Use of prothrombin complex concentrates for urgent reversal of dabigatran in the Emergency Department

New oral anticoagulants (NOACs) are being implemented for use in daily clinical practice, anticoagulants that should theoretically replace the well-known vitamin K antagonists in the near future. Based on their inhibitory properties, NOACs can be classified into two main groups: direct thrombin inhibitors with dabigatran as the only available compound[1] and factor Xa inhibitors, namely rivaroxaban and apixaban.[2] Dabigatran has a low oral bioavailability, a low protein binding (35%) and its half-life reaches 14-17 hours in patients with normal renal function, but is longer in patients with impaired renal function and advanced age.[3,4] A number of advantages of dabigatran over vitamin K antagonists have been reported, such as the lack of need for periodic blood testing or for any dose adjustment.[5,6] Specific blood tests, such as the diluted thrombin time (Haemoclot®), are being developed but are not yet universally available at any given moment. However, the main limitation in the use of dabigatran is that there is currently no available antidote for this drug. A small number of options have been proposed in the event of an overdose: activated charcoal whenever possible, dialysis and/or the use of prohemostatic agents such as prothrombin complex concentrates (PCC), activated prothrombin complex concentrates (FEIBA), and recombinant activated factor VII (rFVIIa).[1,7]

We describe our experience in the emergency department (ED) with the urgent reversal of dabigatran anticoagulation using PCC. We collected data from all patients administered dabigatran who were treated at the ED between July 2011 and June 2012. From among these cases, any patient who developed a hemorrhagic complication was included. Relevant data from the electronic clinical history and prescriptions were collected. Additionally, we followed up patients for six months and we reviewed thrombotic complications. A descriptive data analysis was performed and we compared the blood parameters at the start of the treatment with dabigatran, at the moment of the hemorrhagic episode, and before and after the administration of PCC. The study was approved by the hospital Ethics Committee.

From a total of 68 patients under treatment with dabigatran, 5 patients developed bleeding complications in the intestinal tract (80% rectal bleedings and 20% melenas) and were therefore included in the study. The demographic data related to the start of treatment with dabigatran and the types of hemorrhagic complications are summarized in Table 1. The reason for dabigratan treatment in these 5 patients was atrial fibrillation. Patients had a median age of 82 years (range 76-88 years), were predominantly male (80%), had a median body weight of 57 kg (range 51-67 kg), and had a median creatinine-clearance of 53.7 mL/min (range 35.5-113 mL/min). None of the patients had any history of prior GI bleeding, one of the patients developed hepatopathy and all patients were being treated with antiplatelets. We calculated the HAS-BLED Score for all patients (Table),[8] showing all of them to have a high estimated bleeding risk, with an estimated rate of major bleeding within the first year of between 5-20%. Probably these patients, especially those with 5 points or those with kidney function impaired, should not be treated with oral anticoagulants. Furthermore, 3 patients were being treated with proton-pump inhibitors. All of these patients were receiving a dosage of 110 mg dabigatran twice a day (for a total daily dose of 220 mg). The median time from the start of treatment to the hemorrhagic episode was 27 days (range 6-122 days). Figure 1 shows activated partial thromboplastin (aPTT) ratios. We found no significant differences in the coagulation tests performed before and after the bleeding episode, although a tendency was noted in the INR values (1.8±1.2 *vs.* 1.2±0.2) and in the aPTT ratio (2.4±1.5 *vs.* 1.5±0.6). All patients received treatment with a prothrombin complex concentrate (Octaplex®, Octapharma, Vienna, Austria). Table 1 lists the dosage/weight, the administration of vitamin K, the need for transfusion, the time from ED admission to the cessation of bleeding, and the final patient allocation. Four patients required hospital admission, and one patient (20%) died of septic shock of abdominal origin and coagulopathy secondary to massive/severe hemorrhage (rectal bleeding) 24 hours after admission. No patient had a thrombotic event during the next six months of follow up.

We present our initial experience in the reversal of dabigatran using PCC. Studies performed in animal models have produced conflicting results. Pragst *et al.*[9] demonstrated the potential efficacy of PCC (Beriplex®) in the reversal of the dabigatran effect in a rabbit model. However, studies developed in murine models suggest that PCC treatment prevents excess bleeding much more effectively in warfarin-induced coagulopathy than in dabigatran-induced coagulopathy.[10] In healthy volunteers, the effects of PCC on the dabigatran biological activity could not be confirmed, which differs from the findings of studies using rFVIIa or FEIBA.[11] Of note, a study on 12 healthy volunteers showed that PCC did not reverse the biological effects of 150 mg dabigatran b.i.d.[11] When compared to placebo, there was no difference in the decrease of the pro-

Table 1. Demographic and clinical characteristics, bleeding complications.

