

Cardiovascular Drug Interactions of Diclofenac and Dobutamine

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Objectives: To find the effects of diclofenac and dobutamine during myocardial ischaemia.

Methods: The project has been designed to find out the individual and combined effects of diclofenac and dobutamine on the cardiovascular functions[Heart Rate, Blood Pressure and Coronary Blood Flow] and ECG Parameters (QRS complex, R wave and T wave) in the pentobarbitone anesthetized rabbits before and after coronary occlusion.

Results: Diclofenac in the dosage of (500-750ug/kg/min) has stimulant effect on normal heart rate while after coronary occlusion heart rate is significantly suppressed with diclofenac in the dosage of (500-1000ug/kg/min). Moreover diclofenac resulted into suppression of normal blood pressure. After coronary occlusion the combined effect of diclofenac and dobutamine resulted into suppression of heart rate though not significant statistically. Diclofenac in the dosage of (250-1000ug/kg/min) results into significant increase in the normal amplitude of R wave while T wave remains unaffected. Diclofenac with dobutamine after coronary occlusion also leads to significant widening of QRS complex.

Conclusion: Diclofenac alone and with dobutamine after coronary occlusion not only slows down heart rate but also aggravates myocardial ischaemia.

Key Words: Myocardial ischaemia (MI), NSAIDs, Coronary occlusion (C.O), Heart Rate (H.R), Mean Arterial Pressure (MAP), Blood Pressure (B.P).

Introduction

Current evidence indicated that selective nonsteroidal anti-inflammatory analgesics have important adverse cardiovascular effects increasing the risk for myocardial infarction, stroke, heart failure, and hypertension. The risk for these adverse effects are likely to be greatest in patients with a prior history of cardiovascular disease. More data is needed concerning the cardiovascular safety of conventional NSAIDs. Until such data are available, the use of any COX inhibitor, including NSAIDs, for long periods of time should only be considered in consultation with a physician.¹

Dobutamine is given to the patients having a history of traumatic or cardiogenic shock. In dobutamine stress test the drug may interact with NSAIDs if patient has already taken NSAIDs with long half life like piroxicam. Surgery with its associated trauma, anaesthesia and analgesia, intubation and extubation, pain, hypothermia, bleeding, anaemia, and fasting, are analogous to an extreme stress. These factors initiate inflammatory hypercoagulable stress and hypoxic state which is associated with perioperative elevations in troponin levels, arterial thrombosis and mortality.²

The data demonstrated that dobutamine is a powerful inotropic agent at a dose that has a relatively small influence on heart rate. In patients without coronary artery disease dobutamine greatly increased coronary arterial perfusion. In

patients with severe coronary artery diseases dobutamine resulted in a much smaller increase in coronary perfusion and the pattern of perfusion became more inhomogeneous. The results suggest that dobutamine has a potential inotropic value but raise concern about its influence on regional myocardial perfusion in patients with serious coronary artery disease.³ Because of the technical difficulties with exercise 2D echocardiography, dobutamine echocardiography has become increasingly popular. This technique is based upon the concept that the contractile function of myocardial regions perfused by arteries with significant stenoses will be impaired when regional ischemia is provoked by the inotropic and chronotropic effects of dobutamine.^{4,5} Since dobutamine increases heart rate and myocardial contractility. The onset of action is within one to two minutes of intravenous infusion, the half-life is two minutes, and the drug is metabolized via methylation and conjugation. At the dose of 20 µg/kg per min, there is a significant increase in systolic blood pressure (mean 12 mmHg in one report) and at 40 µg/kg per min, the mean heart rate is 120 to 125/min.⁶

For more than half a century, analysis of the ST segment of the surface ECG has been the most commonly used diagnostic test in the detection and evaluation of coronary artery disease in asymptomatic subjects and in patients with chest pain syndrome.⁷ However, myocardial ischaemia can also affect components of the surface ECG other than the

ST segment. Other findings include an occasional increase in the QRS amplitude, subtle prolongation of QRS axis shifts and/or T-wave morphology changes.⁸ Since ischaemia causes changes in conduction, an irregular depolarization (activation) of the myocardium may occur.⁹ This would be manifested as intra-QRS changes. There is much evidence that ischaemic changes in the heart muscle may cause alterations in the QRS spectrum, as an expression of fragmentation of ventricular depolarization. For example, Okajima et al. studied frequency components between the onset and offset of the QRS complex and found them to be different for normal subjects and patients with coronary artery disease.¹⁰ The latter had prominent mid-QRS peaks in the frequency range of 40-100 Hz. In addition, under myocardial ischaemia induced by percutaneous transluminal coronary angioplasty, a focal reduction in high frequency components of the QRS complex (150-250 Hz) has been shown.^{11,12} Increased dispersion of the QT interval has also been observed during pacing or exercise stress testing in patients with coronary artery disease (CAD).¹³

Materials and Methods

Animals: Male rabbits (1-2 kg) were purchased from the local market of Lahore and Veterinary Research Institute, Lahore. They were kept in a separate animal house and were provided with liberal amount of water and food. Initially all groups were fed on normal diet for a period of two weeks for acclimatization before starting the experiment.

