DRUG CORNER

Dabigatran Eteixilate in Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) affects millions worldwide. Stroke is the most devastating complication of AF and is associated with a huge disease burden. As a preventive measure, anticoagulant therapy is recommended for most AF patients based on presence of stroke risk factors. For the past six decades warfarin remained the gold standard for stroke prevention in AF (SPAF). However, it is associated with numerous limitations such as a high risk of drug-drug, drug-food interactions and need for frequent INR (2-3) monitoring. Novel oral anticoagulant (NOAC) dabigatran etexilate is a selective, specific, reversible direct thrombin inhibitor that has been approved in India for SPAF and primary venous thromboembolism prevention. The efficacy and safety of dabigatran in AF has been established the “Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY)”, a randomized clinical trial. RE-LY (n=18,113) demonstrated that the efficacy of dabigatran 110 mg BID was as good as well controlled warfarin and dabigatran 150 mg BID reduced the risk of ischaemic stroke by 25% (P=0.03). Till date, 150mg dabigatran is the only NOAC offering a superior reduction in most commonly seen ischemic strokes due to AF compared to warfarin. Additionally, both doses of dabigatran significantly reduced the risk of total bleeds, intracranial, and life threatening bleeds versus warfarin (p<0.05). Dabigatran has advantages over warfarin including predictable pharmacokinetic/ pharmacodynamic profile, minimal drug-drug and no drug-food interactions while no monitoring is needed. The 150 mg dose of dabigatran should be considered in younger patients with a low risk of bleeding and good renal function to achieve a superior ischemic stroke reduction, whereas, the 110 mg dose should be considered in elderly patients, those with mild to moderate renal function or those with high risk of bleeding.

Introduction

Atrial fibrillation (AF) is a common disorder that affects millions of people worldwide. The number of patients diagnosed with AF is expected to rise steeply across the globe, as the prevalence of the disease is reported to increase with age. AF is associated with fivefold increase in the risk of stroke, and is also predisposed for future recurrences.1 Anticoagulant therapy is recommended for all patients with AF, except those at low risk (age < 65 years and lone AF) or with contraindications.2 Recent advances in the field of pharmacology have opened the doors to a whole new generation of anticoagulants such as dabigatran, rivaroxaban, apixaban and edoxaban, which hold the potential to overcome the current limitations in the management of stroke prevention in atrial fibrillation (SPAF). The newer generation anticoagulants are more effective and have a favourable pharmacokinetic and pharmacodynamic profile when compared with warfarin1. The current review is of the drug dabigatran etexilate, the molecule so far approved for SPAF by the Indian DCGI.

Dabigatran Eteixilate

Dabigatran etexilate is a prodrug that is rapidly converted to the active molecule dabigatran...
Clinical Trials of Dabigatran

The efficacy and safety profile of dabigatran was demonstrated in the RE-LY study. The trial included a total of 18,113 AF patients with one or more risks for stroke. All the patients were randomly assigned to receive either 110 mg or 150 mg twice-daily dose of dabigatran in a blinded fashion or dose-adjusted warfarin in an un-blinded fashion. International normalised ratio (INR) in the warfarin group was well controlled, with 64% of the patients being maintained within the range throughout the study period. Efficacy outcomes were based on occurrence of stroke or systemic embolism.

Table 1: Recommendations for discontinuation of dabigatran etexilate before elective invasive or surgical procedures

<table>
<thead>
<tr>
<th>Renal function (CrCl [mL/min])</th>
<th>Estimated half-life (hours)</th>
<th>Timing of discontinuation after the last dose of dabigatran before surgery</th>
<th>Standard risk of bleeding</th>
<th>High risk of bleedinga</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>13</td>
<td>≥ 24 h before</td>
<td>2 d before</td>
<td>4 d before</td>
</tr>
<tr>
<td>≥ 50 – &lt; 80</td>
<td>15</td>
<td>1–2 d before</td>
<td>2–3 d before</td>
<td>4 d before</td>
</tr>
<tr>
<td>&gt; 30 – ≤ 50</td>
<td>18</td>
<td>≥ 2 d before</td>
<td>2–3 d before</td>
<td>4 d before</td>
</tr>
</tbody>
</table>

aTypes of surgery associated with a high risk of bleeding (or major surgery where complete haemostasis may be required), including, but not limited to, cardiac surgery, neurosurgery, abdominal surgery or surgeries involving a major organ. Other procedures such as spinal anaesthesia may also require complete haemostatic function.

in the body. Dabigatran is a direct thrombin (IIa) inhibitor that has no antithrombin activity, but is a potent, competitive and reversible inhibitor of thrombin. Dabigatran is effective in inhibiting both circulating and clot-bound thrombin. Dabigatran has a rapid onset of action, and reaches peak plasma concentration in approximately 0.5 to 2 h. The half-life (t½) of the drug ranges between 12 and 17 h. The average absolute bioavailability is approximately 6.5%. The linear pharmacokinetic profile of dabigatran allows fixed-dose administration without regular blood level monitoring. As the drug is metabolised through glucuronide conjugation and has no involvement with the cytochrome P450 isoenzymes, it has relatively fewer drug interactions than warfarin; moderate hepatic impairment does not affect the efficacy or the safety profile of dabigatran. Moreover, dabigatran does not interact with food. Dabigatran is predominantly eliminated by the kidneys. Thus, reduced kidney function results in elevated plasma levels and prolonged half-life. Although the lower dose of the drug can be used in patients with moderate renal impairment (creatinine clearance [CrCl] 30–50 mL/min), it is contraindicated in patients with severe renal impairment (CrCl 10–30 mL/min).

