in a pharmacokinetic study that the magnitude of haemodynamic responses differed considerably amongst 6 patients with NYHA Class III-IV chronic CHF.

Fig 1. Haemodynamic responses to intravenous enoximone in four patients.

CI: Cardiac Index. CVP: Central Venous Pressure. HR: Heart Rate. MAP: Mean systemic arterial pressure. N.D.: Not done.

PAWP: Pulmonary Artery Wedged Pressure. SI: Stroke Index. SVRI: Systemic Vascular Resistance Index. ●: value before enoximone.

x: value after enoximone.

In terms of haemodynamic change, the first patient (case 1) responded as expected but also became disorientated. This side effect related to enoximone administration was described by the same group of workers in two separate studies where one of 10 patients(15) and one of 15 patients(16) were affected similarly. No report has commented on the consistent occurrence of drowsiness during enoximone administration as has been observed with the present patients.

No reports of an increased cardiac index virtually solely due to an increase in heart rate as seen in the second patient (case 2) have been found. Similarly, the co-incident lack of vasodilation in these circumstances appears unique. Worsening of ventricular arrhythmia due to enoximone as seen in this patient has not been described.

Khalife *et al*(17) in a study of 17 patients found that enoximone did not worsen a pre-existent ventricular arrhythmia which was present in five of these patients. Several workers have reported that enoximone can precipitate ventricular and supraventricular arrhythmias in up to 20% of patients with CHF(15,17–20) and this may be dose related.

The fairly rapid onset of hypotension following enoximone administration to the third patient (case 3)

has been described before but has not been emphasized as an adverse effect to beware. Crawford(19) observed hypotension after enoximone in 3 (2.5%) of 119 patients with CHF whilst in 12 patients with idiopathic dilated cardiomyopathy studied by Heiss *et al*(21), enoximone caused a 28% fall in mean arterial pressure. In this group, stroke index either remained unchanged or fell and heart rate increased such that there was no significant change in cardiac index, a very similar situation to that seen in case 3. While Heiss *et al*(21) did not mention whether rapid remedial infusion of volume-expanding fluid was necessary, Boldt *et al*(22) reported that this was required for 4 of 6 patients who responded to enoximone given for inotropic support when weaning from extra-corporeal circulation following CABG surgery. In relation to the administration of enoximone in the early period following myocardial infarction as was necessary in case 3, Renard *et al*(20) did not report hypotension in eleven patients given enoximone for acute left ventricular failure complicating recent myocardial infarction. It should be noted that in case 3, the left ventricular filling pressure as indicated by pulmonary artery wedged pressure (17 mm Hg) was adequate before enoximone was given.

The failure of haemodynamic response to intravenous

enoximone as seen in the fourth patient (case 4) has occurred in some patients in the majority of studies and can be related to both severity of cardiac disease(23) and the dose of enoximone given(19). It was decided not to give further doses of enoximone to case 4 as although no clinically significant haemodynamic response occurred, the patient became very drowsy indeed. This effect gradually resolved spontaneously. In view of a previous report which suggested that prior administration of diazoxide inhibits the effects of enoximone(24), it is important to mention that diazoxide had not been given to this patient.

This report has demonstrated that intravenous enoximone can precipitate widely-varying haemodynamic responses, some of which are potentially dangerous. It is suggested that, at present, this variability of response is emphasized inadequately. These observations endorse the recommendations of the manufacturer that intravenous enoximone should be given only when systemic arterial blood pressure, central venous pressure and electrocardiogram are closely monitored. However, it is believed that the present observations provide sufficient grounds for an even more cautious approach as suggested by Latimer(25). He questioned seriously the wisdom of using intravenous enoximone in circumstances other than those where the patient was in the intensive care unit with the means to monitor cardiac output. This would appear to be sound advice.

