Release of Thyroid Hormones from Protein-Binding Sites by Low-Molecular-Weight Heparin in Hemodialysis Patients

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Dear Sir,

Anticoagulation is necessary for hemodialysis (HD) therapy. As a standard, unfractionated heparin (UFH) is administered comprising a mixture of different molecular weights (3-30 kD). For more than 10 years, low-molecular-weight heparins (LMWH, 4 kD) have been used [1,2] that comprise only the low-molecular-weight fractions of UFH. UFH induces a rise in TT3, FT3, TT4 [3, 4] and, depending on the assay, FT4 [5]. So far, data on the effect of LMWH on the levels of thyroid hormones in HD patients during HD are lacking. The aim of this study was to supply these data by a prospective longitudinal study that compared two short phases with UFH (pre- and postphase) to a 6-week LMWH phase in a double crossover design. The results were to be compared with those of Beyer [3] who was to our knowledge the only author to measure serially thyroid hormones during HD.

Study design: During the prephase of 1 week, UFH (Thrombophob®; Nordmark, Germany) was administered in the usual dose for each patient (mean initial bolus of 3,500 IU, followed by an infusion with 800 IU/h, the infusion was stopped 1 h before the end of the HD session. In the LMWH phase lasting 6 weeks, Fragmin R (Kabi, Sweden) in 70% of the UFH dose (mean bolus, 2,500 U, infusion with a mean of 550 U/h) was given. This dosage had been proven to be effective by measuring factor Xa and produced no side effects in 5 patients of a pilot study before this study. In the postphase, UFH was administered at each session for 1 week. Blood was drawn each hour of each session in the pre- and postphase and each week in the LMWH phase. Twelve stable chronic HD patients (4 women, 8 men) who had been on HD for at least half a year were examined after informed consent. Median age was 51 years, range 25-76. Mean dry body weight was 63.4 kg, and mean interdialytic weight gain 2.7 kg. The mean albumin level was 4.3 g/dl. TT3, TT4 and FT4 were measured by radioimmunoassay with an indirect method using low-affinity monoclonal antibodies in coated tubes (SPAC T3 and SPAC T4/FT4 by Byk-Mallinckrodt, Germany). The reference ranges were: T3, 80-220 ng/dl; T4, 4.5-12.5 µg/dl and FT4 0.6-1.8 ng/dl. For calculation the LMWH phase was divided in two so that four blocks resulted: UFH prephase,

LMWH phase 1, LMWH phase 2, and UFH postphase. The values were calculated as median with SEM and compared by Student's t test for paired observations. Tables 1-3 show the values of the three thyroid hormones at different times. For TT3 and TT4 a continuous rise during HD is found in all phases. In each phase of the study the basal serum level is significantly lower than at the end of the HD session ($p < 0.001$). No differences were found between the four study phases. FT4 shows no significant change either during the HD session or between the different study phases. The basic levels of all thyroid hormones as a median were in the low normal range, but if the individual values are considered for TT3, 45 out of 144 were subnormal, 1 was borderline and 98 were normal. 52 TT4 concentrations were subnormal, 4 borderline and 88 normal. For FT4 the respective numbers are 25 subnormal, 11 borderline and 108 normal according to other author's data [6, 7]. There were no signs of hypothyroidism in the patients studied here. There also was no sign of hyperthyroidism at the end of HD though TT3 and TT4 had continuously risen in accordance to Beyer [3]. Beyer [4] assumed a shift from the hepatic stores of TT4 into the vascular space, if that holds true for TT3 also is a matter of debate. In this study there are no significant differences between the different study phases, that means whether the patients got UFH or LMWH. FT4 did not change significantly either over the HD sessions or in the different phases of this study. This finding is discrepant to the results of Beyer [3], the reason for this most probably being the difference between the assays [5, 8]. In conclusion, no significant differences of thyroid hormone levels were caused either by LMWH or UFH during HD.

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Table 1. TT3 values of the different study phases (ng/dl)

Hour

UFH prephase

X ± SEM

LMWH phase 1 X ± SEM

LMWH phase 2 X ± SEM

UFH postphase

X ± SEM

Table 2. TT4 values of the different study phase (µg/dl)

Hour

UFH prephase

X ± SEM

LMWH phase 1

X ± SEM

LMWH phase 2

X ± SEM

UFH postphase X ± SEM

Table 3. FT4 values of the different study phases (ng/dl)

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TH Release by LMW Heparin in Hemodialysis

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