Effects of argatroban as an anticoagulant for haemodialysis in patients with antithrombin III deficiency

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Abstract

Background. In congenital or acquired antithrombin III-deficient patients undergoing haemodialysis, coagulation or residual blood in the blood circuit and dialyser is commonly observed under anticoagulation with heparin. Argatroban, a synthetic thrombin antagonist, directly inhibits thrombin activity in a manner that is different from that of heparin, thereby displaying an anticoagulating effect without the activation of antithrombin III. For this reason, the anticoagulating effect of argatroban in haemodialysis patients with antithrombin III deficiency was investigated.

Methods. A retrospective nationwide survey was conducted among patients with congenital or acquired antithrombin III deficiency who had undergone haemodialysis with argatroban as an anticoagulant from April 1996 to April 2000. Inclusion criteria were patients with antithrombin III activity <70% of normal, and patients in whom blood coagulation or residual blood in the extracorporeal circuit could not be prevented by the use of heparin during haemodialysis.

Results. Of 80 patients who underwent haemodialysis with argatroban, 59 met the inclusion criteria. Compared with the data before the administration of argatroban, significant improvements of residual blood in the dialyser and arterial and venous drip chambers were observed at the last administration of argatroban. A significant rise in antithrombin III activity was also observed. Among 80 safety analysis cases, no adverse events were reported in 66 patients (82.5%). As severe adverse events, one showed bleeding tendency and one had prolongation of prothrombin time.

Conclusion. Argatroban was an effective and safe anticoagulant for haemodialysis in patients with congenital or acquired antithrombin III deficiency.

Keywords: anticoagulation; antithrombin III; argatroban; haemodialysis; thrombin inhibitor

Introduction

One important aspect of haemodialysis treatment is the use of an anticoagulant. While heparin has been widely used as an anticoagulant in haemodialysis, it has been pointed out that the use of heparin was accompanied by several adverse reactions including the development of haemorrhagic lesions and osteoporosis, activation of platelet function, lipid degradation, and so on. Furthermore, cases have been reported in which even the use of large amounts of heparin could not prolong coagulation time sufficiently, resulting in coagulation of the extracorporeal circuit [1]. One of the factors responsible for blood coagulation in the blood circuit is antithrombin III deficiency. Since heparin inhibits blood coagulation by activating antithrombin III, it is thought that blood coagulation cannot be prevented by a large dose of heparin in patients with congenital and acquired antithrombin III deficiency and patients with a decreased affinity between antithrombin III and heparin.

Argatroban is a synthetic antithrombin agent that has been developed in Japan. Since argatroban selectively inhibits thrombin to prevent blood coagulation without affecting antithrombin III activity, it is expected that its use as an anticoagulant in haemodialysis patients with antithrombin III deficiency may be beneficial. Therefore, a nationwide survey of the efficacy and the safety of argatroban was conducted on all congenital or acquired antithrombin III deficiency patients who had undergone haemodialysis with argatroban as an anticoagulant.

Subjects and methods

Patients

A retrospective nationwide survey was conducted on congenital or acquired antithrombin III-deficient patients under haemodialysis, receiving argatroban as an anticoagulant for haemodialysis from April 1996 to April 2000, whose antithrombin III activity was <70% of normal activity
and in whom blood coagulation or residual blood in the extracorporeal circuit could not be prevented by the use of heparin.

Two kinds of surveys were carried out: (i) sending questionnaires twice (1997 and 1999) to institutes which belonged to the Japanese Society for Dialysis Therapy as an institutional member; and (ii) sending questionnaires four times (annually from 1977 to 2000) to all facilities commercially receiving argatroban. Precise investigations were performed in all patients identified as having been administered argatroban for haemodialysis.

Concerning questionnaire (i), among the 2646 institutions which belonged to the Japanese Society for Dialysis Therapy, 1320 institutions (49.9%) returned the questionnaires in 1997, which increased to 52.9% (1507/2851 institutions) in 1999. Concerning questionnaire (ii), the facilities receiving argatroban, 1198, 1428, 1826 and 2076 (all 100%) responded to the questionnaires in 1997, 1998, 1999, and 2000, respectively. Therefore, a total of 9355 responses to the questionnaires over the 4-year survey period was obtained, capturing a total number of 96 haemodialysis patients who had been treated with argatroban.

