ANTICOAGULATIVE EFFECTS OF THE INHALED LOW MOLECULAR WEIGHT HEPARIN CERTOPARIN IN HEALTHY SUBJECTS

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Inhalation of heparin results in local anti-inflammatory and anti-fibrotic effects as well as an inhibition of blood coagulation. A number of experimental and clinical studies demonstrated that inhalative administration of heparin or low molecular weight heparin (LMWH) is a feasible and save tool for anti-coagulative treatment. However, heparin and LMWH differ in respect to their molecular weight, pulmonary absorption, and principle of their anti-coagulative pattern. In this study, we investigated the anti-coagulative effects of different doses of the LMWH certoparin after inhalation (3000-9000 IU) and subcutaneous injection in healthy individuals (3000 IU) in a cross-over design. Inhalations were performed using a new device allowing inhalations with optimized and standardized breathing patterns. The anti-coagulative effects were determined by the measurement of anti-factor-Xa-activity. Lung function parameters were measured before and after drug inhalation. An analysis of the anti-factor-Xa-activity as a function of time after administration revealed values of the area under the curve (AUC) of 5.70 ±1.58 U•hour/ml, 2.60 ±1.74 U•hour/ml, 7.17 ±3.0 U•hour/ml, and 8.43 ±1.31 U•hour/ml (means ±SD) with interindividual coefficients of variation of 28%, 66%, 41%, and 13% after injection of 3000 IU, inhalation of 3000 IU, inhalation of 6000 IU, and inhalation of 9000 IU, respectively. The AUC after inhalation of 6000 IU was not significantly different from that after injection of 3000 IU ($P=0.28$). Inhalation of 3000 IU resulted in a lower AUC than injection ($P<0.01$) whereas a higher AUC was achieved after inhalation of 9000 IU ($P=0.0007$). In consequence, in order to obtain plasma anti-factor-Xa activities of 0.1 U/ml to 0.2 U/ml, which is considered sufficient for prophylaxis of venous thromboembolism, at least 6000 IU LMWH have to be inhaled. Compared to the subcutaneous administration, the action of certoparin is longer after inhalation. Obviously, the drug is released rapidly according to a two-compartment kinetics, and its anticoagulant activity lasts over a long time without a marked plasma peak after administration. In detail, an elevation of plasma anti-factor-Xa-activity is achieved for 12 hours to 24 hours without a distinct peak shortly after inhalation. Inhalation of LMWH does not result in any changes in lung function or other side effects. So the administration of LMWH by inhalation bears several advantages: the non-invasive route of drug application, the low interindividual variability of the anti-coagulative effect, and a long-time pharmacological effect. These properties suggest that controlled inhalation of heparin is an attractive alternative to its subcutaneous administration.