Apixaban dosing guidelines in atrial fibrillation: implementation in the real world.

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Objective

The Australian product guidelines recommend a dose reduction of apixaban in atrial fibrillation (AF) from the standard 5mg twice daily to 2.5mg twice daily (BD) in patients with any two of the following:

1. age ≥ 80 years
2. weight ≤ 60kg
3. serum creatinine (serum Cr) ≥ 133 micromol/L.

This case illustrates the challenges of applying guidelines based on hard stop points to real world practice. The basis of the Australian product guidelines dosing recommendations and published literature were reviewed to assist with the decision making process.

Clinical Features

An 87 year-old female in AF presents with acute ischaemic stroke. The plan is to commence apixaban for stroke prevention. She weighs 59 kg and has a serum Cr of 58 micromol/L. Based on the Australian guidelines she should receive a reduced dose of apixaban of 2.5mg orally BD. Discussion with the stroke team and pharmacist raised the following questions:

1. What is the basis of the dose reduction in AF, but not in the treatment of venous thromboembolism (VTE)?
2. As this patient is just under 60kg and has reasonable renal function – will a dose reduction provide the best outcome for the patient?

Question 1 – what's behind the dose recommendation?

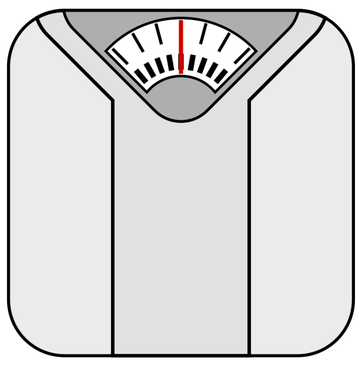
- Information obtained from the drug company (Bristol-Meyers Squibb) indicated that the suggested dose reduction recommendations were based on pharmacokinetic modelling not outcome data (see box 1).
- Their assessment was that whilst an individual criterion did not have enough pharmacokinetic impact to warrant a dose reduction, those who met 2 out of 3 criteria were classified as **fragile** patients.
- The dose recommendations in the setting of venous thromboembolism treatment (ie. DVT or PE) are quite different (see box 2).
- Reasoning for variance per drug company was the different patient population (less likely to be 'fragile') and the urgency of ensuring adequate treatment for active embolism.[2]

Box 1: Pharmacokinetic parameters used as basis for dose reduction in product guidelines.[1]

Age:
Above 65 years: mean AUC values approximately 32% higher

Body Weight:
Subjects <50kg compared with subjects with body weight 65 to 85kg: mean AUC approximately 30% higher

Renal impairment: – Apixaban 27% renally cleared.
Increase in apixaban AUC correlated to decrease in renal function, as compared to individuals with normal creatinine clearance (CrCl):
-mild (CrCl 51-80 mL/min): 16% increase
-moderate (CrCl 30-50 mL/min): 29% increase
-severe (CrCl 15-29 mL/min): 44% increase



Box 2: Dose schedule in VTE treatment[3]

All patients with a CrCl above 25mL/min receive the same dose schedule irrespective of age and weight:

- First 7 days: 10mg orally BD
- From day 8 to 6 months: 5mg BD
- After 6 months the dose can be continued for prevention of recurrence at 2.5mg BD

Fun facts

- Less than 5% of patients in the landmark ARISTOTLE trial of apixaban versus warfarin received the dose reduction to 2.5mg BD.[4]
- This should be taken into account when interpreting the results and when considering dose reductions for those patients who may not clearly satisfy the dose reduction criteria.
- Prescription data suggests that at least 25% of prescriptions are for the lower dose.[5]
- Evidence in the literature suggests that underdosing of direct oral anticoagulants is not uncommon, with unknown consequences.[6]

Question 2 – is there anything in the literature to assist?

A secondary analysis of the ARISTOTLE trial compared the outcomes for patients receiving apixaban 5mg BD with one dose reduction criterion to those with no dose reduction criterion.[7]

- Results indicated that the relative benefits over warfarin remained. In particular the reduced risk of intracranial bleeding.
- This was consistent across the criteria of age, body weight and serum Cr.

At this stage there is limited high quality evidence from prospective, randomised controlled trials that compares the efficacy of 5mg versus 2.5mg BD dosing of apixaban.

Decision and outcome

Once all the information was assessed, the team determined that a critically important question required consideration:
Should the labeled dose reduction parameter in the product information constitute best practice for this patient or is this a situation when clinical judgement should override rigid guidelines?
This patient had 2 dose reduction criteria, however, one of these could be considered borderline (weight 59 kg).

Other relevant factors

- The patient was previously fit and healthy and not considered frail or fragile.
- The deficits of her stroke were minimal.

A collaborative decision was made with the patient to prescribe apixaban 5mg BD with ongoing careful monitoring of the patient by her GP.

Conclusion

Critical analysis of available information is vital when applying product information recommendations.
Decision-making should consider the quality of the evidence available and how it applies to the individual patient.

References

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