# Hypotensive effect of leukotrien C4 and its relationship with protamine administration after cardiopulmonary bypass in humans

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*In order to explain the adverse hemodynamic effect of protamine administration such as pulmonary vasoconstriction, low cardiac output, hypotension, and increase in the capillary permeability after cardiopulmonary bypass, and to determine the relation of blood pressure and the plasma levels of leukotriene C4 (LTC4) we collected serial plasma concenctrations of LTC4 from 20 patients before and at the third and at the tenth minutes of protamine administration. A significant incraese* was *found in the plasma concentration of LTC4 (p<0.001) together with a significant hypotension (p<0.001) three minutes after the protamine administration. And we also noticed that ten minutes after the protamine administration the arterial pressure and the plasma concentration of LTC4 returned to their pre-protamine levels. Thus it seems that the adverse hemodynamic effects of protamine may be due the increased plasma levels of L TC4. [Turk J Med Res 1993; 11 (4):191-194J*

Key Words: Cardiopulmonary bypass, LTC4, Protamine

The leukotrienes have been recognised as biologically important since 1938 when they were isolated in lung perfusates by Feldberg and Kellaway and were subsequently related to slow reacting substances of anaphylaxis (SRS-A) by Brockilhurst (1,2). The active ingredients of the SRS-A were recently identified and named "Leukotrienes" 5-lipoygenase metabolites of arachidonic acid (1,2,3).

The leukotrienes (LT) are a class of physiologically active molecules with potent effecets on the cardiovascular, pulmonary (4,5,6), and some other systems (1,7,8,9,10,11). Some of the hemodynamic effects that can be produced are cororany vasoconstriction (2,6,12) reduction in myocardial contractility (6,13,14), low cardiac output (9,11,13), hypotension (7,11), pulmonary vasoconstriction (5,6,10), bronchospasm (5,7,8) and increases in the capillary permeability and the plasma extravasation (2,15,16). In purified human lung mast cells, histamine release precedes the release of prostaglandin D2 (PGD2) and thromboxane A2 (TXA2), and finally leukotriene C4 (LTC4) is released (17,18,19).

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It is well known that the protamine sulphate administration after cardiopulmonary bypass induces many adverse hemodynamic effects such as pulmonary vasoconstriction, low cardiac output, hypotension, and increase in the capillary permeability (20-23). Most of these adverse effects of the protamine administration have been presumed due to histamine release (24,27).

In the present study we investigated the relationship between the protamine administration after cardiopulmonary bypass and the plasma concentrations of LTC4.

## MATERIALS AND METHODS

Twenty consecutive patients undergoing open heart surgery over a two month period were investigated. Average age was 31.3 years (range 15-61). There were 11 men and 9 women. Four patients had aorto-coronary bypass grafting. Sixteen patients had mitral and/or aortic valve replacement. Anti-coagulation for cardiopulmonary bypass (CPB) was with 5mg/kg body weight of heparin. Anticoagulant effect of heparin was detected by measurement of the activated clotting time (ACT): The safe range being 400-600 seconds. CPB was established between a single two stage right atrial/inferior vena caval cannula and the ascending aorta-coronary bypass grafting. We used two separate canulas for superior and inferior vena cava during the valve replacements. Rapid core cooling to 31 °C was

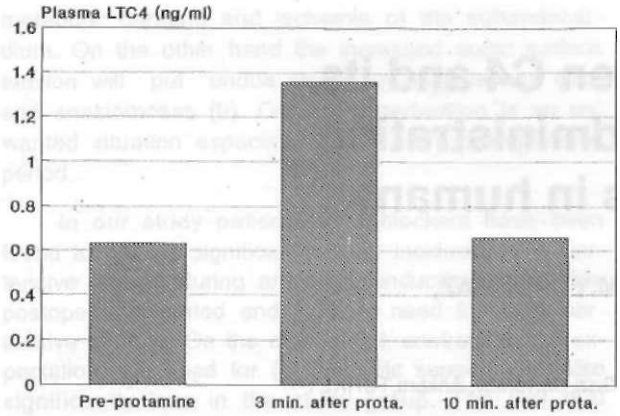


**Figure 1.** The effect of protamine on plasma leukotrien C4 levels.

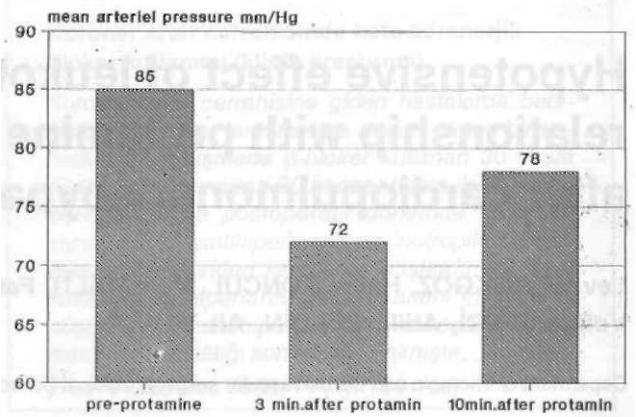


**Figure 2.** The effect of protamine on arterial blood pressure.

used from the outset. None of the patients had used drugs known to interfere with the synthesis of leukotrienes for ten days preceding the operation. One hour before induction of anesthesia, the patients were premedicated with diazepam (0.2 mg/kg). Anesthesia was induced with thiopenthal sodium (5 mg/kg) and pancuronium bromide (0.1 mg/kg) and was maintained with ventilation with 50% nitrous oxide in oxygen. Enflurane (0.5 volume %) was also used. A polystan non-pulsatile pump was used. Perfusion time averaged 67.4 minutes (range 33.133 minutes). During ischemia, the heart was protected by cold hyperkalemic cardioplegic solution. At the end of CPB protamine sulphate was given at a dose calculated from the heparin-ACT diagram. The arterial pressure was monitored from a catheter inserted into the radial artery.

