Recombinant hirudin (lepirudin) as anticoagulant in intensive care patients treated with continuous hemodialysis

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Recombinant hirudin (lepirudin) as anticoagulant in intensive care patients treated with continuous hemodialysis.

Background. Recombinant hirudin (lepirudin) is a potent direct thrombin inhibitor, which has been approved for the treatment of heparin-induced thrombocytopenia type II (HIT). Because the drug is mainly eliminated by the kidneys, a single loading dose of hirudin may induce therapeutic anticoagulation for up to one week in patients with renal insufficiency. Thus, the use of hirudin in critically ill patients with renal failure could markedly increase their bleeding risk. In this study, hirudin was used in critically ill patients with suspected HIT while on continuous venovenous hemodialysis (CVVHD).

Methods. Hirudin anticoagulation was performed in seven critically ill patients with suspected HIT. Four patients were initially anuric. Three patients had residual renal function. In all 64 CVVHD treatments (mean duration 12 hr), a polysulfone high-flux hemodialyzer (0.75 m²) with a dialysate flow rate of 1.5 liter/hr and an ultrafiltration rate of up to 200 ml/hr was used. Hirudin was given either as continuous intravenous infusion or as repetitive intravenous bolus. Monitoring of anticoagulation was performed by measurements of the systemic activated partial thromboplastin time (aPTT).

Results. Hirudin dosage had to be individualized according to the risk of bleeding or clotting. During CVVHD, a continuous intravenous infusion (0.006 to 0.025 mg/kg body wt/hr, N = 2) or repetitive intravenous bolus (0.007 to 0.04 mg/kg, N = 5) were given. Two patients required blood transfusions prior to and during hirudin treatment. In five patients without a high bleeding risk, the hirudin dose was adjusted to achieve the target aPTT (1.5 to 2.0 × baseline) in order to prevent thrombotic complications or frequent clotting in the extracorporeal circuit. Hirudin dose requirements depended on residual renal function and extracorporeal clearance.

Conclusions. We conclude from these first clinical data that anticoagulation with hirudin in critically ill patients on continuous hemodialysis can be performed without excessive bleeding risk by combining close clinical and laboratory monitoring. The hirudin dose has to be reduced because of renal failure, and may require adjustment for residual or recovering renal function and extracorporeal elimination.

Recombinant hirudin (lepirudin, Refludan®) has been approved in both Europe and the United States for the treatment of heparin-induced thrombocytopenia type II (now commonly referred to as HIT) [1]. After intravenous application of hirudin (hirudin refers to recombinant hirudin throughout the text) in healthy individuals, an elimination half-life of 60 to 100 minutes, a mean total clearance of 170 to 190 ml/min, and a volume of distribution of 0.28 liter/kg body wt have been reported [2, 3]. Hirudin is mainly eliminated by the kidneys. Hence, the half-life of hirudin is prolonged in patients with renal insufficiency and may increase from 1.5 to 50 hours in anuric patients [4]. Published experience in dialysis patients is limited. Preliminary studies showed intermittent hemodialysis with hirudin to be possible without major side effects [5, 6]. In these early studies, hirudin was given for one single dialysis session only. In one patient, hirudin was used for more than 50 consecutive dialysis sessions without adverse effects [7].

Given the prolonged half-life of hirudin in patients with impaired renal function, a single loading dose of hirudin may induce therapeutic anticoagulation for up to one week. Thus, the use of hirudin in critically ill patients with renal failure could markedly increase their bleeding risk. A number of patients with proven or suspected HIT on intermittent hemodialysis were successfully treated with hirudin at our center. In these patients, adverse reactions, especially bleeding episodes, have not been observed. Being familiar with hirudin anticoagulation in intermittent hemodialysis, we applied this anticoagulant during continuous venovenous hemodialysis (CVVHD) in critically ill patients with suspected HIT.

