Recovery

The role of autophagy in the metabolism and outcomes after surgery, J. Gunst et al.

Fast-track surgery: a multidisciplinary collaboration, H. Kehlet

The patient voice in Enhanced Recovery After Surgery, A. Balfour & R. Alldridge

The role of physiotherapy in Enhanced Recovery after Surgery in the ICU, T.W. Wainwright et al.

Innovations in monitoring: from smartphones to wearables, F. Michard

Physical rehabilitation in the ICU: understanding the evidence, C. M. Goodson et al.

Optimising nutrition for recovery after ICU, P.E. Wischmeyer

Outcomes after 1 week of mechanical ventilation for patients and families, M. Parotto & M.S. Herridge

Continuing rehabilitation after intensive care unit discharge, S. Evans et al.

The hidden faces of sepsis, what do they tell us? I. Nutma-Bade

PLUS

Ultrasound-guided mechanical ventilation, F. Mojoli & S. Mongodi

Haemodynamic monitoring: stuff we never talk about, C. Boerma

Animal-assisted activity in the intensive care unit, M.M. Hosey et al.

From command and control to modern approaches to leadership, T. Dorman

Enabling machine learning in critical care, T.J. Pollard & L.A. Celi

CSL Behring Supplement from Euroanaesthesia 2017 Symposium
Treatment of bleeding patients during therapy with direct oral anticoagulants

Results from the French registry: GIHP-NACO

Presents results from a registry detailing information about the management of bleeding patients in the emergency room, operating room or intensive care unit during therapy with direct oral anticoagulants.

Background

There is a large literature on the efficacy of direct oral anticoagulants (DOAC) to prevent stroke or systemic embolic events in patients with atrial fibrillation or to treat venous thromboembolism. DOAC, which include direct anti-Xa and thrombin inhibitors, have a favourable risk-benefit profile. However, as for any anticoagulant, they are associated with spontaneous or provoked haemorrhagic risk. The meta-analysis by Ruff and colleagues of trials comparing patients treated with Vitamin K antagonists (VKA) to patients treated with DOAC showed that with DOAC there were significant reductions in stroke, intracranial haemorrhage and mortality, similar to warfarin, but increased gastrointestinal bleeding.

The challenge remains to manage bleeding, emergency surgery or invasive procedures in patients treated with DOAC. Current French and European guidelines recommend use of haemostatic agents, such as prothrombin complex concentrate (PCC) and antidotes for the treatment of life-threatening bleeding associated with the use of DOAC (Albaladejo et al. 2017a; Kozek-Langenecker et al. 2017).

However, there is a lack of data and we are still trying to develop strategies to manage patients receiving DOAC who are bleeding and who need urgent surgery.

DOAC and coagulation assays

Steiner and colleagues showed that the sensitivity of usual coagulation tests to DOAC is quite variable (Steiner et al. 2013). It depends on the test and the DOAC.

For patient management in anaesthesia and critical care, we need a test that can:
1. Detect significant plasma concentration that could interfere with haemostasis.
2. Eventually attest that a reversal strategy is effective.

The mechanism of action of PCC is different to reverse the anticoagulation effects of VKA or DOAC (Figure 1).

In patients anticoagulated with VKA, PCC will replace the factors. In patients anticoagulated with DOAC, PCC acts by overwhelming inhibition of factor IIa or factor Xa, depending on the DOAC involved.

There are several animal studies on direct oral anticoagulants. For example, the study by Pragst and colleagues showed that with 50 IU/kg you reduce bleeding to control animals. Similar studies for apixaban or rivaroxaban have been completed.

In a study that measured thrombin generation times in healthy volunteers receiving a dose of 20 mg rivaroxaban or 150 mg dabigatran, after 2 hours a new measurement was performed for the drug effect of increasing doses of PPSB or FEIBA or rFVIIa. These showed partial or total correction, or even overcorrection (Marlu et al. 2012).

DOAC were first developed without reversal strategies, and antidotes were developed several years after DOAC were approved. Reversal agents include idarucizumab, andexanet alfa (PRT064445) and aripazine (PER977).

Pollack and colleagues (2017) in a prospective cohort study of safety and efficacy of idarucizumab in patients who had serious bleeding or needed an urgent procedure, found that 5g (2 x 2.5g administered within 15 minutes) of idarucizumab reversed the effect of dabigatran.

Lu and colleagues described an antidote for reversal of anticoagulation (Lu et al. 2013). This modified rFXa is produced in Chinese hamster ovary cells. It has no intrinsic procoagulatory effect, but it binds the direct anti-FXa inhibitors.
An investigation of andexanet alfa for acute major bleeding associated with factor Xa inhibitors (Connolly et al. 2016) found that an initial bolus and subsequent 2-hour infusion of andexanet substantially reduced anti-factor Xa activity in patients with acute major bleeding associated with factor Xa inhibitors. Effective haemostasis occurred in 79% of the patients.

Connolly’s study raises all the problems related to the use of antithrombotic antidotes:

What is the relationship between reversion and a clinical effect? How long is this reversion necessary? Is the antidote prothrombotic? And how to highlight it?