Blood samples were collected ten minutes before and at the third and tenth minutes of the protamine administration via the catheter inserted into the radial artery. Plasma was seperated immediately by centrifugation at 4°C. The plasma concentrations of LTC4 were assayed with High Performance Liquid Chromotography (Barst Technique) (28). In Pharmacology Department of Gazi University.

Significance test for matched observations was employed for the statistical analysis of the results. Student's-T test was used for statistical data by using Microstat Program.

## RESULTS

We collected serial plasma concentrations of LTC4 from 20 patients before and at the third and tenth minutes of protamine administration, and the corresponding arterial pressure levels were recorded. Figures below are the mean values of obtained measurements from individual patients.

We found out a significant decrease (pO.001) in the arterial pressure three minutes after the protamine administration which was decreased to 93/61 mm Hg (mean 72 mmHg) from the pre-protamine levels of 114/73 mmHg (mean 85 mmHg). Ten minutes after the protamine administration the arterial pressures returned to their pre-protamine like levels of 101/66 mmHg (mean 78 mmHg).This increase was found significant ($p<0.05$) (Fig 1.).

In the plasma concentration of LTC4, we found out a significant rise from 0.63 ng/ml to 1.36 ng/ml three minutes after the protamine administration ($p<0.001$). We also noticed that after the protamine administration, the pre-protamine like levels of 0.66 ng/ml LTC4 were reached ($p>0.05$). This was statistically significant ($p<0.001$) (Fig 2.).

The values of the plasma concentrations of LTC4 and the mean arterial pressures before and at the third and at the tenth minutes of protamine administration are shown in Figure 1 and Figure 2.

## DISCUSSION

The leukotrienes (LT) are a family of naturally occuring lipids that are oxygenated metabolites of arachidonic acid with potent effects on the lung, on the heart (6,9), on the vascular system (7,11,17), and on some other systems (13,18). Leukotriene C4 (LTC4), LTD4, LTE4, and LTB4 represent major lipoxygenase products of arachidonic acid derived from leukocytes (1), bronchial mast cells (19,29,30), endothelial cells (31), human eosinophils (32), vascular smooth muscle cells (16), and coronary vessels (6).

Biosynthesis of the leukotrienes involves the action of a lipoxygenase on arachidonate to yield a hydroperoxy intermediate which is then dehydrated to the allylic epoxide, LTA4. LTA4 can be hydrolyzed to the dihydroxy acid, LTB4 or it can be conjugated with glutatohine to produce the parent slow reacting substance, LTC4 (31).

Effects of leukotriene in some species occur as a result of the secondary production of cyclooxygenase products such as thromboxane A2 (TXA2), (PGE2), PGI2 and PGF2; thus, there is an interaction and synergy between the two major pathways of arachidonic acid metabolism (18,33,34). Therefore

LTC4, together with its own effects, is able to trigger a process of bioamplification through TXA2 which is one of the most potent contractile agents of smooth muscle of vascular and respiratory origin. It has been shown that prostacylin (PGI2) and TXA2 production is increased during CPB (28,35-40). Wells (19), has showed that the majority of the immunologic release of LTC4, histamine, and PGD2 from the bronchial tissue was mast cell-derived.

The protamine administration after CPB induces many adverse hemodynamic effects such as increase in the pulmonary vascular resistance, increase in the pulmonary arterial pressure, low cardiac output, and hypotension (24-26). Intravenous infusion of LTC4 produce a significant reduction in mean arterial pressure, in cardiac output and in renal blood flow. These effects are abolished by FPL55712, a putative antagonist of leukotrienes. LTC4 also results in an average loss of 20% in plasma volume by virtue of its vasopermeability enhancing effect (13). It is believed that most of these adverse effects of protamine are caused by the release of histamine (23-25).

The variety of physiological responses that occur during CPB makes it difficult to establish clear-cut cause and effect relationships. It may be speculated that the protamine administiation after CPB can produce a rise in the plasma concentration of LTC4 causing the adverse effects of protamine. The significant correlation between protamine infusion and the rise of plasma level of LTC4, as observed in our study, supports this hypothesis.

**LTC4'ün hipotansif etkileri ve onun insanlarda kardiyopulmoner bypass sonrası protamin verilmesi ile ilişkisi**

*Kardiyopulmoner bypass sonrası protamin verilmesinin bazı yan etkileri olmaktadır. Bunlar; pulmoner vazokonstrüksiyon, düşük kardiyak debi, hipotansiyon ve kapiller permeabilitede artıştır. Bu çalışmayla yukarıdaki yan etkilerin sebepleri ve LTC4 plasma seviyesi ile kan basıncı arasındaki ilişki araştırılmış ve 20 hastadan protamin verilmesinden önce ve verildikten sonra 3. ve 10. dakikalarda plazma örnekleri alınmıştır. Protamin verilmesinden sonra 3. dakika örneklerinde belirgin bir hipotansiyon (p<0.001), ayrıca 10. dakika ölçümlerinde arteriyel basıncın ve plazma LTC4 seviyesinin protamin verilmeden önceki değerlerine geriledi̇ği tesbit edildi.*

*Bu sonuçlarla protamin'in hemodinamik yan tesirlerinin artmış olan plazma LTC4 seviyesine bağlı olabileceği düşünülmüştür.*

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