METHODS

Patients

Between January and December 1998, seven intensive care patients (4 males and 3 females; mean age 57 years, range 30 to 70) were suspected to have HIT while additionally requiring continuous hemodialysis because of acute renal failure. Suspicion of HIT was based on the development of thrombocytopenia during heparin treat-
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Main diagnoses</th>
<th>HIT</th>
<th>DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>M</td>
<td>Alcoholic hepatitis, viral pneumonia</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>F</td>
<td>Acute pancreatitis, bacterial pneumonia</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>F</td>
<td>Generalized vasculitis, cardiogenic shock</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>F</td>
<td>Dilated cardiomyopathy, bacterial pneumonia</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>M</td>
<td>COPD, bacterial pneumonia</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>M</td>
<td>CAD, AMI (repeated), cardiogenic shock</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>M</td>
<td>CAD, aortic endocarditis, viral pneumonia</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

Abbreviations are: AMI, acute myocardial infarction; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DIC, disseminated intravascular coagulation; HIT, heparin-induced thrombocytopenia (type II).

Table 2. Residual diuresis and characteristics of continuous renal replacement therapy

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Residual diuresis ml/day</th>
<th>No. of CVVHD sessions</th>
<th>Total hours</th>
<th>Average hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0–100</td>
<td>30</td>
<td>394</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>0–100</td>
<td>14</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>7</td>
<td>138</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>800–3000</td>
<td>3</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>2750–2950</td>
<td>2</td>
<td>9</td>
<td>4.5</td>
</tr>
<tr>
<td>6</td>
<td>0–100</td>
<td>4</td>
<td>78</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>2600–3800</td>
<td>4</td>
<td>41</td>
<td>10</td>
</tr>
</tbody>
</table>

CVVHD is continuous venovenous hemodialysis.

Fig. 1. Time course of platelet counts. Day 0 is the day of platelet count nadir in all patients.

Monitoring of hirudin anticoagulation

Monitoring of anticoagulation was performed by repetitive measurements of the systemic activated partial thromboplastin time (aPTT) according to standard methods (analyzer, Behring Coagulation System; reagent, Pathromtin SL; both by Dade Behring, Liederbach, Germany).

Hemodialysis procedure

Continuous venovenous hemodialysis was performed with a polysulfone high-flux hemodialyzer (AV400, 0.75 m²; Fresenius, Bad Homburg, Germany) using a Fresenius ADM08 dialysis machine (Fresenius) with a bicarbonate dialysate at a flow rate of 1.5 liter/hr. The blood flow was 100 ml/min. The ultrafiltration rate depended on the patient’s need (0 to 200 ml/hr).

RESULTS

Course of platelet counts

All patients had developed severe thrombocytopenia during heparin treatment. The mean platelet counts fell from 202 ± 26/ml to 39 ± 3/ml (Fig. 1). The earliest drop in platelet count was observed on day 3 of heparin treatment. After changing anticoagulation to recombi-
Table 3. Hirudin dosage and corresponding activated partial thromboplastin time

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Diuresis</th>
<th>Bolus mg/kg body wt</th>
<th>Continuous infusion mg/kg body wt/hr</th>
<th>Mean daily dose mg/kg body wt</th>
<th>Mean aPTT reached seconds</th>
<th>Corresponding aPTT ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anuria</td>
<td>0.013–0.025</td>
<td>—</td>
<td>0.013</td>
<td>45</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>Anuria</td>
<td>0.009–0.018</td>
<td>—</td>
<td>0.026</td>
<td>44</td>
<td>1.3</td>
</tr>
<tr>
<td>3</td>
<td>Anuria</td>
<td>0.007–0.014</td>
<td>—</td>
<td>0.054</td>
<td>48</td>
<td>1.7</td>
</tr>
<tr>
<td>4</td>
<td>Polyuria</td>
<td>0.02–0.04</td>
<td>—</td>
<td>0.08</td>
<td>53</td>
<td>1.6</td>
</tr>
<tr>
<td>5</td>
<td>Polyuria</td>
<td>0.013–0.027</td>
<td>—</td>
<td>0.08</td>
<td>45</td>
<td>1.3</td>
</tr>
<tr>
<td>6</td>
<td>Anuria</td>
<td>—</td>
<td>0.006–0.009</td>
<td>0.15</td>
<td>100</td>
<td>3.3</td>
</tr>
<tr>
<td>7</td>
<td>Polyuria</td>
<td>—</td>
<td>0.013–0.025</td>
<td>0.5</td>
<td>62</td>
<td>1.5</td>
</tr>
</tbody>
</table>

nant hirudin, platelet counts recovered within five to seven days (Fig. 1).

