Anti-coagulant bleeding – a clinical challenge

The purpose of this CPD-Accredited review is to provide an update on recent developments in the management of bleeding events with both the established treatment for more than 50 years (warfarin and other Vit K antagonists) and the newer novel anti-coagulants.

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“Anti-coagulant-associated major bleeding is life-threatening”

Anti-coagulant-associated major bleeding is serious and is associated with high in-hospital mortality. US studies have shown that some 15% of patients admitted to hospital with Vit K antagonist-associated bleeding who survive, suffer long-term consequences and require help with daily living after their major bleed.

A recent South African review of warfarin usage in non-valvular atrial fibrillation by Dr Tony Dalby, Dr Piet Wessels and Prof Lionel Opie, provides a useful guide to the correct use of warfarin. Their practical advice on managing bleeding events in patients on warfarin therapy is summarised in Table 1. ¹

Table 1: Management of bleeding with warfarin ¹

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<tr>
<th>Action steps</th>
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<tr>
<td>1.</td>
<td>Check INR (International Normalised Ratio) immediately.</td>
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<td>2.</td>
<td>If INR is within the therapeutic range (INR 2-3), warfarin should be continued and the bleeding treated on its own merits.</td>
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<td>3.</td>
<td>If INR is raised and not a major bleed, treat with 1-3mg Vit K given intravenously or orally.</td>
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<td>4.</td>
<td>In the event of a major bleed with raised INR, reverse warfarin with 25-50U/kg 4-factor non-activated PCC and 5mg Vit K given intravenously.</td>
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<td>5.</td>
<td>If PCC is unavailable, fresh frozen plasma (FFP) is effective (but not as effective as 4F-PCC) but is associated with transfusion-related risks of acute lung injury and circulatory overload. ABO blood typing must be done prior to administering FFP.</td>
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Subsequent to this South African review, the first prospective clinical trial results were published on the effectivity and safety of 4F-PCC (4-Factor Prothrombin Complex Concentrate, containing coagulation factors II, VII, IX and X and proteins C and S) compared to fresh frozen plasma (FFP). In this study of non-surgical patients presenting with acute major bleeding and raised INRs on Vit K antagonist treatment, effective haemostasis was achieved in 73% of patients receiving 4F-PCC versus 65% receiving plasma. Rapid INR reduction within 30 minutes was achieved in 62% of patients receiving 4F-PCC versus 9.6% receiving plasma, showing the superiority of using

The development of a highly specific antibody to dabigatran is on track and showing positive results with sustained ability to reverse the bleeding complications of this novel anticoagulant.

Speaking at a symposium in Cape Town recently, Dr Joanne van Ryn, Department of Cardiometabolic Disease Research, Boehringer Ingelheim, Biberach, Germany explained how Boehringer Ingelheim deals with clinicians’ concerns about bleeding events in patients on anti-coagulation, whether being treated with new anti-coagulants or traditional Vit K antagonists.

New anti-coagulants offer benefits over warfarin as they do not require ongoing monitoring and are effective at easy-to-use fixed doses. Bleeding rates on warfarin and the new novel anti-coagulants are similar. Specific antidotes to these new novel agents are in clinical development and recently South African clinicians were updated on progress with the development of an antidote to dabigatran.

**Reference:**

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**Urgent reversal of anti-coagulation – antidote to dabigatran**

The development of a highly specific antibody to dabigatran is on track and showing positive results with sustained ability to reverse the bleeding complications of this novel anticoagulant.

The approach of Boehringer Ingelheim to the development of a dabigatran antidote is to avoid interference in the coagulation cascade. We are not using a thrombin mimic, but have elected to develop a specific antibody fragment to the drug itself. This development is successfully on track. The antibody binds to dabigatran with high specificity, enfolding the drug so that no dabigatran activity is left in plasma. This antibody fragment (Fab) has now been tested in 145 healthy males and has shown reversal of the anticoagulant action of dabigatran. The antibody fragment was safe and well-tolerated,” Dr van Ryn said.

The current mainstay of treatment in cases of serious bleeding in patients being treated with either warfarin or dabigatran is supportive therapy, using either fresh frozen plasma or Prothrombin Complex Concentrate (PCC).1

Dialysis has been shown to effectively remove dabigatran from plasma (there is clinical evidence for this). “This strategy is not useful with the other anti-coagulants such as rivaroxaban or apixaban as they are highly bound to plasma proteins in the circulation. Using charcoal in overdose also works with apixaban and rivaroxaban”.

“The use of PCC has only recently been prospectively evaluated in patients presenting with major acute bleeding on warfarin who require urgent reversal that cannot be addressed by Vit K administration only. “Up until the publication last month of this study, the efficacy of PCC for urgent Vit K antagonist (warfarin) reversal had not been established, although it is often used clinically in severe bleeding settings,” Dr van Ryn noted.2

Referring to the Phase III clinical trial programme of dabigatran versus warfarin, Dr van Ryn noted that the
recent publication of patients receiving either dabigatran or warfarin, who experienced an adverse acute bleeding event were reviewed for 7 and 30 day outcomes and interventions used in these patients.

Overall outcomes showed a trend to less 30-day mortality with dabigatran versus warfarin with dabigatran 150mg in the RELY cohorts having significantly less 30-day mortality after a major bleed when compared to warfarin. “This is very reassuring and although not a randomised study it showed that dabigatran offers an alternative to warfarin with similar or lower risks for major bleeding that can be managed satisfactorily”, Dr Van Ryn concluded.

References:

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