**Evaluated factors**

The following data of patients were collected for this study: gender, age, duration of haemodialysis, underlying renal disease, body weight, diagnosis of antithrombin III deficiency or decrease, the dosage of argatroban used, duration of argatroban administration, names of anticoagulants prior to argatroban administration, residual coagulation in the extracorporeal circuit, dialysis conditions and antithrombin III activity. The evaluation criteria of the residual blood coagulation in the dialyser and blood circuit are shown in Table 1.

Patients displaying greater than score II of residual blood in any one of three places (dialyser, arterial or venous chambers) before the use of argatroban and patients with antithrombin III activity < 70% of normal subjects were subjected to an efficacy evaluation for analysis. The changes in residual blood coagulation and antithrombin III activity were evaluated at the last dialysis with argatroban. Antithrombin III activity levels were measured at each institute, but the method for evaluation did not change before and after the usage of argatroban.

All patients were subjected to a safety evaluation, in which adverse events were assessed. The overall safety evaluation was judged according to the incidence rate and the severity of adverse events, for which a causal relationship to argatroban could not be excluded.

**Statistical analysis**

Results were expressed as mean ± SD. The appearance of residual blood in the dialyser and the arterial and venous drip chambers was analysed by Wilcoxon’s two-sample test. The profile of antithrombin III activity was analysed by the paired t-test. Statistical significance was regarded to be \( P < 0.05 \).

**Results**

**Patient’s baseline data**

Of the 96 patients receiving argatroban, 80 were eligible for the safety study analysis; 16 patients were not included due to refusal to participate in the study or because a complete study could not be done.

Of the 80 patients in the safety analysis, 59 were included for the efficacy study analysis. Those patients excluded from the analysis were classified as follows: anticoagulant for plasmapheresis (two patients), antithrombin III activity not less than 70% (seven patients), antithrombin III activity undetermined (eight patients), no residual blood in either the dialyser or drip chambers (three patients) or efficacy evaluation not done (one patient).

Patient baseline data for both the safety and efficacy analysis groups are summarized in Table 2. The mean age in the safety and efficacy analysis groups was 63.9 ± 12.9 and 63.9 ± 13.4 years, respectively. The mean duration of haemodialysis was 3.9 ± 6.0 and 4.6 ± 6.5 years, respectively. The mean duration of argatroban use in both groups was 18.4 ± 56.2 and 18.0 ± 62.7 weeks, respectively. Most patients received argatroban at the dose of 10 mg initially and 20–30 mg/h during continuous administration.

**Residual blood coagulation in the blood circuit**

Of the 59 patients in the efficacy analysis, 52 (88.1%) displayed more than score II of residual blood in the dialyser before dialysis with argatroban administration. This number had decreased to 17 (28.8%) on the last dialysis with argatroban administration. A significant improvement in the appearance of residual blood in the dialyser was observed in patients after argatroban treatment as compared with pre-treatment levels (Figure 1). Prior to argatroban administration, residual blood above score II in the arterial drip chamber was observed in 43 patients (78.2%), but was seen in only 12 patients (21.8%) at the last dialysis with argatroban administration. A significant improvement in the appearance of residual blood in the arterial drip chamber was observed after argatroban treatment when compared with that before treatment (Figure 2).

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**Table 1. Classification criteria of residual blood coagulation in the dialyser and blood circuit**

