

## Two new papers on dabigatran etexilate (Pradaxa) and intracranial hemorrhage

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The *Journal of Neurosurgery* Publishing Group is pleased to announce publication of two new studies on dabigatran etexilate (Pradaxa®) and intracranial hemorrhage: one in the *Journal of Neurosurgery* and the other in *Neurosurgical Focus*.

Dabigatran is an oral anticoagulant (blood thinner) approved by the US FDA in 2010 to lower the risk of stroke and prevent systemic embolism in persons with nonvalvular atrial fibrillation. Unlike warfarin, the most popular drug prescribed for this condition, dabigatran carries a lower risk of intracranial hemorrhage. In addition, dabigatran does not require repeated blood testing and has little interaction with other drugs or food. This makes dabigatran an attractive alternative, and since its FDA approval, use of this pharmaceutical agent has rapidly increased.

Coagulation involves many steps, and anticoagulant drugs inhibit various steps in the coagulation cascade. Warfarin, an inhibitor of vitamin K-dependent synthesis of coagulation factors, acts at earlier steps in this cascade and there are readily available means to counter its effects. Dabigatran, a synthetic direct thrombin inhibitor, acts near the end of the cascade, and to date there is no readily available pharmacological agent that has consistently proved effective in reversing the drug's anticoagulant effects in humans.

Despite the fact that dabigatran is less likely to cause intracranial hemorrhage than warfarin, if such a hemorrhage occurs, it is more difficult to reverse dabigatran's anticoagulant effects. This is especially



important when treating a patient with active hemorrhage and when considering the risks of neurosurgical intervention.

## Paper in the Journal of Neurosurgery

In the article "Dabigatran bleed risk with closed head injuries: are we prepared? Clinical article," <u>trauma surgeon</u> Dr. Michael Parra and his colleagues reviewed the case files of all <u>adult patients</u> who were examined and treated for a closed head injury from a ground-level fall at the Delray Medical Center Level I Trauma Center in Delray Beach, Florida, between February and May 2011. All of these patients suffered from subarachnoid, subdural, and/or intraparenchymal hemorrhages. The researchers separated the patients into three groups depending on their anticoagulant therapy: warfarin (15 patients), dabigatran (five patients), and no anticoagulant therapy (25 patients).

To reverse the effects of anticoagulant therapy and thus control the hemorrhages, patients who had taken warfarin were placed on a standard protocol that had proved effective in the past: transfusion of fresh frozen plasma, administration of vitamin K, and neurosurgical assessment. The five patients who had taken dabigatran were given a variety of anticoagulant therapies because there was no definitive treatment protocol in place at the authors' institution to counter dabigatran's anticoagulant effect. These therapies included use of recombinant factor VIIa (four patients), fresh frozen plasma (four patients), platelets (three patients), and dialysis (two patients).

New or progressive hemorrhages occurred more often in patients who had taken dabigatran (four of five patients) than in those who had taken warfarin (three of 15 patients). Two patients (40 percent) on a regimen of dabigatran died as a result of hemorrhage progression. None of the patients in the warfarin or no-anticoagulant-therapy group died.



The authors examined numerous demographic and clinical characteristics in patients in the three groups and found only one statistically significant difference: patients who had taken dabigatran were significantly more likely to exhibit hemorrhage progression after arrival at the hospital.

The authors point out that the purpose of the paper is not only to highlight the higher mortality rate associated with closed head injuries when dabigatran is in use, but also to make physicians aware that time is of the essence in these cases and the mortality rate could increase if there is no anticoagulation reversal protocol in place. They discuss findings of other papers on anticoagulation reversal in animals and in patients on dabigatran regimens. At their hospital, a prospective study is currently planned involving the use of a dabigatran reversal protocol for closed head injury that will include administration of activated charcoal, fresh frozen plasma, and recombinant factor VIIa, as well as hemodialysis.

Dr. Lloyd Zucker, a neurosurgeon and coauthor of the report, said, "For us, the take-away message is that studies that have demonstrated noninferiority [of agents such as dabigatran] seem to have ignored the potential effect of these drugs in the face of trauma. Certainly, with the greater propensity for utilization in the more senior members of our population—a group with a higher risk for fall and head trauma—this cannot be ignored. The potential is that this is the proverbial 'tip of the iceberg' as more agents enter the market prior to a reversal agent being available."

Parra MW, Zucker L, Johnson ES, Gullett D, Avila C, Wichner ZA, Kokaram CR. Dabigatran bleed risk with closed head injuries: are we prepared? Clinical article. *Journal of Neurosurgery*, published online, ahead of print, May 1, 2013; <u>DOI: 10.3171/2013.3JNS12503</u>.



## Paper in Neurosurgical Focus

In "Dabigatran, intracranial hemorrhage, and the neurosurgeon," Dr. Ahmed Awad and colleagues (An-Najah National University in Palestine, Massachusetts General Hospital, and Harvard Medical School) provide background information on dabigatran etexilate, review other papers on treatment of intracranial hemorrhage in patients taking dabigatran, present their own case, and offer management strategies.

Topics discussed by the authors include dabigatran's mechanism of action and pharmacokinetics, difficulties in reversing the drug's anticoagulant effects, and the potentially catastrophic effects dabigatran may have in patients who suffer intracranial hemorrhages.

Awad and colleagues recount other authors' anecdotal accounts of three elderly patients who fell while taking dabigatran and suffered intracranial hemorrhages. One patient was given recombinant factor VIIa; the treatment was ineffective and the patient died of uncontrolled hemorrhage. The second patient was treated with vitamin K and the third with factor VIII inhibitor bypassing activity (FEIBA) and hemodialysis; both patients survived. The authors also describe a case of their own: an 85-year-old woman who arrived at the emergency department with progressive confusion, difficulty in finding words, and gait problems two weeks after she had sustained a mild head injury. The patient was taking dabigatran at the time for <u>atrial fibrillation</u>. The woman was found to have a subdural hematoma that required removal; however, because of the anticoagulant effects of dabigatran, surgery could not be performed until the drug cleared her system. The authors tried hemodialysis, but the procedure had to be aborted and they took a "watchful waiting" approach until the effects of dabigatran had dissipated. Surgery was performed on the patient's third day in the hospital; despite increased hemorrhage, the procedure was successful.



Because dabigatran is a direct thrombin inhibitor, which acts near the end of the coagulation cascade, many of the usual agents used to reverse the effects of anticoagulants are ineffective. Awad and colleagues review agents that they do not expect to reverse the effects of dabigatran (such as fresh frozen plasma, vitamin K, and recombinant factor VIIa) as well as others that they say have shown some success (such as prothrombin complex concentrate and FEIBA). Despite the fact that the authors find no clear consensus on the appropriate emergency treatment of patients with intracranial hemorrhage who have taken dabigatran, they conclude that dialysis is usually effective in removing the agent and encourage its use. They also call for the development of drugs that can quickly and efficiently reverse the anticoagulant effects of dabigatran. When asked about this, Dr. Brian Walcott, a neurosurgical resident at Massachusetts General Hospital and a coauthor of the paper, said, "Dabigatran has the potential to provide an important health benefit when used for the proper indications. The lack of an available reversal agent should be recognized as an important current limitation of its use, particularly in <u>patients</u> at a high risk for falls."

Awad AJ, Walcott BP, Stapleton CJ, Yanamadala V, Nahed BV, Coumans JV. Dabigatran, intracranial <u>hemorrhage</u>, and the neurosurgeon, *Neurosurgical Focus* 34 (5):E7, 2013, published online May 1, 2013; <u>DOI: 10.3171/2013.2.FOCUS1323</u>.

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