THE STUDY OF THE EFFECT OF ENOXIMONE - A PHOSPHODIESTERASE TYPE III INHIBITOR-VERSUS ADRENALINE IN CASES OF ACUTE MYOCARDIAL INFARCTION IN AN EXPERIMENTAL CAT MODEL

ABSTRACT

Introduction: Nowadays, many authors recommend early surgical intervention to treat myocardial infarction as it usually leads to proper myocardial salvage.

Objective: This study was done to evaluate and compare the hemodynamic effects of Enoximone versus Adrenaline in an experimental model of acute myocardial infarction in cats.

Methods: The study included 20 cats (males and non-pregnant female cats) with a mean weight of 2.7 Kg +/- 0.75. They were anesthetized using intramuscular Ketamine 1 mg/kg, then ventilated with cannulation of both femoral artery and vein. Anaesthesia was maintained with Ketamine as intravenous shots of 0.3 mg. Through a left anterolateral thoracotomy the heart was exposed so as to fix a CVP and Pulmonary artery cannulae and to prepare a Homonymous Coronary Artery snare (equivalent to the LAD vessel in humans). Measurement of pulse rate, ST segment analysis, systolic, diastolic, mean arterial blood pressures, CVP, PAP were taken as baseline data, before, on and after coronary occlusion.

Results: All animals exhibited major hemodynamic derangement upon clamping of the homonymous coronary artery and two died out of serious myocardial infarction. Enoximone group showed restoration of the hemodynamics toward the baseline data and gradual decrease of the ST segment elevation. Adrenaline group showed restoration of the Blood pressure values; however, pulmonary artery pressure and ST segment analysis showed no appreciable drop.

Conclusion: Enoximone exhibited better hemodynamic effects in the restoration of the deranged hemodynamic status caused by acute MI in cats rather than adrenaline.

INTRODUCTION

There is an increased enthusiasm, nowadays, toward the surgical intervention in acute stages of myocardial infarction (1). Far more are dealing with acute complications of Percutaneous transluminal Coronary Angioplasty (PTCA), including

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Coronary occlusion, dissection, spasm, embolism, perforation or frank myocardial infarction (MI) (2), (3).

Coronary artery Bypass Graft (CABG) in the early stages of myocardial infarction was found to restore the coronary circulation and hence the viability of the cardiac muscle (4), (5).

However, these cases carry higher risks and an expeditious management is critical (7), (8): increased myocardial irritability with increased risks of cardiac dysrhythmias; (or even cardiac arrest) (9); fluctuation of the blood pressure, (10) and increased vulnerability to excessive intraoperative blood loss and postoperative bleeding caused by the wide variety of anticoagulant drugs including aspirin, heparin, and thrombolytic drugs such as streptokinase) (11), (12).

Still, the major dilemma is the depressed contractility state associated with the acute phase of the myocardial infarction and the selection of the proper inotropic support that would be able to cause inotropism without increasing the heart rate and subsequently the oxygen demand so as not to expand the ischemic or the infracted zones (6), (13).

In 1978, Bernoti and colleagues (14), declared the first clinical experience with the Bipyridine derivative, amrinone, as an alternative inotropic therapy. In 1987, Weber (15), declared the narrow therapeutic index of Amrinone. Okerholm and associates, on 1987, investigated the Biotransformation and the biological action of Enoximone as a new phosphodiesterase type III inhibitor with both inotropic and vasodilator properties (16).

We compared the effects of both Enoximone and Adrenaline as inotropics in the acute phase of MI in 20 experimental model of acute MI in cats (10 cats per group) in which induced (selective and reversible) occlusion of one of the coronary arteries was done.

Methods

This protocol was approved by the general rules of the institutional Animal Care and Use Committee. All the cats were cared for in accordance with the National Institutes of Health guide for the care and use of Laboratory animals. This study was carried out in the labs of the Pharmacology department of Kasr El Ain3T Faculty of Medicine Cairo University between March 1998 and June 1999.

Animal preparation. Cats in the range of 2.5-3.5 kg. of both sex were used in this study. Female cats were no pregnant. Cats were anesthetized while being trapped using Ketamine 1 mg/Kg intramuscularly diluted to a concentration of 1 mg/ml. As the cat loses consciousness and movement, it was fixed in the supine position by special limb braces. The neck was dissected to expose the trachea where a tracheal cannula was introduced and connected to a mechanical ventilator (Harvard apparatus Dual phase control Respiratory pump Canine, Harvard apparatus G, South Atrick, Mass). Tidal volume was adjusted at 10ml/kg with a frequency of 16-20 breath /min.

