HOSPITAL CHRONICLES 2014, VOLUME 9, SUPPLEMENT 1: 54–56

Management of Bleeding with Newer Anticoagulants

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KEY WORDS: *dabigatran; rivaroxaban; apixaban; bleeding*

Abbreviations
aPTT = activated partial thromboplastin time
CCU = cardiac care unit
FFP = fresh frozen plasma
HIV = human immunodeficiency virus
ICU = intensive care unit
NOACs = novel oral anticoagulants
PCC = prothrombin complex concentrate
PPI = proton pump inhibitor(s)

INTRODUCTION

Several novel oral anticoagulant drugs (NOACs) have recently been approved for use in patients with non-valvular atrial fibrillation or venous thromboembolic disease.[1] These drugs are either direct thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and all have been compared in large randomized trials with warfarin. In general, NOACs are considered, at least, non-inferior to warfarin in terms of stroke prevention but their risk of bleeding is variable.[2] Specific antidotes for NOACs are not currently available and concerns about managing bleeding episodes have been expressed. The management of a bleeding episode from NOACs has some similarities but also differences from the management of bleeding from warfarin.

RISK OF BLEEDING WITH NOACS

All NOACs are associated with lower risk of intracranial or intracerebral bleeding than warfarin. In contrast, the risk of gastrointestinal bleeding with NOACs is not lower in comparison with warfarin. More specifically, dabigatran at a dose of 150 mg twice daily, rivaroxaban at the usual dose of 20 mg once daily, and edoxaban at the high dose of 60 mg daily have higher risk of gastrointestinal bleeding than warfarin. Dabigatran at the lower dose of 110 mg twice daily has higher risk only in patients above 75 years old. Apixaban, in general, has similar risk of gastrointestinal bleeding with warfarin. Bleeding risk from other sites (epistaxis, intraocular, subcutaneous hematomas, hematuria) with NOACs is either smaller or equal to the risk of warfarin.[2]

In order to minimize the risk of bleeding with NOACs some precautions are necessary.[3] Renal function should be assessed initially and at least yearly or when a deterioration is suspected. NOACs cannot be used in patients with severe renal dysfunction. In moderate renal impairment a smaller dose is recommended. Use of proton pump inhibitors (PPI) is recommended in patients at high risk for gastrointestinal bleeding. Although drug interactions are fewer with NOACs than with warfarin, it must be noted that several concomitant medications may increase the antithrombotic effect of dabigatran (verapamil, amiodarone, quinidine), rivaroxaban (HIV protease inhibitors) or apixaban (diltiazem). In such cases a dose reduction should be considered. In order to reduce bleeding risk, as a general rule, patients with stable coronary artery disease who receive NOACs do not need aspirin co-administration.

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MANAGEMENT OF BLEEDING

The management of a bleeding episode depends on the location and the severity. Some forms of bleeding require specific intervention. Examples include urgent endoscopy for upper gastric blood loss, cauterization for continuing epistaxis or surgical evacuation for subdural hematoma. Still, most bleeding episodes will eventually stop spontaneously. Therefore, just discontinuation of the drug, while taking general supportive measures, is sufficient. Ensuring adequate urine output, administration of fluid or colloids, blood transfusion or administration of fresh frozen plasma (as volume expander and not as a reversal agent) are usual and important non-specific measures. Drug elimination depends on renal function. The longest drug effect is expected in patients treated with dabigatran who have a reduced creatinine clearance. In patients with good renal function coagulation is back to normal within 12-24 hours for all NOACs (Table 1).