**Continuous hemodialysis**

Continuous venovenous hemodialysis had to be initiated because of acute renal failure. Upon anticoagulation with hirudin, a total of 64 CVVHD treatments was performed with an overall duration of 785 hours (Table 2). The mean duration of individual continuous hemodialysis treatment was 12 hours, with a range of 3 to 30 hours.

**Hirudin anticoagulation**

Anticoagulation with recombinant hirudin had to be individualized according to the risk of bleeding or thrombosis. In addition, hirudin dose requirements depended on residual renal function and extracorporal clearance.

In five patients, hirudin was applied as repetitive intravenous bolus. In three anuric patients, the respective dose per single intravenous bolus ranged from 0.007 to 0.025 mg/kg body wt, corresponding to a mean daily dose of 0.013 to 0.054 mg/kg body wt (Table 3). The mean aPTT reached by this regimen was 44 to 48 seconds (aPTT ratio 1.3 to 1.7). In two polyuric patients, the dose of intravenous bolus ranged from 0.013 to 0.04 mg/kg body wt, corresponding to a mean daily dose of 0.08 mg/kg body wt in both patients. The mean aPTT in these patients was 45 and 53 seconds (aPTT ratio 1.3 and 1.6), respectively (Table 3).

In two patients, hirudin was applied as continuous intravenous infusion. In one anuric patient (patient 6), anticoagulation was aimed to markedly reduce the high risk of thrombosis. The respective dose was 0.006 to 0.009 mg/kg body wt/hr, resulting in a mean daily dose of 0.15 mg/kg body wt. With this regimen, the mean aPTT was 100 seconds (aPTT ratio 3.3). Overt bleeding was not observed, and blood transfusion was not required. The other patient was polyuric (patient 7). Anticoagulation was performed with an intravenous infusion of hirudin in a dose of 0.013 to 0.025 mg/kg body wt/hr (mean daily dose 0.5 mg/kg body wt). In this patient, the mean aPTT was 62 seconds (aPTT ratio 1.5; Table 3).

In two patients (patients 2 and 4), hirudin application was switched from intravenous bolus to intravenous infusion after the recovery of renal function and the termination of continuous hemodialysis treatment (data not shown).

**Adverse reactions**

No patient developed allergic reactions on hirudin application. Overt bleeding was not observed. Despite this, two patients (patient 1 and patient 2) required blood transfusion prior to and during hirudin treatment. The transfusion requirement did not increase upon changing anticoagulation to hirudin.

**Patients’ outcome**

Two patients died. One patient (patient 6) suffered from repeated acute myocardial infarction. The other patient (patient 3) showed severe refractory vasculitis. Both died of prolonged cardiogenic shock. Fatal outcome in both patients was not related to hirudin anticoagulation. The five survivors showed no thromboembolic events after starting hirudin. They recovered from multiple organ dysfunction syndrome. Two initially anuric patients (patients 1 and 2) and all three polyuric patients (patients 4, 5 and 7) eventually recovered renal function. Further hemodialysis treatment was not necessary after discharge from the hospital.

**DISCUSSION**

Heparin-induced thrombocytopenia type II is a severe complication of heparin anticoagulation, which in spite of low platelet counts often leads to potentially life-threatening thromboembolic complications [1, 8]. Upon suspicion, immediate stop of heparin treatment and switch to a suitable alternative anticoagulant are mandatory [1], which in Europe is increasingly performed with recombinant hirudin. In patients with renal failure requiring continuous dialysis, uncertainty exists regarding the safe use of hirudin. In our study of critically ill patients with acute renal failure who were suspected of having developed HIT, anticoagulation was performed with recombinant hirudin to prevent white clot forma-
tion sufficiently. Low doses of hirudin were applied to avoid bleeding complications.