<table>
<thead>
<tr>
<th>Score</th>
<th>Residual blood in haemodialyser</th>
<th>Residual blood in arterial/venous chamber</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No thrombus or a few hollow fibres with thrombus</td>
<td>No blood coagulation</td>
</tr>
<tr>
<td>II</td>
<td>A small number of thrombi in a bundle of hollow fibres</td>
<td>Slight blood coagulation</td>
</tr>
<tr>
<td>III</td>
<td>Thrombus in half of the hollow fibres</td>
<td>Moderate blood coagulation</td>
</tr>
<tr>
<td>IV</td>
<td>Difficult to continue dialysis due to blood coagulation</td>
<td>Difficult to continue dialysis due to blood coagulation</td>
</tr>
</tbody>
</table>
The incidence of above score II residual blood in the venous drip chamber was observed in 45 patients (81.8%) before argatroban administration, vs 15 patients (27.3%) on the last dialysis with argatroban administration. The decrease of residual blood found in the venous drip chamber following argatroban treatment, as compared with pre-treatment, was significant (Figure 3). Pre-dialysis haematocrit (Ht) and haemoglobin (Hb) levels within 2 weeks at the evaluation of residual blood coagulation of the dialyser and blood circuit were recorded in 49 cases. These values did not change
before and at the last dialysis with argatroban (Ht: 27.8 ± 5.1 vs 27.9 ± 5.4%; NS, Hb: 9.0 ± 1.7 vs 8.9 ± 1.7 g/dl; NS, respectively). For these 49 patients, residual blood coagulation in the dialyser and blood circuit was also significantly decreased at the last dialysis with argatroban (Table 3). Mean blood flow rate before and at the last dialysis with argatroban was 221 ± 24 and 218 ± 21 ml/min in the above 49 patients, respectively (NS). Residual blood coagulation before and at the last use of argatroban was evaluated at the same session of the week in 46 out of 49 patients.

**Antithrombin III activity**

Antithrombin III activity before argatroban administration was 60.8 ± 7.2%, whereas it increased to 71.7 ± 13.9% after argatroban (Figure 4). This significant increase of antithrombin III activity was observed in 38 patients in whom antithrombin III activity was evaluated both before and after argatroban administration.

**Adverse events**

Thirty-two adverse events for which a causal relationship with argatroban could not be excluded occurred in 14 cases (17.5%) (Table 4). There were two patients with serious adverse events. One patient, who had a prolonged prothrombin time, improved after termination of argatroban administration. The other patient, who had undergone continuous haemodiafiltration (CHDF) because of multiorgan failure, displayed bleeding tendency and anaemia. The patient died of multiorgan failure, but a causal relationship with argatroban administration was not clear.

Sixty-six patients (82.5%) underwent haemodialysis using argatroban as an anticoagulant for 18 weeks without any adverse events.

**Discussion**

Argatroban is a synthetic inhibitor of thrombin. Its characteristic is to exert anticoagulating activity through the inhibition of thrombin, a key enzyme in the cascade of the blood coagulation pathway, by specific and reversible binding to the active site of thrombin. Argatroban also inhibits fibrin formation [2], platelet aggregation [3] and vasoconstriction [4]. Argatroban brings about its anticoagulation effect without requiring antithrombin III. The inhibitory action of argatroban is highly selective against
thrombin, and is extremely low against other serine proteases, such as trypsin, plasmin and factor X [5].

Heparin is a cofactor of antithrombin III and displays catalytic anticoagulant properties. Therefore, the anticoagulating effect of heparin is antithrombin III dependent, which is quite different from the action of argatroban.

The antithrombotic effect of argatroban and heparin was examined in antithrombin III-deficient rats. Argatroban significantly reduced the size of the thrombus formed in the experiment as compared with the control, whereas no such effect was observed with heparin treatment [6]. On the basis of these results, it was expected that argatroban could be beneficial as an anticoagulant for haemodialysis patients with antithrombin III deficiency.

A report from a nationwide survey conducted in 1991 by Ota et al. [1] in Japan demonstrated that only 84 patients (0.14%) with residual blood in the extracorporeal circuit after haemodialysis displayed antithrombin III activity <70%, suggesting that patients with residual blood in the extracorporeal circuit due to a decrease in antithrombin III activity are very rare. In the present study, there were only 96 haemodialysis patients receiving argatroban over the 4-year study period.

Although the number of antithrombin III-deficient patients complaining of residual blood in the blood circuit was not large, it is important to study the effect and safety of argatroban for these haemodialysis patients in order to provide an adequate dialysis dose and good prognosis.