REFERENCES

1. Editorial. Enoximone *Lancet* 1988; **i**: 1085-1086.
2. WEBER K T, Editor. A symposium: The use of enoximone in heart failure. *Am J Cardiol* 1987; **60**: 1c-90c.
3. BRISTOW M R, CHATTERJEE K, LATIMER R D, (Editors). Enoximone in intensive care. *Br J Clin Pract* 1988; **42**: Symposium Supplement 64.
4. MATTAR J A, BURUZZI A C A, DIAMANT D, *et al.* A clinical comparison between cardiac output measured by thermodilution versus non-invasive thoracic electrical bioimpedance. *Acute Care* 1986; **12**: 58-60.
5. APPEL P L, KRAM H B, MACKABEE J, FLEMING A W, SHOEMAKER W C. Comparison of measurement of cardiac output by bioimpedance and thermodilution in severely ill surgical patients. *Crit Care Med* 1986; **14**: 933-935.
6. SPINALE F, REINES H D, CRAWFORD F A. Electrical bioimpedance as a method for continuous non-invasive estimation of cardiac output: experimental and clinical studies. *Crit Care Med* 1987; **15**: 304.
7. SHELLOCK G, JAKUBOWSKI A. Measurement of cardiac output in critically ill patients by a new non-invasive bioimpedance system: comparison with the thermodilution method. *Physiologist* 1987; **30**: 215.
8. WONG D H, TREMPER K K, STEMMER E A, JACCARI J. Non-invasive cardiac output: two measurement methods compared with thermodilution and the importance of measured heart rate and ejection time. *Anesth Analg* 1988; **67**: (Suppl): S262.
9. SALANDIN V, ZUSSA C, RISICA G, *et al.* Comparison of cardiac output estimation by thoracic electrical bioimpedance, thermodilution and Fick methods. *Crit Care Med* 1988; **16**: 1157-1158.
10. Editorial. Measurement of cardiac output. *Lancet* 1988; **ii**: 257-258.
11. The German and Austrian Xamaterol Study Group. Double-blind placebo-controlled comparison of digoxin and xamaterol in chronic heart failure. *Lancet* 1988; **i**: 489-493.
12. The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with Captopril and Digoxin in patients with mild to moderate heart failure. *J Am Med Assoc* 1988; **259**: 539-544.
13. CHATTERJEE K. Enoximone in heart failure: mechanisms of action. *Br J Clin Pract* 1988; **42**: Suppl 64 19-25.
14. OKERHOLM R A, CHAM K Y, LANG J F, THOMPSON G A, RUBERG S J. Biotransformation and pharmacokinetic overview of enoximone and its sulfoxide metabolite. *Am J Cardiol* 1987; **60**: 21c-26c.
15. INSTALLE E, GONZALEZ M, JACQUEMART J L, *et al.* Comparative effects on haemodynamics of enoximone (MDL 17,043), dobutamine and nitroprusside in severe congestive heart failure. *Am J Cardiol* 1987; **60**: 46c-52c.
16. GONZALES M, DESAGER J P, JACQUEMART J L, CHENU P, MULLER T, INSTALLE E. Efficacy of enoximone in the management of refractory low output states following cardiac surgery. *Br J Clin Pract* 1988; **42**: Suppl 64 53-64.
17. KHALIFE K, ZANNAD F, BRUNOTTE F, *et al.* Placebo controlled study of oral enoximone in congestive heart failure with initial and final intravenous haemodynamic evaluation. *Am J Cardiol* 1987; **60**: 75c-79c.
18. ERBEL R, MEYER J, DIEFENBACH C, *et al.* A dose-response study of intravenous enoximone in congestive heart failure. *Am J Cardiol* 1987; **60**: 31c-36c.
19. CRAWFORD M H. "Intravenous use of enoximone". *Am J Cardiol* 1987; **60**: 42c-45c.
20. RENARD M, DEREPE H, HENUZET C, STEVENS E, BERNARD R. Effects of enoximone in patients with cardiac failure after myocardial infarction. *Br J Clin Pract* 1988; **42**: Suppl 64 37-40.
21. HEISS H W, HASENFUSS G, HOLUBARSCH C, MEINERTZ T, JUST H. Cardiac energetics after intravenous enoximone in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1987; **60**: 53c-56c.
22. BOLDT J, DIETRICH H A, HEMPLEMANN G. Comparison of haemodynamic efficacy of enoximone and dobutamine in coronary surgery patients. *Br J Clin Pract* 1988; **42**: Suppl 64 41-45.
23. DUBOIS-RANDE J L, LOISANCE D, DUVAL A M, *et al.* Enoximone, a pharmacological bridge to transplantation. *Br J Clin Pract* 1988; **42**: Suppl 64 73-79.
24. ODURO A, LATIMER R D, DAVIES A, JANI K. Effects of enoximone in patients with low ejection fraction undergoing coronary artery bypass graft surgery *Br J Clin Pract* 1988; **42**: Suppl 64 50-52.
25. LATIMER R D. Comment during panel discussion, *Br J Clin Pract* 1988; **42**: Suppl 64 86.