Table 2: Overview of Dabigatran in Stroke Prevention in AF

Dose selection:
150 mg twice daily for adults
110-mg dose may be considered in patients with an increased bleeding risk
- Age ≥75 years
- Moderate renal impairment (30-50 mL)
- Patients on concomitant antiplatelet therapy, NSAIDs or strong P-glycoprotein inhibitors
- Previous GI bleeding

The efficacy of dabigatran 110 mg was similar to that of warfarin. Dabigatran 150 mg reduced the risk of ischaemic stroke by 25% (P=0.03). The rates of major haemorrhages were reduced by 22% with the lower dose of dabigatran, and the rates were similar with the higher dose of dabigatran when compared with that of warfarin. Intracranial bleeding, which is one of the most common and devastating complications of anticoagulation therapy, was significantly lower in both the dabigatran groups (relative risk reduction [RR] of 70% and 59% with the 110- and 150-mg dabigatran doses, respectively) when compared with warfarin. The rates of adverse effects of dabigatran were comparable to that of warfarin, except with dabigatran the events of dyspepsia and gastrointestinal (GI) bleeding were higher. A recent study conducted by Eikelboom suggested that the total number of fatal bleeding and intracranial haemorrhage cases are expected to be much lesser with dabigatran in real-life practice when compared with warfarin, and similar to that of aspirin. Thus, the authors concluded that dabigatran is much more effective than warfarin and is as safe as aspirin (Figure 1).

Dabigatran is effective in all forms of AF, and there was similar reduction in the risk of stroke with dabigatran, regardless of the CHADS2-VASc scoring. It is also a better alternative than warfarin in patients requiring cardioversion.

In the RE-LY study, it was found that the rates of myocardial infarction (MI) were slightly more in both the dabigatran groups (0.82% in the 110-mg group and 0.81% in the 150-mg group) when compared with the warfarin group (0.64%). However, the RR of MI with the 150-mg dabigatran dose was not statistically significant when compared with the warfarin arm (RR: 1.27, 95% CI: 0.94–1.71, P = 0.12). Both the doses of dabigatran demonstrated superior efficacy in terms of net clinical benefit (defined as a composite outcome of stroke, systemic embolism, pulmonary embolism, MI, death and major bleeding in the RE-LY study) when compared with warfarin.
Monitoring and Reversing the Action of Dabigatran

Although dabigatran does not require regular blood level monitoring, conditions of serious bleeding, potential overdosing and emergency surgery may require assessment of the blood anticoagulant levels. In such cases, the activated partial thromboplastin time (aPTT) and thrombin clotting time (TT) are the most accepted methods for determining the levels of anticoagulants in blood. A trough aPTT value of > 80 s (two- to threefold more than the baseline value) is associated with increased risk of bleeding. No specific antidote is available to antagonise the action of dabigatran. However, owing to its rapid offset of action, excessive drug action is usually reversible in case of overdosing, simply by drug discontinuation. In case of potential overdosing and life-threatening bleeding, the use of activated charcoal, charcoal filtration, haemodialysis, fresh frozen plasma, recombinant factor VII and prothrombin complex concentrates may be considered.10,11

Use of Dabigatran in Patients Undergoing Elective Surgery

Similar to other anticoagulants, patients undergoing surgery or invasive procedure are at an increased risk of bleeding while on dabigatran therapy. CrCl test should be carried out to assess the renal function, and aPTT test should be carried out 6 to 12 h before the surgery to assess the bleeding risk of patients.11 Table 1 lists the recommendations to be followed for discontinuation of dabigatran etexilate before surgical procedure.

Switching Therapy

Dabigatran should be started 0 to 2 h before the next dose of the parenteral anticoagulation is due when switching therapy from a parenteral anticoagulant to dabigatran. When switching from warfarin to dabigatran, warfarin has to be stopped and dabigatran has to be started once a patient’s INR reaches < 2.0. For switching back to the parenteral anticoagulant from dabigatran, a gap of 12 to 24 h is needed after the last dabigatran dose before starting the parenteral therapy. While switching from dabigatran to warfarin the CrCl profile of the patient should be evaluated.11

Conclusion

Dabigatran etexilate is a drug with favourable pharmacokinetic and pharmacodynamic profile. When oral anticoagulants are clearly indicated (CHADS2-VASc score ≥ 1), dabigatran can be used for stroke prevention in AF. Dabigatran can be a useful alternative in patients who have had problems with vitamin K antagonists (ischaemic strokes or bleeding complications), fluctuant INR, and who have difficulty in regular monitoring and to avoid chances of drug-drug and drug-food interactions. The RE-LY trial proved dabigatran to be an effective drug for stroke protection in AF. The 150-mg dose of dabigatran should be considered in patients with a low risk of bleeding, whereas the 110-mg dose should be considered in patients with a high risk of bleeding (Table 2). The recent post marketing survey of dabigatran published by the FDA has reiterated the efficacy and overall lower bleeding risk in the real world, out of trial use.12 However dabigatran is not to be used in patients with rheumatic valvular heart disease and those with prosthetic valves. The daily cost of the drug and accumulating real-life experience will determine its usage.

References