ETMIS 2012; Vol.8 : Nº 2

Summary

Optimal use guide Companion report

Anticoagulant Therapy with Dabigatran (Pradax™) in Atrial Fibrillation

January 2012

A production of the Institut national d'excellence en santé et en services sociaux

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SUMMARY

Introduction

In a *Notice to the Minister* issued to the Minister of Health and Social Services with regard to the update of the lists of medications scheduled for April 20, 2011, the Institut national d'excellence en santé et en services sociaux (INESSS) recommended that Pradax™ 110 mg and 150 mg should be added to the "Exceptional Medications" section for people with non-valvular atrial fibrillation requiring anticoagulant therapy, according to certain conditions. INESSS also indicated that it intended to monitor the use of this drug, to re-evaluate it within the next two years and to develop an optimal use guide.

An optimal use guide has been developed by INESSS. Its simple, user-friendly format provides clinicians with quick access to practical information. INESSS also produced a companion report to the guide. This report is designed to help Québec clinicians understand the rationale for the decisions made by the expert committee that worked with INESSS throughout this process.

Methodology

No formal conceptual framework was selected to develop the optimal use guide on anticoagulant therapy with dabigatran in atrial fibrillation or the explanatory report. However, a systematic literature search on subgroup analyses and laboratory tests was conducted. The search also included examination of several regulatory agency reports, grey literature and website documents. A health network expert committee was formed. This committee was consulted on several occasions. Hematologists, family physicians, emergency physicians and pharmacists were also consulted. Lastly, INESSS took into account the comments submitted by professional groups and citizens. The report was then sent to three practitioners for external review.

Indications and consensus of learned societies

Dabigatran (Pradax™) is covered by the Régie de l'assurance maladie du Québec (RAMQ) for the following recognized indication:

- in persons with non-valvular atrial fibrillation requiring anticoagulant therapy:
  - for whom anticoagulation with warfarin or nicoumalone is not within the targeted therapeutic range;

  or
  - for whom anticoagulation monitoring with warfarin or nicoumalone is not possible or is not available.

The main recommendations on the use of dabigatran drawn from guidelines on the treatment of atrial fibrillation issued by the American College of Cardiology Foundation (ACCF)/American Heart Association/Heart Rhythm Society (HRS), the Canadian Cardiovascular Society (CCS) 2010 and the European Society of Cardiology (ESC) 2010 address the use of dabigatran in atrial fibrillation. They support its use. The recommendations may vary according to each group's values and preferences.

Pharmacology and pharmacokinetics

Dabigatran etexilate is a prodrug of dabigatran, a potent, direct, competitive inhibitor of free or fibrin-bound thrombin. After oral administration, dabigatran etexilate is absorbed by the intestinal wall by binding especially to P-glycoprotein. Its bioavailability is low, on the order of 6% to 7% in an acidic medium. After administration of repeated doses, the half-life of dabigatran is from 12 to 17 hours. Most of it is excreted by the kidneys, 80% in unchanged form.

Major study and subgroup analyses

A multi-centre phase III non-inferiority trial (RE-LY) compared doses of dabigatran 110 mg and 150 mg in a blinded fashion twice daily against warfarin (open label) administered once daily in a dose adjusted to maintain an international normalized ratio (INR) of 2.0 to 3.0 for the purpose of preventing thromboembolic events in non-valvular atrial fibrillation requiring anticoagulant therapy.

The RE-LY study population was divided into various subgroups to measure the interaction between the effects of dabigatran and different variables such as age, history of transient ischemic attack (TIA) or stroke, prior exposure or not to warfarin, and the mean time for each study center, in therapeutic range with an INR of 2,0-3,0. The results of these analyses in terms of efficacy endpoints (stroke or systemic embolism) and safety endpoints (major bleeding) do not make it possible to identify any subpopulations that could particularly benefit from dabigatran.

