The anticoagulant dabigatran etexilate was approved by the U.S. Food and Drug Administration last October to prevent stroke in patients with atrial fibrillation, and it has been studied for treating acute venous thromboembolism. As James Roberts, MD, discussed in these pages several months ago (http://bit.ly/02VMax), dabigatran has several potential advantages over warfarin, including minimal interactions with other drugs and food, allowing for predictable pharmacokinetics and fixed-dose administration without the need for frequent routine laboratory testing and dose adjustment.

But dabigatran (Pradaxa, Boehringer Ingelheim) represents an entirely new class of anticoagulants, and emergency physicians and toxicologists should be prepared for patients presenting with overdose or life-threatening bleeding.

What is dabigatran etexilate? This preparation is an inactive prodrug. Once absorbed, it is rapidly hydrolyzed by esterases in the GI tract, blood, and liver into dabigatran, a direct thrombin inhibitor. Through its effects on thrombin, dabigatran blocks the last stages of the coagulation cascade: cleavage of fibrinogen into fibrin, activation of platelets, and stabilization of the forming clot.

How is dabigatran metabolized? Excretion is primarily renal, with approximately 80 percent eliminated unchanged in the urine. It is not metabolized by — and does not induce — hepatic cytochrome P450 enzymes, which is why, unlike warfarin, it has few reported interactions with other drugs.

Dabigatran Toxicity: The Top 10 Questions

By Leon Gussow, MD

Management of Dabigatran in Cases of Bleeding

Patient with bleeding on dabigatran therapy

- Mild bleeding
  - Delay next dose or discontinue treatment as appropriate
- Moderate-severe bleeding
  - Symptomatic treatment
  - Mechanical compression
  - Surgical intervention
  - Fluid replacement and hemodynamic support
  - Blood product transfusion
  - Oral charcoal application* (if dabigatran etexilate ingestion <2 hrs before)
  - Hemodialysis
- Life-threatening bleeding
  - Consideration of rFVIIa or PCC*
  - Charcoal filtration*

* Based on limited nonclinical data; no experience with volunteers or patients. PCC = prothrombin complex concentrates (non-activated or activated). rFVIIa = recombinant activated factor VII.

Source: Adapted from Thromb Haemost 2010;103(6) 1116.

What is its pharmacokinetics? Peak anticoagulant effect of dabigatran occurs one to three hours after ingestion. The half-life in patients with normal renal function is approximately 12 to 14 hours, but may exceed 24 hours if creatinine clearance is significantly reduced. With renal insufficiency, drug levels can build up if the dose is not adjusted or discontinued. It is not known how, if at all, the pharmacokinetics of dabigatran change in massive overdose.

Are there significant drug interactions with dabigatran? The package insert states that rifampin “reduces exposure to dabigatran [that is, decreases blood levels] and should generally be avoided.” Although quinidine, ketoconazole, amiodarone, and verapamil may increase levels, it is not known if, at all, the pharmacokinetics of dabigatran change in massive overdose.

In Brief

The Embalming Fluid High

Three teenagers in Corpus Christi, TX, overdosed on embalming fluid in July, according to a report from MSNBC.com, and police there also are investigating two burglaries of formaldehyde from a funeral home.

Users apparently are soaking marijuana joints in formaldehyde to create a hallucinatory effect, Dr. Bret Nicks, an assistant professor of emergency medicine at Wake Forest Baptist Health in Winston-Salem, NC, told MSNBC. He said emergency physicians first saw cases of formaldehyde overdoses in the early 1990s. Symptoms include toxic psychosis and hallucinations similar to PCP, he said, adding that users can also experience blurred vision, headaches, panic, paranoia, and
What is the treatment for a patient on dabigatran who presents with bleeding? Given the limitations of testing and lack of proven antidote, this situation will be a real challenge for emergency practitioners and toxicologists. This is uncharted territory, with current recommendations based on limited data and speculation. Van Ryn et al recently presented a treatment algorithm that may be the best we have at this point. (Thromb Haemost 2010;103[6]:1116; see figure.)

Comments about this article? Write to EMN at emn@lww.com.

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Evidence exists to make an informed clinical risk-benefit analysis regarding the use of PCCs. There is no reason to believe that protamine or vitamin K would be helpful in dabigatran-associated bleeding, and there is no clinical experience or evidence regarding use of fresh frozen plasma.

Is there any role for hemodialysis in dabigatran toxicity? Possibly. Dabigatran is a small molecule with low binding to plasma proteins and a moderate volume of distribution, making it amenable to dialysis. One study found that two hours of dialysis removed about 60 percent of the drug in end-stage renal failure patients on maintenance hemodialysis who were given a single subtherapeutic dose of dabigatran etexilate. With the overdose patient who is not bleeding, hemodialysis would seem unnecessary. Patients on dabigatran who present with life-threatening bleeding might theoretically benefit from dialysis, but no clinical data address this question, and the logistics of accomplishing dialysis in these patients would be formidable.

What is the best treatment for an acute dabigatran overdose? Dabigatran etexilate is absorbed to activated charcoal. Administering a single dose of activated charcoal within one or two hours of ingestion would be reasonable if there are no contraindications. Measuring aPTT or TT may indicate anticoagulation effect, but we still don’t know how to determine the clinical implications of numerical results. Some authors suggest that if renal function is normal, significant drug effect will resolve within one day. If this is the case, 24 hours of observation should suffice.