There are no specific antidotes for NOACs (at least clinically available currently) and the administration of vitamin K, protamine or fresh frozen plasma (FFP) are ineffective.[4] Prothrombin complex concentrate (PCC), which is particularly effective in reversing quickly coagulopathy from vitamin-K antagonists, may be tried at a dose of 25 u/kg once or twice with NOACs but there is no clinical evidence of benefit. In healthy volunteers who were treated with dabigatran, PCC had no effect on aPTT. In contrast, in healthy volunteers treated with rivaroxaban, PCC corrected the prolonged PT value within 15 min.[5] Similar lack of evidence for any benefit applies for activated factor VII which may be given as an off-label option. High dose of recombinant factor VII (rFVII) (7.2 mg) reduces dabigatran-associated bleeding.[6]

Dabigatran can be removed from the circulation by dialysis. In a small open study, 6 patients with end stage renal disease were given a 50 mg dose of dabigatran. At 4 hours, 68% of the drug was removed by dialysis.[7] The anti-Xa agents due to high plasma binding are not expected to significantly reduce their plasma level with dialysis.

The use of activated charcoal may inhibit further absorption of any NOAC, provided it is given within the first few hours from the last dose.

Specific antidotes are being developed and tested. For dabigatan the reversal agent is an antibody fragment that does not induce hypercoagulability. For the anti- Xa agents a recombinant protein is being developed. It acts as a decoy that binds the anti- Xa drug in the blood. Both antidotes are currently being tested in phase II studies.

In clinical practice, what is reassuring is that the outcome of a patient who bled with a NOAC is no worse than that of a patient who bled with warfarin. In the RE-LY trial patients who had intracranial bleeding on dabigatran or warfarin had similar mortality.[8] A recent analysis of 5 randomized trials comparing dabigatran with warfarin reported the 30 day out-

TABLE 1. Time to normalization of coagulation and therapeutic options in case of bleeding with novel anticoagulant drugs.

NOAC	Time to normalization of hemostasis	Options
Dabigatran	12-24 h (CrCl >80 ml/min) 24-36 h (CrCl 50-80 ml/min) 36-48 h (CrCl 30-50 ml/min) >48 h (CrCl <30 ml/min)	Maintain adequate diuresis, fluid replacement, supportive measures Dialysis (4 h at 200 ml/min) PCC 25 u/kg rVII (off-label) FFP only as volume expander Antidote: monoclonal Ab (phase II)
Rivaroxaban	12-24 h	Fluid replacement, supportive measures PCC 25 u/kg rVII (off-label) FFP only as volume expander Antidote: PRTT4445 r-protein Xa (phase II)
Apixaban	12-24 h	Fluid replacement, supportive measures PCC 25 u/kg rVII (off-label) FFP only as volume expander Antidote: PRTT4445 r-protein Xa (phase II)

Ab = antibody; CrCl = creatinine clearance; h = hour(s); NOAC=novel oral anticoagulant drug; PCC=prothrombin complex concentrate; FFP=fresh frozen plasma; rVII=recombinant factor VII.

comes of 1034 patients who suffered a major bleed. Mortality was non-significantly lower for dabigatran in comparison with warfarin.[9] This result confirms the notion that the lack of a specific antidote is not as important as one might think. Moreover, in this report the length of stay in ICU/CCU was shorter with dabigatran.

AFTER THE BLEEDING EPISODE

The need to continue with anticoagulation must be reassessed after the bleeding episode. If the risk of recurrent hemorrhage is considered smaller than the thrombotic risk of atrial fibrillation, anticoagulation should be resumed. Avoiding concomitant drugs, especially aspirin and non-steroidal anti-inflammatory drugs is important. Use of PPI in case of upper gastrointestinal bleeding is recommended. Renal function must be checked and a smaller dose of NOAC might be considered. If dabigatran was given at the high dose of 150 mg twice daily then switching to 110 mg twice daily is reasonable. This dose has been tested and found non-inferior to warfarin. Rivaroxaban has been given at a dose 15 mg daily and apixaban at a dose 2.5 mg twice daily in patients with renal dysfunction, but it is unclear whether these smaller doses are effective in stroke prevention when administered to patients with normal renal function who have bled with the standard dose.

Switching to a different agent is an option but it should be mentioned that there are no direct comparisons between different NOACs. In the case of gastrointestinal bleeding, apixaban is probably safer.

Switching to vitamin-K antagonist is also a fair option, since anticoagulation intensity can be monitored. In this case we may accept a small increase in intracerebral hemorrhage risk.

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