U.S. Food and Drug Administration
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Atrial fibrillation, oral anticoagulant drugs, and their reversal agents

Ellis F. Unger, M.D., Director of FDA's Center for Drug Evaluation and Research's Office of Drug Evaluation I in the Office of New Drugs, discusses atrial fibrillation along with oral anticoagulant drugs and their reversal agents.

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More than 3 million Americans have atrial fibrillation, a problem with the electrical system of the heart that causes an irregular heart rhythm. Atrial fibrillation can produce palpitations, shortness of breath, lightheadedness, weakness, and chest pain, or may occur without symptoms. The main concern, however, is that atrial fibrillation can lead to the formation of blood clots in the heart, which can travel to the brain and cause a stroke.

There are a number of treatments—drugs and procedures—intended to correct the fundamental heart rhythm problem in patients with atrial fibrillation, but the main focus of treatment is to try to decrease the rate of stroke by preventing the formation of blood clots. This is accomplished with taking anticoagulant drugs or "blood thinners."

Decreasing stroke risk

Anticoagulants have been known for many years to produce a striking (more than 50%) decrease in the rate of stroke, but they also prevent clotting in locations and situations where clotting is desirable. In other words, they can cause bleeding.

Until recently, warfarin (approved in 1954 and marketed under the brand names Coumadin and Jantoven) had been the only drug approved for the prevention of stroke in patients with atrial fibrillation. But the anticoagulant effect of warfarin must be carefully monitored with periodic blood tests. If the effect is too small, it will fail to prevent strokes; if the effect is too high, it will cause excess bleeding. Thus, the dosage of warfarin must be carefully adjusted to keep the blood thinning effect in the right range.

Since 2010, FDA has approved four new oral anticoagulant drugs – Pradaxa (dabigatran), Xarelto (rivaroxaban), Eliquis (apixaban), and Savaysa (edoxaban). Like warfarin, all four are "blood thinners" that reduce the overall risk of stroke related to atrial fibrillation, but they can also cause bleeding.

Comparing blood thinner options

On the basis of clinical trials that included more than 50,000 patients from around the globe, FDA concluded that all four drugs were either equivalent to, or more effective than, warfarin in preventing strokes, with an acceptable risk of bleeding. Of particular interest, the four new drugs were substantially less likely than warfarin to cause a particular kind of bleeding leading to stroke – a “hemorrhagic stroke,” a stroke caused by bleeding into the brain, which is different from the strokes caused by the clots that go to the brain in atrial fibrillation.

Pradaxa, Xarelto, Eliquis, and Savaysa have some additional advantages, including fewer interactions with food and other drugs, rapid onset, and freedom from the need to have periodic blood test monitoring. And whereas the effects of these new drugs wane within a short time frame after they are stopped (within a day or so), the effects of warfarin persist for many days after it is discontinued.

Reversal agents – the best antidote

Reversal agents are used to counter the effects of anticoagulants in life-threatening situations of uncontrolled bleeding. Vitamin K is the reversal agent for warfarin, and FDA recently approved the first reversal agent for the class of “new anticoagulant drugs,” Praxbind (idrucizumab). Praxbind is the reversal agent for Pradaxa and is approved for use in emergency situations when bleeding due to Pradaxa’s anticoagulant effects can’t be controlled.

With reversal agents now available for Pradaxa and warfarin, we have been asked if FDA should continue to allow marketing of anticoagulant drugs that do not have a reversal agent. The short answer to that question is yes. The approvals of Pradaxa, Xarelto, Eliquis, and Savaysa were based on large clinical trials where the rates of strokes and bleeding were carefully monitored and compared, and they caused no more bleeding than warfarin. In fact, two drugs, Eliquis and Savaysa, caused less bleeding than warfarin. Three of the drugs (Pradaxa, Eliquis, and Savaysa) were superior to warfarin in preventing strokes and other important blood clots, and Xarelto was very similar to warfarin. As noted above, all four drugs caused fewer intra-cranial hemorrhages than warfarin. For these reasons, it was clear that the drugs were worthy of approval and continue to provide valuable options for patients who require anticoagulant therapy.

We recognize, however, that patients with severe, life-threatening bleeding require immediate therapy, and these patients might benefit from a reversal agent. Pradaxa and warfarin now have reversal agents, and there is much interest in developing such agents for the other drugs in this class.

Fatal bleeding, a rare occurrence

It is important to understand, however, that most of the bleeding associated with anticoagulants is not life-threatening; in fact, fatal bleeding is quite rare. We have concluded for all of the anticoagulants used in atrial fibrillation that the benefit of preventing strokes outweighs the increased risk of bleeding. Although bleeding can cause significant morbidity, most of the bleeding that occurs with these agents is not serious, and does not cause the kind of permanent disability or death that strokes cause.

Importantly, only about half of the 3 million U.S. patients with atrial fibrillation use anticoagulants. Those who do not use anticoagulants are largely unprotected from the high risk of life-altering strokes, even if they take aspirin. Data show that many patients who start anticoagulants take them for less than six months instead of taking them on a long-term basis as they should. We hope that by providing new anticoagulant options for patients with atrial fibrillation, more patients will be protected against devastating strokes.

Post-marketing assessment

We are constantly examining patient safety data and conducting other surveillance activities after products are on the market to ensure that the labels reflect current knowledge with regard to benefits and risks. These data are quite valuable for understanding possible side effects and for assessing whether reported concerns are caused by the drug.

Following the approval of Pradaxa, FDA received a large number of reports of bleeding among Pradaxa users. In a study of Medicare beneficiaries, we investigated the actual rates of gastrointestinal (GI) bleeding, stroke (including intracranial hemorrhage, i.e., bleeding in the head), and death for new users of Pradaxa compared to new users of warfarin. Compared to patients who were new users of warfarin, new users of Pradaxa had lower risks of clot-related stroke, bleeding in the brain, and death. New use of Pradaxa was associated with an increased risk of major GI bleeding compared to warfarin. These results are consistent with observations from the large clinical trial used to approve Pradaxa.

Based on this evaluation, FDA has not changed its recommendations regarding the use of Pradaxa; it provides an important health benefit when used as directed. In addition, with the approval of Praxbind, Pradaxa now has a reversal agent for life-threatening situations.

Xarelto, Eliquis, and Savaysa were approved after Pradaxa, and we are performing similar monitoring for their safety in the marketed setting.

We will continue to communicate to health professionals and the public any relevant information about the risk of bleeding associated with anticoagulant drugs.

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Dr. Ellis Unger is the Director of the Office of Drug Evaluation I in the Office of New Drugs. Dr. Unger earned his medical degree from the University of Cincinnati and received post-doctoral training at the Medical College of Virginia (internal medicine) and The Johns Hopkins Hospital (clinical cardiology).

Related Information

- **FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa (/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm)**
- **FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death**

but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin (/Drugs/DrugSafety/ucm396470.htm)

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