Bleeding in patients treated with DOAC
When we have a patient bleeding while treated by any anticoagulant, we must always consider the use of appropriate supportive and symptomatic treatment:

- Compression
- Surgery
- Embolisation
Reversal strategies

After all these treatments are used, there are several options to specifically reverse either VKA or DOAC.

a) Time
Waiting is the best antidote. Elimination half-lives are short, unless the patient has a renal dysfunction, particularly with dabigatran.

b) Antidotes
Antidotes exist for dabigatran, and are being developed for anti-Xa agents, and phase III studies are in progress for idarucizumab, for example.

c) Dialysis
This can be considered if the patient is treated with dabigatran, but it is not a simple situation.

d) Charcoal

GIHP-NACO registry results

The GIHP (French Working Group on Perioperative Haemostasis) established a registry in June 2013 across 41 emergency centres in France and Belgium to collect data on the management of major bleeding in patients receiving DOAC (dabigatran, rivaroxaban or apixaban), who have been hospitalised for major bleeding or emergency surgery (Albaladejo et al. 2017b). The registry prospectively collected data on patient management, focusing on the use of haemostatic agents and the plasma concentration of DOAC. This registry data can be compared with data from large series treated with DOAC antidotes. Our published results are from 35 centres, between June 2013 and November 2015 (Albaladejo et al. 2017b).

732 patients treated with

- Dabigatran (n=207)
- Rivaroxaban (n=472)
- Apixaban (n=53) and
- Severe bleeding

GI bleeding was present in 37% of patients, intracranial in 24%.

In November 2015 we analysed results from 732 mainly elderly patients, (median age: 78) and most with renal dysfunction.

On admission we took the laboratory results on plasma concentration of DOAC (Figure 2) (see p. I). This could be determined in 62% (452/732) of cases.

Figure 3 (see p. II) shows the relationship between activated partial thromboplastin time and prothrombin time ratio and concentration of dabigatran and rivaroxaban. These results confirm the uselessness of this lab tests in these situations.

Figure 4 (see p. II) shows DOAC plasma concentration depending on time since last dose.

Figure 5 shows plasma concentration in DOAC depending on the time since the last dose in patients with clearance < 60 ml/ min.

Activated or nonactivated prothrombin complex concentrates were administered in 38% (281/732) of patients.

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<tr>
<th>Table 1.</th>
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<tr>
<td>Transfusion n [%]</td>
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<tr>
<td>Packed red blood cells</td>
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<tr>
<td>Platelets</td>
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<tr>
<td>Fresh frozen plasma</td>
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<tr>
<td>aPCC Total dose IU.Kg⁻¹; median (25th-75th)</td>
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<td>2nd Dose; n [%]</td>
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<tr>
<td>2nd Dose; n [%]</td>
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<tr>
<td>Recombinant Factor VIIa</td>
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<td>Tranexamic acid [%]</td>
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<td>Haemodialysis [%]</td>
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<td>Mechanical means*</td>
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<td>Intervention for haemostasis control</td>
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<td>Endoscopy</td>
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<td>Surgery</td>
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<td>Embolisation</td>
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* compression, gauze packing

Did the bleeding stop after PCC?

Table 2. Did bleeding stop after PCC?

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<thead>
<tr>
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<th>Percentage</th>
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<tr>
<td>Yes, completely</td>
<td>42.7%</td>
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<tr>
<td>Yes, partially</td>
<td>39.7%</td>
</tr>
<tr>
<td>No</td>
<td>17.7%</td>
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It is quite difficult with this method and in these heterogeneous patients to assess the efficacy of PCC. In this study adequacy of haemostasis was assessed by local investigators.

By day 30 mortality was 13.5%, variable according to the bleeding site. Patients were also assessed for suspected major cerebral and cardiovascular events (MACCEs) after the bleeding event (Table 3).

Conclusion

The GIHP-NACO registry study showed that plasma concentration was positively related to use of PCC. In this cohort, the mortality rates of patients with severe bleeding were similar to those observed for large series treated with DOAC antidotes. Plasma concentration could therefore be important to identify patients for whom the use or an antidote or PCC (if antidotes are not available) could be useful.

Conflict of Interest

Pierre Albaladejo has received research support from CSL Behring, LFB, Octapharma and Sanofi. He is on the scientific advisory board of Boehringer Ingelheim, Bayer, BMS-Pfizer, Daiichi-Sankyo and a consultant for Boehringer Ingelheim, Bayer, BMS-Pfizer, Daiichi-Sankyo, LFB and Sanofi. He has received honoraria from Boehringer Ingelheim, Bayer, BMS-Pfizer, Daiichi-Sankyo, LFB, CSL Behring and Sanofi and travel support from CSL Behring, B Braun, Boehringer Ingelheim, Bayer, BMS-Pfizer, Daiichi-Sankyo, LFB and Sanofi.

Key Points

- Treat major bleeding in patients receiving DOAC with predetermined approach
- Perform laboratory tests to show plasma concentration
- GIHP-NACO study showed positive relationship between plasma concentration and use of PCC
- Take symptomatic and supportive measures—and time to treat patients with major bleeding
- DOAC antidotes are increasingly available
- PCC or aPCC use differs depending on bleeding sites and plasma concentrations of DOAC.

Abbreviations

- DOAC direct oral anticoagulant
- FEIBA factor eight inhibitor bypass activity
- FFP fresh frozen plasma
- MACCE major cerebral and cardiovascular events
- PCC prothrombin complex concentrate
- PPSB prothrombin-proconvertin-Stuart factor-antihemophilic factor B
- rFVIIa recombinant factor VIIa
- VKA Vitamin K antagonists

References


