Title: PREVENTION OF ADVERSE HEMODYNAMIC SIDE EFFECTS FOLLOWING HEPARIN/PROTAMINE BY A THROMBOXANE A_2 RECEPTOR ANTAGONIST

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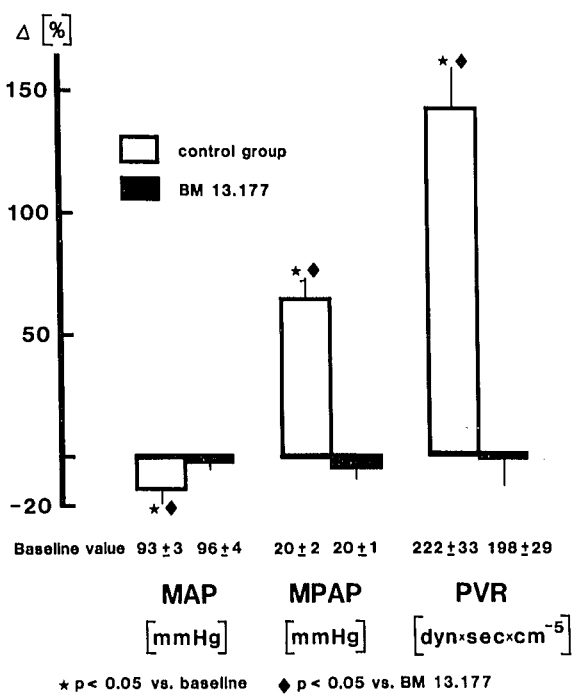
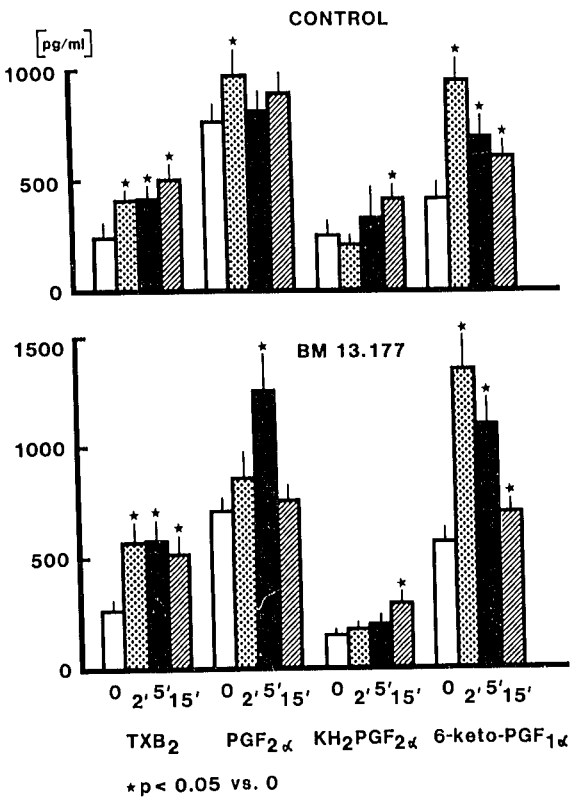
INTRODUCTION: It was reported recently, that the hemodynamic reactions following heparin reversal by protamine were accompanied by an activation of the arachidonic acid cascade with increased levels of thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) (1). Also, inhibition of cyclooxygenase cascade by indomethacin effectively inhibited the side reactions following protamine (2). We tested the hypothesis, that TXA_2 release is the pivotal step for the adverse hemodynamic effects of heparin/protamine.

METHODS: 21 pigs (body weight 20-30 kg) were anesthetized with fentanyl and enflurane. Catheters were placed for hemodynamic monitoring. Prostanoids were measured in arterial and in mixed-venous plasma samples by radioimmunoassays: TXA_2 by its metabolite TXB_2, PGI_2 by its metabolite 6-keto-PGF_{1a}; PGF_{2a} and its degradation product KH_2 PGF_{2a} were also determined. The animals were randomly assigned to two experimental groups: One control group (n=10) in which heparin/protamin effects were tested without further treatment; the animals of the second group received a thromboxane receptor antagonist (BM 13.177; 10 mg/kg) intravenously 5 min prior to heparin reversal by protamine. All animals received heparin 250 iU/kg into the right atrium. This was followed by 100 mg protamine after 15 minutes. Blood samples were collected and hemodynamic measurements obtained immediately before protamine (t0), and 2, 5 and 15 minutes after protamine infusion had been accomplished. Data are presented as means ± SEM; for statistical analysis the Friedman-rank-analysis of variance and the Wilcoxon-U-test were applied.





RESULTS: Protamine reversal of heparin was followed by significant increases of plasma prostanoid concentrations. No differences were detected between both groups. Significant hemodynamic alterations were only observed in the animals of the control group. Figure 1 gives the maximum hemodynamic responses at 2-5 minutes following protamine. No hemodynamic changes were detected in the animals pretreated with the thromboxane antagonist, albeit plasma TXA_2 concentrations increased comparably in both groups (fig. 2).

DISCUSSION: The results of this study indicate, that the release of the potent pulmonary vasoconstrictor TXA_2 obviously mediated pulmonary vasoconstriction in our experiments since the adverse protamine effects were effectively inhibited by a thromboxane receptor antagonist. The slight, but nevertheless significant increase in PGI_2 plasma concentrations apparently was without hemodynamic consequences. We conclude from these results, that pretreatment with a thromboxane antagonist might prove useful for preventing the adverse hemodynamic side-reactions following protamine reversal of heparin.

LITERATURE:

1. Morel DR, et al. Anesthesiology 66: 597-604, 1987
2. Hobbhahn J, et al. Anesthesiology 67: A25, 1987