Then the right inguinal region was shaved, dissected to expose the right femoral artery and vein. With a 22 G. indwelling cannula the femoral artery was
cannulated and connected to an invasive arterial measuring system

Hewlett Packard Viridia mark Compaq monitor. The Femoral vein was also cannulated with 22FG. Cannula and connected to a venous extension line for fluid and anesthesia. Anesthesia was maintained with 0.3 mg of Succinyl choline given as intravenous bolus as needed to maintain apnea throughout the procedure.

Five leads ECG monitors in the form of hypodermic needles were connected to have a pulse rate, monitor of dysrhythmia and ST segment analysis.

All animals had left anterolateral thoracotomy in the fifth intercostal space. The pericardium was opened longitudinally anterior to the phrenic nerve and vessels and was suspended with silk sutures The Superior vena cava (SVC) was exposed and cannulated with a 20 FG cannula for Central venous pressure measurement and inotropic injection. Pulmonary artery was cannulated using a 20 FG Cannula, which was connected to an arterial extension line for pulmonary pressure measurement.

4 zero Polypropylene snares were placed around the homonymous and the second diagonal coronary arteries, approximately 40% from the apex (The homonymous artery is equivalent to the human left interior descending artery LAD). The anticipated infarct area of approximately 23% of the Left Ventricular mass.

Baseline data: Pulse rate, ST segment analysis, systolic, diastole, mean arterial blood pressure, CVP, PAP were, all taken just following the institution of the monitoring aids. These readings were repeated every 10 min. for 30 minutes.

Clamping After 30 minutes from the start of anesthesia, the polypropylene snares were tightened around the coronary vessels so as to obstruct the coronary flow to the defined vessels. Hemodynamic readings that were taken as baseline were measured and repeated every 10 minutes for the next 30 minutes. The pattern of cardiac contractility was also reported.

Inotropic support: 30 minutes following clamping, cats were divided sporadically into two groups: Group I, (n=10) were given Enoximone in a dose of 0.025 mg/kg (Corresponds to a dose of 1 mg/kg in human as corrected by Paget's formula for animals). Group II, (n=10) were given adrenaline in a dose of 0.01 mg/kg corresponds to mg/kg that corresponds a dose of 0.04 mg/kg in human. In each group the same readings were repeated every 5 minutes for 30 minutes.

Statistics: Measurements were reported as Mean ± Standard Deviation (S.D). Differences between readings at different times with subsequent measurements were compared by the 2-way ANOVA. When there was significant difference between measurements, or the group effect was significant, differences between groups at specific times were compared by the unpaired student "t" test. P value <0.05 denoted significant statistical difference.

Results

A total of 22 cats underwent the study in the pharmacology department labs - Kasr El Elm University between Mars, 1998 and June 1999. The average weight of the cats was 2.74+/-.6 kg. Both groups showed almost the same hemodynamic pattern (Table. I).
Table (1): Study of the Changes in Heart Rate between the Study Groups.

Table (2): Study of Changes in Systolic Blood Pressure between Study Groups.

No comparable differences were parameters measured in the pre-clamp noticed between the baseline data period the P value for all these elicited in the postanesthetic period and parameters were > 0.05 (Table: 2).

Upon Clamping, marked haemodynamic events happened. Two cats- died within 2-4 minutes, postclamping due to fatal dysrhythmias and were discarded from the study.
In group I, blood pressure, dropped to a mean of 106.66±1.22 mmHg and a diastole of 99.5±0.44 mmHg (P value 8.6E-10). Whereas, in group II the mean systolic was 107±0.7 mmHg over a diastole of 98.3±0.7 mmHg (P value of 6.83E-08). Heart rite and pulmonary artery pressure showed marked rise with a highly significant value P value (Table: 4) in both groups of the study. Ventricular extrasystole was recorded (n=4) in group I and (n=5) in group II. Contractility showed an outstanding hypokinesia of the left ventricular mass. The study was continued for 30 minutes after snaring of the coronary vessels to stabilize the ischemic insult and
To express the depressed contractility status before the introduction of any, inotropic.

The inotropic was injected 30 minutes from the clamping. In Enoximone group the heart rate, CVP and PAP showed a significant drop from the clamping value (P-value of 3E-5, 1E-7 and 0.0005 respectively) after 20 minutes from the injection of Enoximone (Table:5) Systolic blood pressure showed rise to the preclampip values and diastolic dropped further. ST segment exhibited a
Considerable drop (P value of 1E-05 after 25 minutes of injection) (Table: 6). Contractility pattern showed gradual but marked improvement.

In adrenaline group, heart rate at the contrary of group I showed further rise together with systolic, diastolic and mean blood pressures in all of these (P value <0.05). (Table: 7) However, ST segment analysis didn't show and improvement. Contractility still showing the hypokinesia of the left ventricular mass.

Table (5): Study of the Changes in Central Venous Pressure between the Study Groups

Discussion

The search for more effective cardiotonic agents was renewed in the early seventies when the assessment of many patients with myocardial failure kept on the available lines of treatment revealed that they remained symptomatic. Amidarone hail evolved on 1977 (2), (3), (4).

