

THE USEFULNESS OF THE MULTI-ENZYME INHIBITOR, NAFAMSTAT MESILATE, IN HIGH BLEEDING RISK HAEMODIALYSIS

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Summary

Nafamstat mesilate, an inhibitor of multi-enzymes including the coagulation and complement cascade, was examined as an anticoagulant for haemodialysis in 66 dialysis patients. Nafamstat mesilate prevented coagulation as heparin, and its anticoagulant effect was mostly limited to the extracorporeal circuit. Although very high doses of nafamstat mesilate prevented dialysis associated leucopenia in animal experiments, it failed to suppress complement activation during haemodialysis clinically. Nafamstat mesilate showed no lipolytic activity.

Introduction

Nafamstat mesilate, 5-amidino-2-naphthyl p-guanidinobenzoate dimethanesulfonate (MW 540), is a strong multi-enzyme inhibitor. As nafamstat mesilate inhibits the enzymes of the coagulation cascade, it may possibly be applied as an anticoagulant for haemodialysis. Furthermore, it has several beneficial features over heparin. Firstly, as the biological half-life is very short, it can be expected not to affect systemic coagulation when used as an anticoagulant. Secondly, its complement-inhibitory effect may result in a suppression of complement activation during haemodialysis with cellulose membrane. Thirdly, due to absence of lipolytic activity, it may prevent some harmful clinical effects on free fatty acids, and, finally, because of lack of Ca-binding activity, it may favourably affect the bone disease of dialysis patients.

Materials and methods

Clinical study

Nafamstat mesilate was used as an anticoagulant in 66 patients (mean age 49.1±13.2) on regular haemodialysis for 12 weeks, and the effects were compared with heparin. The initial infusion rate was set at 40mg/hr, and subsequent

dosage was adjusted according to the coagulation status of the extracorporeal circuit. At an optimum dose in each individual, residual blood volumes in the dialysers and blood chambers and the coagulation times were studied. The coagulation time was measured by the celite clotting time on blood specimens drawn from each of three points in the blood circuit (Figure 1). The clotting

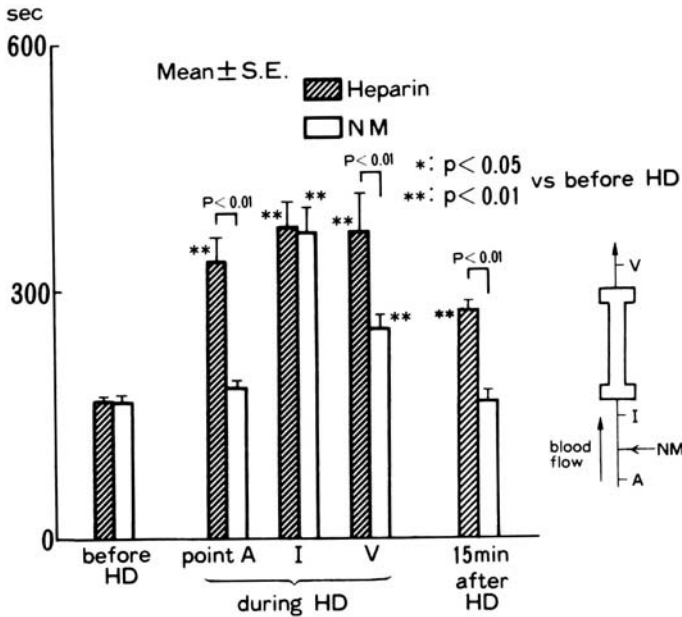


Figure 1. The change in celite clotting time during haemodialysis (HD) with heparin or nafamstat mesilate (NM)

time at the puncture sites after removal of the needles was also determined. Changes in lipids, blood cell counts, blood gas and complement activation during haemodialysis were studied. Other laboratory parameters such as antithrombin III, fibrinogen and hepatic enzymes were evaluated only at the start and at the end of the 12 week study.

Animal experiment

Effects of nafamstat mesilate on blood cell counts and CH_{50} during haemodialysis were examined in three mongrel dogs with infusion of high doses of nafamstat mesilate combined with pre-infusion, hourly infusion rates being 200 or 300mg for both infusion periods.