Drugs: Diclofenac sodium 50 Gms was obtained on request from Siza International, 18 km Main Ferozepur Road, Lahore Pakistan. Heparin Inj. (1000 units/ml) 5ml Vial Rotex Medica Germany, Pentobarbitone Injection 60 mg/ml 100 ml vial RMB Animal Health Ltd. Degenham, England RM 10 7XS, Normal saline 1000 ml I/V solution, Shahzeb Pharmaceutical Industries Haripur, NWFP, Pakistan, Dobutamine 250mg/5ml Ampoules Ningo DHY Pharmaceutical Co Ltd, China and Norepinephrine 4mg/ml Vials Bedford laboratories, Bedford England were used in the research.

Grouping of the Animals

The rabbits (n=114) were divided into seven groups.

Group I (Control) (n=6)

In this group normal cardiovascular and ECG parameters were recorded before and after coronary occlusion without any drug.

Group II (n=24)

In this group effects of diclofenac were observed.

Group III (n=6)

In this group effects of dobutamine were observed.

Group IV (n=24)

In this group combined effects of diclofenac and dobutamine were observed.

Group V (n=24)

In this group effects of diclofenac were observed after coronary occlusion.

Group VI (n=6)

In this group effects of dobutamine were observed after coronary occlusion.

Group VII (n=24)

In this group combined effects of diclofenac and dobutamine were observed after coronary occlusion.

In group II, IV, V and VII subgrouping of the animals was done in the following way.

D1 (n = 6) Diclofenac 250 µg/kg/min I/v

D2 (n = 6) Diclofenac 500 µg/kg/min I/v

D3 (n = 6) Diclofenac 750 µg/kg/min I/v

D4 (n = 6) Diclofenac 1000 µg/kg/min I/v

We used (114) *Oryctolagus cuniculus* male rabbits of 1.5-2Kg in our experimental model. Pentobarbitone sodium, 30 mg/kg i/v was used as anaesthetic agent, both for induction and maintenance. Ventilator (pressure operated) was adjusted at 32 strokes per minute, 16-20 ml/stroke of air. This was adjusted according to the respiratory minute volume which maintained the acid base balance of the blood of the animal to optimum level. The temperature of the top of operation table was kept at $38.4 \pm 1^\circ\text{C}$ during experiment. The heart was then exposed by thoracotomy at the 4th intercostal space. Circumflex branch of left coronary artery was ligated close to its origin as this site caused negligible fall in B.P after occlusion.¹⁴ The vessel was ligated with 6/0 braided silk suture with reverse cutting needle as minimum bleeding occurs with it. Mean arterial pressure was recorded by direct cannulation of femoral artery and connecting it to the pressure transducer.¹⁴ The following parameters were recorded: Heart rate (HR), Mean arterial pressure (MAP), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and ECG changes. The above parameters were recorded at one of the stage in different groups of rabbits: (a) just after anesthesia and surgical intervention (b) after administration of test drug (c) during and after dobutamine infusion (250 µg /kg/min) (d) just after ligation of circumflex (Cx) branch of left coronary artery (LCA) (e) after administration of test drug (f) during and after dobutamine infusion (250 µg/kg/min) and (g) after administration of test drug.

Animals in which surgical procedure produced arrhythmias or severe fall in mean arterial pressure were discarded. Myocardial Ischaemia causes: occasional increase in QRS complex, prolongation of QRS Complexes, QRS axis shift, T wave morphology and change in R and T wave amplitude.

Results

Effects of Diclofenac on the Heart Rate of Anaesthetized Rabbit

1. Normal Heart Rate

Diclofenac 500µg/kg/min and 750µg/kg/min i/v (Group D2 and D3) produced stimulant effects on the heart rate while

the effect produced with 250µg/kg/min and 1000µg/kg/min i/v (group D1 and D4) was depressant (Table # 1).

2. Heart Rate after Coronary Occlusion

All groups (D1-D4) produced suppressant effect on heart rate. The effects produced in D2 and D4 were statistically significant (Table # 2).

3. Effects of Drug Interaction of Dobutamine with Diclofenac after Coronary Occlusion

The effects of diclofenac in group D3 and D4 were highly significant while in group D1 and D2 the effects were also depressant (Table # 6).

4. Effects of Diclofenac on Systolic Blood Pressure

In all groups (D1 – D4) suppressant effects in systolic blood pressure were observed. However in the group D1 the result was statistically significant (Table # 1).

Effects of Diclofenac on ECG of Anaesthetized Rabbit

1. Effects of Diclofenac On Amplitude of R Wave after Coronary Occlusion.

All groups (D1 – D4) caused statistically significant increase in the amplitude of R wave (Table # 4).