Though it was proved to have a narrow therapeutic index, several important facts emerged from amrinone experience: Firstly, the myocardium was not refractory in that its pumping function could not be enhanced. Secondly, a potent drug with a mechanism of action that differed from more traditional pharmacologic methods of augmenting myocardial contractility, offered an additional strategy, to improve ventricular performance. Thirdly, if this cardiotonic agent has a vasodilating effects this will add more to the improved overall cardiac performance. (4), (5), (6).

All that, opened the door to the introduction of Enoximone. It is a rather new cardiotonic agent first introduced on 1986, with both positive inotropic and vasodilator properties that are active by both intravenous and oral routes of administration (7). It belongs to the imidazolone (4-arylimidazol 2-one) class of cardiotonics and was shown to produce inhibition of only the membrane - bound high affinity cAMP, phosphodiesterase III or type IV phosphodiesterase by the revised
nomenclature) (8). Hence, this agent was found to produce its peak inotropic effect through an increase of the cAMP in the ventricular muscles (9).

This study compared the effect of Enoximone versus adrenaline in one of the critical situations, acute myocardial infarction caused by complete snaring of the homonymous coronary artery in cat which resulted in interruption of the coronary flow to the (quarter of the whole left ventricular mass, a condition that simulates an extensive infarction in human.

The effect of snaring resulted in an intense hemodynamic derangement from impaired left ventricular group, with pulmonary and subsequently right ventricular congestion, that was apparent in the study by an elevation of the ST segment indicating injury of the left ventricle and subsequent elevation of the CVP and PAP.

Heart rate showed a compensatory tachycardia in attempt to maintain the cardiac output within normal ranges. The arterial blood pressure showed marked drop indicating failure of the cardiac pumping action that frequently accompanies the acutely infracted heart.

Fatal ventricular ectopics resulted into death of two cats (not included), and mild to moderate ventricular ectopics m (n=9) of the 20 cats.

Enoximone administration in a depressed contractility state following myocardial infarction was associated with marked improvement of the ventricular performance, contractility and cardiac output. These effects were mediated almost entirely by an elevation in stroke volume.

Many studies concluded that the increased filling volume with the associated decrease in filling pressure implies that a reduction in the stiffness of the ventricular chamber can occur with Enoximone (10). This makes the left ventricular chamber size and distensibility able to increase after the unloading of the right heart with Enoximone (11), (12), and (13).

Another study, plotted the slope for $E_{max}$ which is the maximum elastance of the ventricle for a given contractile state, before and after Enoximone and they found to be increased from a mean of 0.336 to 8.547 mmHg/ml, which corresponded to a 63% increase in contractility (14), (15).

However, the clue of the value of any inotropic used in acutely infracted patient is its relation to the myocardial oxygen consumption (MVO2), which is a function of the mechanical component of the ventricular contraction. These include myocardial systolic wall force, heart rate and rate of development of systolic force (16), (17), (18).

On basis of the above mentioned, Enoximone was reported not to increase heart rate and marked increase of contractility associated with its use was obtained without a significant increase in MVO2 (19). This was consistent with our study where the extent of ST segment elevation was much decreased and the contractility pattern had improved markedly minutes after enoximone injection.

An adding effect that was also evident in our study was the vasodilating properties affecting the preload of the right atrium by
decreasing the CVP and of the left atrium evident through the decrease of the PAP. Certain studies proved a vasodilating effects over the coronary vessels themselves.

On the other hand adrenaline, a combined alpha and beta-adrenergic receptor stimulant drug had resulted into marred elevation of the heart rate. The beta stimulant effect moreover resulted in increase myocardial systolic wall force and the rate of systolic force. These effects resulted in much elevation of the MVO2, which is specifically deleterious in compromised acutely ischemic ventricles.

An adding effect of adrenaline was its alpha stimulating effect with an evident peripheral vasoconstriction that resulted in much elevation of the systolic, diastolic, and means blood pressures. The mild but limited effects on the CVP and PAP were attributed to the improved contractility secondary to the beta stimulant effects of adrenaline (18), (19).

Conclusion

This study has identified the inotropic value of Enoximone versus adrenaline in the support of acutely infracted cats. Enoximone was proved to improve the contractility state of the ventricles without a concomitant increase in MVO2, as it does not result in elevation of the heart rate or myocardial systolic wall force. Meanwhile it has a vasodilating effects that decreases the preload, decreases pulmonary congestion and facilitates forward flow by lowering the afterload. An adding effect is a coronary vasodilating property.

The study recommends the use of Enoximone in the coronary artery bypass grafting of acutely infracted patients done on emergency bas is whenever an inotropic support is needed and the patient's hemodynamics fit with Enoximone pharmacologic effects.

References