Results

Optimum dosages of nafamstat mesilate ranged from 3 to 80mg/hr, the average hourly infusion rate being 28.2 ± 15.6 mg/hr. Although there were no differences

in residual blood volumes in dialysers between haemodialysis with heparin and nafamstat mesilate, slight increase in fibrin clot was noted with nafamstat mesilate in both arterial and venous drip chambers.

Figure 1 illustrates changes in celite clotting time during haemodialysis with the two anticoagulants. Heparin induced a significant prolongation of celite clotting time of arterial, dialyser and venous blood, and the prolongation of celite clotting time was maintained at 15 minutes after haemodialysis. On the other hand, nafamstat mesilate induced prolongation of celite clotting time of only dialyser blood, and the celite clotting time of arterial blood did not increase and prolongation of celite clotting time of venous blood was significantly diminished. Furthermore, unlike heparin, celite clotting time after 15 minutes of haemodialysis completely recovered to the level prior to dialysis. These data indicate that the anticoagulant effect of nafamstat mesilate was mostly limited to the extracorporeal circuit. The clotting time at the puncture sites after removal of the needle was also shorter with nafamstat mesilate than with heparin.

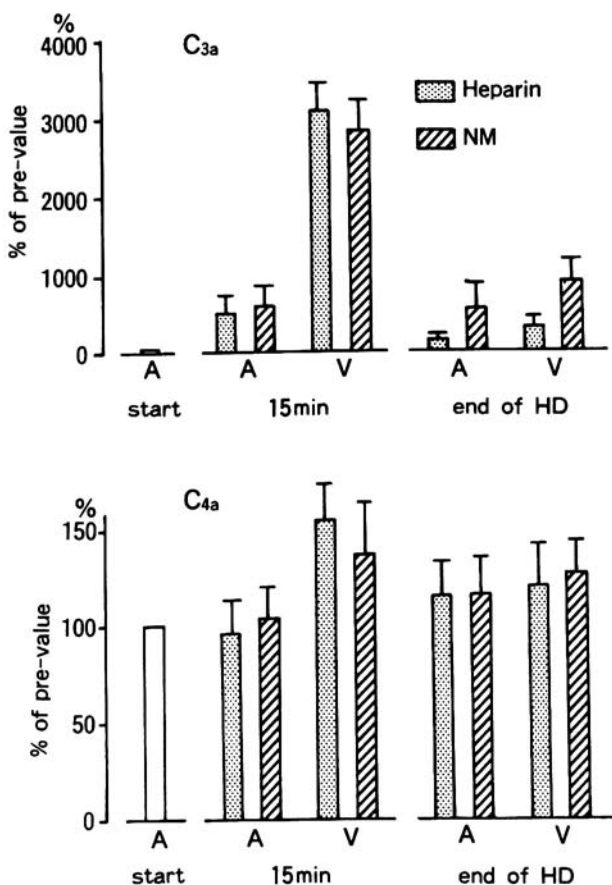


Figure 2. The effect of nafamstat mesilate (NM) on activated complement levels during haemodialysis (HD)

To examine the effect on lipid metabolism, fasting patients were dialysed with heparin or nafamstat mesilate. During haemodialysis with heparin, significant decrease in triglyceride and an increase in free fatty acids were noted at two hours of haemodialysis. On the contrary, there were no significant changes in lipids during haemodialysis with nafamstat mesilate.

Figure 2 illustrates the complement activation, as measured by C_{3a} and C_{4a} , during haemodialysis with cellulose membranes. Both levels increased significantly during dialysis with nafamstat mesilate or heparin, not significantly different. Nafamstat mesilate at a clinical dose does not suppress complement activation by cellulose membranes. Similarly, the alteration in blood cell counts and blood gas during dialysis with nafamstat mesilate did not differ from heparin dialysis. Antithrombin III activity and antigen concentration, fibrinogen and hepatic enzymes did not show any significant changes during the study.

Adverse effects, supposed to result from nafamstat mesilate, were observed in three of 66 patients. The symptoms were anorexia, general lassitude, and slight myalgia and arthralgia. All symptoms disappeared promptly after cessation of nafamstat mesilate.

Animal experiment

Figure 3 illustrates the change in leucocyte counts and CH_{50} during haemodialysis with cellulose membranes and with very high doses of nafamstat mesilate.