2. Effects of Drug Interaction of Dobutamine with Diclofenac after Coronary Occlusion on QRS Complex.

In group D1 QRS complex was significantly widened. There was also widening of QRS complex in group D2, D3 and D4 (Table # 6).

3. Effects of Drug Interaction of Dobutamine with Diclofenac after Coronary Occlusion on T Wave.

Group D1-D2 produced significant suppressant effects on amplitude of T wave while the effects produced with D3 and D4 were also suppressants. (Table # 6).

The data were collected on pharmacological parameters and statistically analyzed to test various null hypotheses about the mean values of these parameters. Treatments were estimated at 5% level of significance. Wherever necessary, paired or unpaired 't' tests were performed.

Discussion

NSAIDs are extensively used for various inflammatory conditions and musculoskeletal disorders. Aspirin is the NSAID which is used to produce analgesia, to suppress fever, in prophylaxis of migraine and preclampsia and treatment of colorectal carcinoma. Aspirin is potent platelet disaggregator. It has antifibrillatory activity as well. Similarly diclofenac is the second NSAID which is most abundantly used. Piroxicam is also drug of choice by rheumatologists. It is prescribed as a long term treatment in musculoskeletal disorders like osteoarthritis, ankylosing spondylitis, neuritis and myositis.

Dobutamine is adrenergic drug used in a state of shock. Shock may be traumatic or cardiogenic. Traumatic shock is

usually after some injury or perioperatively while cardiogenic shock is usually due to some ischaemic event like myocardial infarction. As NSAIDs are frequently used drugs and dobutamine is drug of emergency. There is very likelihood of drug interaction of dobutamine and NSAIDs. This interaction may be in a population with or without history of myocardial ischaemia. Both myocardial ischaemia and dobutamine may give different types of drug interactions with different types of NSAIDs. We have tried to find out combined effects or drug interactions of dobutamine and diclofenac in our experimental model of non ischaemic and ischaemic rabbits.

Although NSAIDs have anti-inflammatory and antiplatelet effects similar to those of aspirin, we did not find that these drugs confer a protective effect against AMI. However, use of one specific NSAID, naproxen, appeared to be associated with a reduced rate of AMI, an effect recently suggested by a large randomized controlled trial as well.¹⁵

First several weeks after stopping nonaspirin NSAID therapy represent a vulnerable period for MI, particularly among previous long-term NSAID users and patients with inflammatory disease. Still, future research must confirm the findings and must determine whether aspirin users and non-users are both vulnerable to MI after cessation of nonaspirin NSAID therapy. For now, it is prudent to consider the potential for MI risk when stopping therapy in the vulnerable groups identified by this study.¹⁶ Moreover, continuing uncertainty regarding the direction and magnitude of any cardiovascular effects of selective COX-2 inhibitors, coupled with their widespread and increasing use, mandates prospective randomized evaluation of their efficacy and safety in patients at increased risk of future cardiovascular events.¹⁷

Aspirin in low dose is antiarrhythmic. Nimesluide has calcium channel blocking affect on the human myometrial myocytes. It seems that in small doses aspirin inhibits the release of destructive enzymes, platelet aggregation and prostaglandin synthesis. Aspirin in low dose has significant suppressant effects on all sorts of ventricular arrhythmias. This is important for reperfusion arrhythmias, which are highly resistant to almost all conventional antiarrhythmic drugs.¹⁸ Tachyarrhythmias in the anesthetized rabbits are suppressed both by propranolol and aspirin. The effects of both drugs are potentiated. This combination suppresses tachyarrhythmias both during ischaemia and reperfusion and moreover there is no significant fall in M.A.P.¹⁸ Indomethacin in low doses also has suppressant effects on the ischaemia induced tachyarrhythmias while reperfusion arrhythmias are unaffected by indomethacin. Moreover there is no significant effect on M.A.P. by these drugs.¹⁹ Pretreatment with low dose combination of indomethacin and propranolol suppresses all sorts of ventricular arrhythmias. It is concluded that combination of indomethacin and propranolol is useful in suppressing tachyarrhythmias and ventricular arrhythmias.²⁰

Diclofenac in the dosage of 250µg/kg suppresses the heart rate while diclofenac in the dosage of 500µg/kg incre-

ases the heart rate significantly. There is significant depression of T wave with dobutamine both before and after coronary occlusion. Our findings conclude that diclofenac has antiarrhythmic effect in small doses as it suppresses tachyarrhythmias.

Significant suppression of heart rate can occur with diclofenac after coronary occlusion and small dose of diclofenac can cause widening of QRS complex which is also considered to be a factor of aggravated ischemia. Low serum level of diclofenac during myocardial ischaemia can oppose the effects of dobutamine given in a state of cardiogenic shock or in the pharmacological stress test.

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Source of Finding:

King Edward Medical University, Lahore-Pakistan.

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