Laboratory monitoring of hirudin treatment

In HIT patients, hirudin is given to avoid clot formation, but at the same time the risk of bleeding has to be minimized. The ideal laboratory monitoring parameter should reliably guide anticoagulation between the risk of bleeding and clotting. aPTT has frequently been used to monitor hirudin treatment [9]. However, its inadequacy for monitoring hirudin anticoagulation has been debated because a correlation with hirudin levels is not linear at higher hirudin concentrations [10, 11]. Above that concentration, a nonlinear relationship between hirudin plasma levels and respective aPTT prolongation was observed, resulting in a smaller extent of aPTT prolongation at higher hirudin concentrations [10, 11]. aPTT appears to be a useful monitoring parameter, provided that hirudin anticoagulation is performed in the low-dose range, as was done in this study. Clotting tests based on thrombin time such as activated clotting time (ACT) are not helpful with regard to hirudin monitoring because of their narrow linear dose–response curve [11]. A recently developed test, ecarin clotting time (ECT) allows the anticoagulation effect to be monitored with an almost linear correlation to hirudin concentrations over the whole range from subtherapeutic to toxic hirudin levels (0.05 to 5.0 μg/ml) [11]. The ECT assay is currently not commercially available, hindering its broad use as a bedside test. Chromogenic assays for accurate determination of hirudin plasma levels are commercially available in Europe but are not yet introduced in laboratory routine. Since completion of this study, a chromogenic assay for determination of hirudin concentrations (analyzer, Behring Coagulation System; reagent, Berichrom Hirudin; both by Dade Behring) has been established at our center. However, in a large prospective, recently published multicenter study on hirudin treatment of HIT patients, hirudin plasma levels did not correlate with bleeding complications [9]. This may be due in part to sustained antithrombotic activity of hirudin even after its plasma clearance, which is most likely based on its action on clot-bound thrombin [12]. Because even an accurate test for measurement of hirudin plasma levels may not predict the bleeding risk, we attempted to keep aPTT levels between 1.5 and 2.0 × baseline values. Moreover, repetitive evaluation of the clinical situation is mandatory.

Use of hirudin in patients with a high bleeding risk

In our study, one patient suffering from alcoholic hepatitis, severe malnutrition, and viral pneumonia (patient 1) needed repetitive blood transfusions prior to hirudin treatment. To minimize bleeding, a mean daily hirudin dose of only 0.013 mg/kg body wt was given in bolus form, which resulted in a mean aPTT of 45 seconds (aPTT ratio 1.3; Table 3). The transfusion requirement did not increase after switch of anticoagulation to hirudin. In case of hirudin overdosage, the rapid elimination of the drug may be required, which could be performed by high-volume hemofiltration using high-flux hemodialyzers [13]. Compared with hemofiltration, hemodialysis provides lower hirudin elimination, as the high molecular weight of hirudin impairs diffusion. Thus, if patients are treated with hemofiltration, a higher dosage of hirudin may be required than that used in our study.

Use of hirudin in patients with a high clotting risk

In our study, one patient suffering from severe coronary artery disease repeatedly developed thromboembolic complications during the prehirudin period (patient 6). Hirudin anticoagulation was thus aimed to reach a high aPTT ratio despite anuria. To avoid clotting, a mean daily dose of 0.15 mg/kg body wt was applied as continuous intravenous infusion, which resulted in a mean aPTT of 100 seconds (aPTT ratio 3.3). Overt bleeding was not observed, and blood transfusion was not required. When applying larger doses of hirudin in patients with renal failure, the use of additional monitoring tests such as ECT or chromogenic assays for determination of hirudin plasma levels is recommended, because aPTT may no longer correlate with hirudin levels and bleeding risk.

Increasing hirudin dose requirements with recovery of renal function

Hirudin dosing depends on the volume of extracellular fluid and on drug elimination by residual renal function and extracorporal elimination, and hirudin removal by nonrenal clearance pathways can be neglected. Its distribution volume may increase because of volume substitution often necessary in critically ill patients. Initially and for maintenance dosing, the same boluses were used, guided by the aPTT response. Increasing renal clearance caused by recovering renal function will contribute to necessary hirudin dose adjustments. When patient 2 was initially anuric, the mean daily hirudin dose to achieve an aPTT of 44 seconds (aPTT ratio 1.3) was 0.026 mg/kg body wt. Upon recovering renal function, dose requirements increased in correlation to increasing daily urine volume. A mean daily hirudin dose of 1 mg/kg body wt did not prolong aPTT during that period.

In summary, these first clinical data show that anticoagulation with hirudin in critically ill patients on continuous hemodialysis can be performed without excessive bleeding risk by combining close clinical and laboratory monitoring. The hirudin dose has to be reduced because of renal failure but requires adjustment for residual or recovering renal function and extracorporal elimination.
To provide optimal anticoagulation in this setting will nevertheless be a challenge in intensive care nephrology.

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REFERENCES