Safety of Combining Ticlopidine with Nadroparin in the Routine Treatment of Chronic Hemodialysis Patients

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Dear Sir,

In patients with end-stage renal disease, hemodialysis has been routinely performed using standard heparin as the anticoagulant drug. During the last years low molecular weight heparins (LMWH) have been increasingly used. LMWH possess a specific activity towards activated factor X. There is on the contrary a reduced effect on general clotting tests such as activated partial thromboplastin time (APTT) and on platelet functions. With a prolonged elimination time LMWH can be administered as a single predialysis dose. Although the safety of this approach has been shown in chronic and acute dialysis procedures [1-3], alternatives for high risk patients have been proposed recently [4]. Due to accelerated atherosclerosis and increasing age of the dialysis population, there is a growing tendency to use antiplatelet drugs. Ticlopidine is a powerful inhibitor of the second phase of ADP-induced platelet aggregation and has proven efficacy in the prevention of thrombosis in the general population and of arteriovenous fistula occlusion in dialysis patients [5, 6]. In dialysis patients the safety of the combination of this drug with standard heparin has been challenged by the surgeons, because of hemostatic problems in subsequent surgery, especially for kidney transplantation. This has led to exclusion from treatment for transplant candidates. A 50% reduced dose has been used successfully in these patients without bleeding problems [7]. Because of scarce information in the literature, we studied the safety and effect on nadroparin dose after adding ticlopidine to the standard LMWH anticoagulation in a group of hemodialysis patients. The study design was open, placebo-controlled, randomized and prospective. All 51 chronic hemodialysis patients at Stuivenberg General Hospital were considered for participation. Twenty-four patients had to be excluded according to predefined inclusion and exclusion criteria. Eight were dialyzed through a central catheter, 10 were already taking anti-platelet drugs and 6 refused to participate in the study. The 27 remaining patients gave their informed consent after approval of the study by the local ethical committee. They were randomly assigned to continue on nadroparin (Fraxiparine®, Sanofi) anticoagulation (group N, n = 14) or to start with ticlopidine (Ticlid®, Sanofi) in a dose of 250 mg once a day (group NT, n = 13) in addition to nadroparin.

After randomization there was a 2-week baseline period for stabilization of the nadroparin dose. In the 3rd week the patients randomized to the ticlopidine group started on active treatment. During the 4th week the dose of nadroparin was lowered in both groups with 1,250 AXa IC units (0.05 ml) during each session, until a decreased quality of blood restitution in the dialyzer or a visible clot in the extracorporeal circulation was noted. Then, the dose was increased again with one step. The quality of blood restitution was graded as good (1 = clear dialyzer), medium (2 = pink dialyzer), poor (3 = partly clotted) or very poor (4 = complete clotting

and need for changing the extracorporeal circuit). The active treatment period was 3 weeks. The following variables were analyzed: minor and major hemorrhage, manual compression time after dialysis, presence of visible clots in the extracorporeal circulation, number of packed cell transfusions and laboratory parameters: plasma hemoglobin, AXa, APTT, thrombin time and bleeding time. All values are expressed as mean $\pm$ CI. The non-parametric Mann-Whitney U test was used for comparison of both groups and different time periods throughout the study period. Significance was set at the 0.05 level.

Both groups were comparable for age, sex, months on dialysis, dry weight, and dose of nadroparin at start. Mean $\pm$ CI for groups N and NT were 265 ± 82 and 252 ± 62 AXa ICU/kg, respectively ($p = 0.9$). There was however a significant difference between both groups in the number of platelets: $189 \pm 103 \pm 36 \times 10^3/\text{mm}^3$ for group N and $312 \pm 103 \pm 55 \times 10^3/\text{mm}^3$ for group NT ($p = 0.003$). This difference could not be explained by outliers or by differences in other coagulation tests, which were similar in both groups. After adding ticlopidine to the nadroparin treatment the dose of nadroparin could be reduced from 252 ± 62 to 204 ± 65 AXa ICU/kg ($p = 0.006$). Anti-Xa activity decreased correspondingly from 0.74 ± 0.09 to 0.56 ± 0.19 IU/ml ($p = 0.048$), while the quality of blood restitution after dialysis remained constant (before 1.3 ± 0.3 ; after 1.3 ± 0.3).

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From an economic point of view anticoagulation represents less than 1 %, even using LMWH, of total expenditures for dialysis per patient per year in Belgium ($\pm$ 83,000 US\$), but it is nevertheless worthwhile mentioning that about 0.2% can be gained from the combination with an antiplatelet drug without decreasing the quality of blood restitution. It can be concluded from this short-term study that it is safe to combine LMWH with a reduced dose of an antiplatelet drug in hemodialysis. To show the long-term safety and efficacy of this combination in the prevention of cardiovascular thrombosis a large, randomized, placebo-controlled, multicenter study would be needed.

Acknowledgment

This study was partially supported by a grant from Sanofi, Belgium.

However, at the end of the study there was no significant difference between groups N and NT (table 1) for the dose of nadroparin, anti-Xa activity, quality of blood, percentage of dialysis sessions with good quality of blood restitution, manual compression time, minor and major hemorrhage (none in both groups), presence of visible clots, number of packed cells administered, plasma hemoglobin, APTT, thrombin time and bleeding time. There was a

small, albeit statistically not significant difference in the number of dialysis sessions with poor quality of blood restitution: four in group N during the active treatment phase against one episode during the baseline period in both groups and in group NT during the active treatment phase. The difference in platelets however was confirmed during the whole study (table 1). The decrease in nadroparin dose would cause annual savings of 190 US\$ per patient for anti-coagulation during dialysis.

These short-term data show that nadroparin and ticlopidine can be combined safely.

Moreover, the dose of nadroparin can be reduced, at least under close supervision in an experimental design even without adding an antiplatelet drug. However, even in combination with a lowered number of platelets existing before the start of the study, there was a tendency for clotting in group N when attempts were made to decrease the nadroparin dose, both expressed as the quality of blood restitution and as the number of poor restitutions. Therefore we can assume that the reduced dose of ticlopidine that was used in this study has an additive effect. This hypothesis has to be interpreted with some caution, due to the difference in the number of platelets at the start of the study, that could not be explained by any difference in drug intake, the use of drugs that are known to cause thrombopenia, differences in dialyzer use or dialysis strategy, or differences

Table 1. Results after 3 weeks of active treatment with nadroparin (group N) and nadroparin combined with ticlopidine (group NT)

Group N (n=14)	Group NT (n = 13)		
Dose AXa, ICU/kg	204 ± 79	204 ± 65	NS
Anti-Xa, IU/ml	0.62 ± 0.17	0.56 ± 0.19	NS
Blood restitution	1.4 ± 0.4	1.3 ± 0.3	NS
Blood restitution, %	83	79	NS
Manual compression time	20.8 ± 4.8	20.8 ± 7.0	NS
Hemorrhage	0	0	NS
Platelets, IOV/mm ³	200 ± 42	326 ± 78	0.022

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Nephron 1997;77:484-485
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