The results of this study demonstrated that the administration of argatroban to patients showing decreased antithrombin III activity and who had residual blood when heparin was administered significantly decreased the appearance of residual blood in the dialyser and arterial and venous drip chambers, and was able to significantly increase the antithrombin III activity. Blood viscosity (Ht level) and blood flow rate are the determinant factors for the residual blood coagulation in the extracorporeal circuit. However, these factors did not change in at least 49 patients in whom data had been recorded. The ultrafiltration volume during a dialysis session, which also contributes to the residual blood coagulation, seems not to be changed by the fact that residual blood coagulation was evaluated at the same session of the week in 46 out of 49 patients. These results suggest that the improvement in residual blood coagulation did not result from a change in dialysis condition or Ht level.

Although argatroban administration decreased the residual blood in the extracorporeal circuit more than was the case with heparin, there were five patients in whom argatroban showed no effects. Of these, one patient had received argatroban only once, and one
The patient had received it twice. The dose of argatroban continuously administered during haemodialysis was usually 5–40 mg, but the amount of argatroban should be changed depending on residual blood or other patient conditions. It is therefore possible that the dose adjustment was not adequate for these two patients. In one patient, there was no residual blood when argatroban and an oral antiplatelet drug were taken together, but once the patient stopped taking the antiplatelet drug, residual blood was observed, suggesting that enhanced platelet function was responsible for the formation of the residual blood. In the other patients, it was suspected that the residual blood was formed due to reasons other than coagulation/platelet system, since these patient not only received an increased dose of argatroban, but also received the antiplatelet drugs.

Marciniak et al. [7] reported a deficiency of antithrombin III from the long-term use of heparin. Brant et al. [8] reported that a depletion of antithrombin III was also observed in haemodialysis patients receiving heparin. It is speculated that there may be an increase in the number of haemodialysis patients in whom insufficient anticoagulating effects will be achieved by heparin administration, due to chronic antithrombin III consumption. Yoshida et al.
reported that a significant decrease in the antigen and activity level of antithrombin III was observed in patients receiving haemodialysis for >1 year, based on the 2-year survey of antithrombin III. The results from the present study suggest that argatroban is a promising new anticoagulant to replace heparin for patients with decreased antithrombin III activity. Furthermore, argatroban has been approved for an indication to prevent and treat thrombus formation in heparin-induced thrombocytopenia in the USA and Canada. The usefulness of argatroban administration was also reported in patients with thrombus formation induced by heparin [10]. Therefore, these results suggest that the administration of argatroban is effective not only for the prevention of thrombus formation (residual blood) in patients with decreased antithrombin III activity due to heparin use, but also for the prevention of thrombocytopenia and thrombus formation in patients with heparin-induced thrombocytopenia.

Regarding the safety during argatroban administration, liver and biliary tract dysfunction was the most frequent adverse reaction observed in patients with chronic arterial obliteration and cerebral thrombosis, which had been major approved indications of argatroban in Japan. However, the incidence of liver and biliary disorder in this study was only 2.5%, whereas that of haematological disorders was much higher (the incidence rates of platelet, bleeding and clotting disorders, and anaemia were 12.5 and 6.25%, respectively). This finding is specific to the haemodialysis patients who have been receiving anticoagulants for long periods of time.

About a quarter of the dose of administrated argatroban is excreted in urine within 24 h. Argatroban could not be removed by dialysis. Therefore, in patients with renal failure, careful attention should be paid to the onset of bleeding tendency due to overdose of argatroban.

In conclusion, argatroban was administered as an anticoagulant for haemodialysis to antithrombin III-deficient haemodialysis patients with <70% of normal activity in whom sufficient anticoagulation could not be achieved using heparin. A significant decrease in the appearance of residual blood in the extracorporeal circuit and an increase in antithrombin III activity were observed after the use of argatroban. No adverse reactions were observed in 82.5% of patients. These results suggest that argatroban is a very effective and safe anticoagulant for haemodialysis patients whose antithrombin III activity is <70% of normal activity, and in whom residual blood in the extracorporeal circuit could not be prevented by heparin. On the basis of these results, argatroban appears to be very effective and safe as an anticoagulant for the treatment of haemodialysis patients with reduced antithrombin III activity.

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**Appendix**

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