Dabigatran: Australia issues bleeding warning

OCTOBER 7, 2011 Sue Hughes

Woden, Australia - The Australian regulatory authority, the **Therapeutic Goods Administration** (TGA), has issued a "safety advisory" on the new oral anticoagulant **dabigatran** (Pradaxa, Boehringer Ingelheim) because of an increase in the number of bleeding-related adverse events reports received since more people starting taking the drug [**1**].

Dabigatran was first approved in Australia in November 2009 for the prevention of venous thromboembolic events in patients who have undergone major orthopedic surgery of the lower limb. It is reimbursed for this indication, with limited usage, the TGA reports. In April of this year, the indications were expanded to include the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF) and at least one risk factor for stroke. An increase in adverse-event reports occurred after this extension of indications.

The TGA says it has received a total of 203 adverse-event reports for dabigatran since 2009. Of these, 124 were for serious adverse events; 47 are described as serious bleeding adverse events, 30 related to serious gastrointestinal bleeding and six documented serious intracranial bleeding. There have been a total of 121 adverse events reported in patients aged 75 years or older, of which 76 have been described as serious.

The TGA adds that its analysis shows that some of the bleeding adverse events occurred during the transition from **warfarin** to dabigatran. Many of the adverse events are occurring in patients on the reduced-dosage regimen, and the most common site of serious bleeding for dabigatran is the gastrointestinal tract, whereas for warfarin it is intracranial.

The agency notes that in clinical trials the risk of bleeding per year of treatment with dabigatran was 16.6% (one in six patients) when taking 150 mg twice daily and 14.7% (one in 6.8 patients) taking 110 mg twice daily, compared with 18.4% (one in 5.4 patients) for warfarin.

Consider suitability of patients carefully

It urges clinicians to give careful consideration to the suitability of their patients for dabigatran, "particularly with regard to the risks of bleeding and their current stability on warfarin or other anticoagulants." And it adds that "special consideration should be given to the perioperative management of patients taking Pradaxa."

The advisory notes that Australian experts are currently developing guidelines for the management of bleeding in patients taking dabigatran, but in the meantime it refers clinicians to the New Zealand guidelines on the subject [**2**].

Coagulation assays for emergency use

It says that while existing standard laboratory tests are not validated for use with dabigatran, in cases of emergency, the most accessible qualitative tests are thrombin time (TT) and activated partial thromboplastin time (aPTT). An aPTT >80 seconds is associated with a higher bleeding risk. Prothrombin time (INR) should not be used. Interpretation of coagulation assay results should consider time of dabigatran administration relative to time of blood sampling.

A safety advisory on dabigatran was also **issued in Japan** in August this year warning of serious side effects, including gastrointestinal bleeding, following the deaths of five patients.

Adverse-drug-reaction data is difficult to interpret

Asked to comment on the latest advisory for **heartwire**, **Dr Deepak Bhatt** (Brigham and Women's Hospital, Boston, MA) said it was difficult to interpret these data. He explained that while randomized trials allow side effects to be evaluated properly and placed in context, they often exclude high-risk patients, noncompliant patients, and other challenging patient subsets. "Thus, when new drugs are initially introduced into real life, there is often a spike in the number of adverse events reported compared with the older drug—but without a valid comparator arm, it is impossible to know whether the new drug really is responsible for the reported events." He added that, as in this case, the number of events reported is often given without knowing the total number of patients treated, including those who are doing well, so it is difficult to know whether the adverse-event rate is really higher with the new therapy.

Another issue, Bhatt pointed out, is that when drugs are new, they may be used in the most difficult patients, including subsets that are off-label or even contraindicated, and this too can lead to a higher-than-expected event rate. "Warfarin under- and overanticoagulation leads to adverse events as well, and careful monitoring reduces this risk but does not eliminate it. However, at this point in time, hardly anyone will report a warfarin-related adverse event. So, a combination of factors likely leads to the reports of more adverse events with new drugs, and it certainly does slow down their uptake—at times appropriately and at other times inappropriately."

New Zealand focus on dabigatran deaths

Separately, a New Zealand newspaper is reporting the launch of a coroner's investigation into the deaths of at least five patients who were taking dabigatran [3]. The investigation has been instigated by Bay of Plenty regional coroner **Wallace Bain**, who is said to be concerned that the deaths were signed off without coroner's hearings.

The New Zealand Sunday *Star-Times* says it has been notified of five deaths of patients taking dabigatran, all of whom were elderly. It reports the Centre for Adverse Reactions Monitoring (CARM) at Otago University has received four such reports, but it is unclear whether they relate to the same patients. Dabigatran became widely available in New Zealand in July.

The newspaper also reports having heard of concerns about dabigatran among doctors relating to the fact that it is not monitored like warfarin and the lack of an antidote if a major bleed occurs. It says there is also evidence that dabigatran has been prescribed to those at higher risk, such as patients over 75 with poor kidney function, low weight, and replacement heart valves.

Although the **New Zealand Medicines and Medical Devices Safety Authority** has said the benefits of the drug outweigh the risks and CARM has stated that the deaths it investigated were caused by other factors, such as infections, the *Star-Times* quotes families of the affected patients saying the troubles began when they switched from warfarin to dabigatran, and infections were only the last straw. But CARM director **Dr Michael Tatley** is quoted as saying that there is no obvious mechanism by which an anticoagulant could cause death by infection.