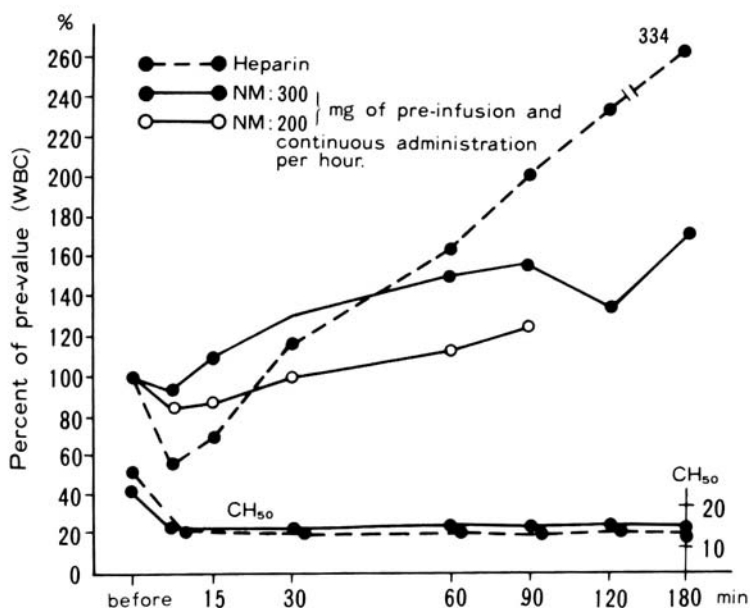


Figure 3. The changes in white blood cells (WBC) and CH_{50} during haemodialysis with heparin and nafamstat mesilate (NM) in mongrel dogs

Leucocytes decreased significantly at the initial phase of haemodialysis with heparin, whereas nefamstat mesilate at high doses, did not cause any haemodialysis leucopenia. Unlike the effect on leucocytes, the change in CH_{50} did not differ during haemodialysis with nefamstat mesilate from during haemodialysis with heparin.

Discussion

Nefamstat mesilate was studied as an anticoagulant for haemodialysis, and its anticoagulant effect was clearly demonstrated to be mostly limited to the extracorporeal circulation. The metabolism of nefamstat mesilate is very rapid and the biological half-life is calculated to be less than eight minutes [1]. Rapid turnover of the anticoagulant is an important characteristic in its use during dialysis of patients with a high bleeding risk. Gabexate mesilate was reported as a short-acting anticoagulant [2], but nefamstat mesilate has several preferable features. The anticoagulant activity of nefamstat mesilate is approximately 100 times as strong as gabexate mesilate. About 2000mg/hr of gabexate mesilate was required for haemodialysis, and even with such a high dose, complete prevention of coagulation could not be achieved. Secondly, the half-life of gabexate mesilate is too short to perform extracorporeal circulation safely. Thirdly, repeated use of gabexate mesilate was reported to result in accumulation of guanidino-caproic acid, the metabolite of gabexate mesilate, which might have several toxic effects. In this regard, the metabolite of nefamstat mesilate did not accumulate at the doses we used.

As nefamstat mesilate inhibits the enzymes of the classical complement pathway as well as those of the coagulation cascade, it was expected that complement activation by the cellulose membrane might be suppressed with nefamstat mesilate. Clinically, nefamstat mesilate could not suppress the complement activation. On the other hand, very high doses prevented the haemodialysis leucopenia in the animal experiment. In these cases, the change in CH_{50} during haemodialysis did not differ between haemodialysis with heparin and nefamstat mesilate. These findings imply the possibility either that CH_{50} in dogs does not accurately reflect the consumption of complement or that enzymes, other than the complement pathway, might participate in the cause of leucopenia. Nefamstat mesilate has a lowered inhibitory effect on the alternative complement pathway as compared with classical activation [3], and this may be a major cause of failure in suppressing complement activation in the clinical study.

Nefamstat mesilate showed no lipolytic activity and few adverse effects were noted. Although the beneficial effects of nefamstat mesilate on long-term lipid and bone metabolism still remain to be clarified, we can conclude that nefamstat mesilate has several preferable characteristics as an anticoagulant over heparin, and that it should be widely available for haemodialysis, especially in patients with high bleeding risks.

References

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