Therapeutic evaluation and spectrum of Novel Oral Anticoagulants, NOACs

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Cerebral thromoboembolism in atrial fibrillation, a life-threatening disease, has been becoming one of the most important disease in advanced ageing countries typically in Japan. Even if the patients were survived, they often would be suffered from various sequelaes including mental, speech and/or movement disturbances. Therefore prevention of cerebral thromboembolism is the most important in atrial fibrillation.treatment

Recently novel oral anticoagulants, NOACs, with inhibiting activity of procoagulant action of thrombin or factor Xa have been sufficiently developed. Therefore next task is how to use these anticoagulants efficiently minimizing bleeding complication.

This study is to investigate the mechanism of NOACs, and propose the rationale of the medicines.

Results of our studies on NOACs leading the investigation

1. Development of novel method for evaluation of thrombogenic activity using whole blood with flow conditions.

   It has been very difficult to predict attacks of athoromboembolism because present coagulation tests had developed do diagnose bleeding tendency. Therefore we developed novel coagulation test which evaluate clotting capacity under the whole blood flow conditions into the synthetic capillaries with narrow portion coated with collagen and tissue factor mimicking atheromatous plaque, named as “Total Thrombus-formation Analysis System, T-TAS”. By this method, we can quantitatively evaluate not only the thrombus generation capacity, but also qualitatively observe the thrombi formed in the capillary under the microscope.

   Using this T-TAS, we could demonstrate the priority of NOACs, optimum or over doses. We also showed the bleeding risk of combination therapy of anti-platelet and NOACs.

2. Presence of prothrombotic activity on the surface of microthrombi.

   We examined the procagulant activity on microthrobi. We could demonstrate that the presence of thrombin and/or fctor Xa activity on microthrombi resulting the growth and enlargement of the thrombi. These procoagulant activity on microthrombi was efficiently inhibited by NOACs. It was assumed that this inhibiting activity of

NOACs partly explains the therapeutic effects of the medicine.

On-going and prospective study

1.Another merit of NOACs

By using T-TAS, we demonstrated that NOACs efficiently inhibited thrombus-generation analyzing the blood from the patients treated by NOACs. Moreover generated thrombi were smaller than those of before treatment. We investigated the procoagulant activity on the thrombus surface and demonstrated that NOACs inhibited the activity resulting the thrombus-growth retardation.This may diminish the microthrombi-induced impairment of neurovascular unit. It has been found that the glymphatic system, a special kind of lymphatic system in the brain, uptakes the microthrombi via the endothelial cells and extravasate them to the Virchow-Robin space, and wash them out through cerebrospinal fluid. However this extravasation is size dependent. The first step of the microthrombi clearance is the engulfment by endothelial cells. Therefore if the size is bigger than endothelial cells, the microthombi can not be uptook by the cells. Thus NOACs may play one more effect to support the microcirculation in the brain minimizing the microthrombi.

2. Affect of procoagulant activity of microthrombin-surface on neurovascular unit

We previously demonstrated that thrombin disrupts endothelial cells, a component of neurovascular unit. Thus thrombin activity on the microthrombin surface may disturb neurovascular unit. We are going to investigate whether the NOACs ameliorate the microthrombi-induced neurovascular unit disturbance through which inhibition of microthrombi-associated procoagulant activities.