Response to Letter by Moll Regarding Article, “Hemostatic Therapy in Experimental Intracerebral Hemorrhage Associated With the Direct Thrombin Inhibitor Dabigatran”

Response:

We appreciate the interest of Dr Moll in our experimental study in which we examined the effect of different hemostatic approaches on early hematoma growth in mice treated with dabigatran etexilate. In contrast to another recently published article using a similar experimental model, treatment with high doses of dabigatran in our study induced an excess early hematoma growth compared with nonanticoagulated mice, which we documented by serial MRI. Moreover, we showed that prothrombin complex (PCC) was the most consistently effective agent preventing the excess hematoma growth in mice treated with either 4.5 mg/kg or 9 mg/kg of dabigatran etexilate intraperitoneally. Finally, we tested the effect of 3 different doses of PCC on systemic hemostasis (ie, tail vein bleeding time) as well as on intracerebral hemostasis. Interestingly, we noted some discrepancy between the effects of PCC on systemic and cerebral hemostasis. The mechanisms underlying this discrepancy as well as the striking differences between risks of systemic and intracranial bleeding in major clinical trial comparing dabigatran against warfarin for stroke prevention in atrial fibrillation are currently unclear.

We also wish to point out that the results in our study are not necessarily contrary to a recent study performed in human volunteers with PCCs and dabigatran; instead, the end points measured are different. One study measured the reversal of anticoagulation by PCCs achieved with therapeutic doses of dabigatran and did not look at bleeding, the obvious limitation being that one cannot dose healthy volunteers with high doses of anticoagulant to induce bleeding and then explore its reversal. In our study, we measured reversal of bleeding at high doses of dabigatran in an experimental model but did not measure in vitro anticoagulation reversal after addition of PCCs. There appears to be discordance between reversal of anticoagulation with dabigatran when PCCs are used to reverse the effect and reversal of bleeding. In another preclinical model, it was also shown that the lack of reversal of anticoagulation with dabigatran when using PCCs does not predict a lack of bleeding reversal.

Consistent with our statement in the concluding sentence of our article, Dr Moll underlines the importance of obtaining clinical data from patients with a hemorrhage during treatment with new oral anticoagulants. First of all, it is unknown whether new oral anticoagulants predispose to intracerebral hematoma growth in patients as has been reported for intracerebral hemorrhage associated with warfarin. Moreover, data regarding the effectiveness of different hemostatic therapies administered in these trials as well as from future stroke center-based registries are desirable. We therefore agree that the translational relevance of our findings remains to be verified in the clinical setting.

Disclosures

R.V. was an investigator in the RE-LY trial and has received speaker’s honoraria, travel support, and consulting fees from Boehringer Ingelheim Inc in the past.

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