Individualized approach: choice of dabigatran or warfarin

Warfarin remains the treatment of choice for preventing stroke or systemic embolism in the case of non-valvular atrial fibrillation, given its efficacy and long-term safety and its favourable cost effectiveness. More specifically, in patients receiving warfarin whose INR falls within the therapeutic range more than 67% of the time, treatment should not be modified. Dabigatran is therefore an alternative to warfarin especially in patients with suboptimal INR control. It is clear that patients who are not good candidates for anticoagulant therapy should not receive dabigatran.

Given the populations excluded from the RE-LY trial and the little data existing on certain patient groups, dabigatran should not be administered to certain individuals. Older persons, in particular, often have several characteristics that make it risky for them to use dabigatran.

Lastly, warfarin and dabigatran have advantages and disadvantages that must be evaluated case by case. Both products have different adverse effects and are associated with different rates of bleeding. They require their own particular clinical supervision. They have different potential food and drug interactions. Their dosage and administration also differ. These elements must be taken into account to ensure that each patient is offered suitable treatment.

Considering the data available on dabigatran and warfarin, along with their respective benefits and drawbacks, INESSS recommends an individualized approach that includes patient participation in choosing the best treatment for preventing thromboembolic and bleeding risks in atrial fibrillation.

Treatment initiation, conversion, interruption and resumption of dabigatran

The methods for using dabigatran differ from those for warfarin. In the absence of quantitative coagulation monitoring for dabigatran, various flowcharts are presented to guide clinicians when an anticoagulant must be replaced with another, such as in planned elective surgery.

Pharmacosurveillance

Pharmacosurveillance must be initiated to assess treatment adherence, adverse effects and drug interactions, for example.

In patients with a history of poor adherence to treatment, dabigatran, administered twice daily, is to be avoided. Forgetting or exceeding dabigatran doses may have major consequences. Dyspepsia linked to dabigatran is worrisome because it is associated with treatment discontinuation by patients. Bleeding is obviously the adverse effect of greatest concern. It is very important to remain highly vigilant and to properly inform patients about these effects. Lastly, drug interactions with dabigatran are still poorly known and little documented. Caution is therefore warranted.

Laboratory monitoring – coagulation tests

Regular laboratory coagulation monitoring is not required with dabigatran, given the predictability and low variability of its anticoagulant effect. However, in the case of major bleeding and in perioperative situations, laboratory tests are required to determine the state of coagulation. Commonly used biological measures have not been validated or standardized for dabigatran monitoring. Activated cephalin time (ACT) appears to be the most useful test. A normal ACT indicates the absence of clinically significant anticoagulant activity. Thrombin time (TT), for its part, is more sensitive to the presence of dabigatran. A normal TT confirms the absence of dabigatran in individuals. However, the ACT and the TT only provide qualitative information on anticoagulation.

Intervention in the case of bleeding

To date no product is capable of reversing the anticoagulant effect of dabigatran. In these circumstances, bleeding is a major concern to clinicians especially since current tests do not make it possible to determine the level of anticoagulation. There is also very little evidence supporting the efficacy of the various treatments commonly used to stop major bleeding with dabigatran. The proposed algorithm for the management of bleeding is therefore based on available data and current clinical practice. It is presented in the report to support clinicians in managing difficult situations.

Conclusion

Anticoagulation therapy in atrial fibrillation is likely to undergo rapid developments over the next few years. Dabigatran is the first drug in the class of direct thrombin inhibitors to be marketed for this indication. Several other molecules are currently being tested in phase II and phase III clinical trials. The development of these drugs would certainly benefit from being accompanied by the availability of antidotes and specific laboratory monitoring tests. The advent of new therapeutic options and anticoagulation monitoring methods (portable

coagulation monitors) supports an individualized approach with patient involvement. The optimal use guide for anticoagulant therapy with dabigatran in atrial fibrillation, along with its companion report, should prove to be very useful tools for ensuring that patients receive the very best treatment. INESSS now expects to direct its work toward monitoring the best use of dabigatran.