ID	Age (years)	Gender	Weight (kg)	HAS-BLED Score	Creatinine clearance (mL/min)	Bleeding complications	Hours from last dose to admission	PCC Dose (IU)	Dose/ weight (IU/kg)	Vitamin K	RBC (N. of units)	Time from admission to bleeding cessation	Death
1	83	Male	57	3	36.5	rectal bleeding	1.5	1000	17	No	No	<6 hours	No
2	82	Male	67	3	73.3	melena	1	1000	15	Yes	Yes (2)	–	No
3	88	Male	51	5	53.7	rectal bleeding	1.1	1000	20	No	Yes (2)	<12 hours	Yes
4	76	Male	54	5	113	rectal bleeding	2	1000	19	No	Yes (1)	<12 hours	No
5	82	Female	60	4	35.5	rectal bleeding	2	1500	25	No	No	<6 hours	No

RBC: red blood cell transfusion.

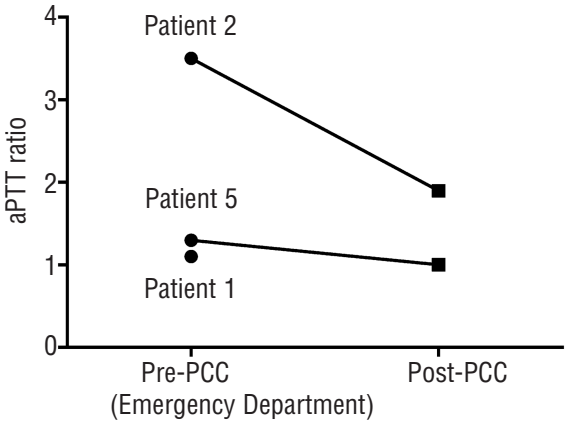

Figure 1. Coagulation tests before and after the bleeding episode. Activated partial thromboplastin (aPTT) ratio at the emergency department during the bleeding episode (before PCC administration) and after the treatment of the hemorrhage (post-PCC administration).

longation of aPTT. The normalization of the aPTT was observed 24 hours after the cessation of dabigatran administration.[12] In our cohort study, only one patient showed a prolonged aPTT ratio that demonstrated a tendency to normalization from 3.2 to 1.4 after administration of PCC. This demonstrates a trend that has not yet been described regarding the effect of PCC in the prolongation of aPTT in patients treated with dabigatran. This correlated with an adequate clinical control of the hemorrhagic complication with only one death in our cohort study and an acceptable control in 4 of the 5 patients. Recently Lillo-Le Louet *et al.*[13] reported the death of 4 patients after the reversal of dabigatran-induced bleeding. In 2 patients, PCC (Kaskadil® and Kanokad®) was used, and one patient was treated with recombinant FVIIa. With regard to these findings, we observe that there are some differences in the characteristics of our patient group. In addition to the fact that the composition of the PCC administered to our patients (Octaplex®) differs from the PCC used by Lillo-Le Louet *et al.* (Kaskadil®), our patients reported no renal impairment and were not administered high doses of dabigatran. We have shown that PCC could be useful and safe in dabigatran-treated patients with intestinal bleeding complications. However, further clinical trials are warranted to confirm this preliminary report.

Manuel Quintana Díaz,[1,2] Alberto M. Borobia,[1,3] Ma Angelica Rivera Núñez,[1] Ana Maria Martínez Virto,[1] Sara Fabra,[1] Marcelino Sánchez Casado,[4] Jose A. García-Erce,[5] and C. Meyer Samama[6]

[1]General Emergency Department, Hospital Universitario "La Paz" de Madrid, IdiPAZ, Spain; [2]Intensive Care Unit, Hospital Universitario "La Paz" de Madrid, IdiPAZ, Spain; [3]Clinical Pharmacology Service, Hospital Universitario "La Paz" de Madrid, School of Medicine. Universidad Autónoma de Madrid, IdiPAZ, Spain; [4]Intensive Care Unit, Hospital Virgen de la Salud. Toledo, España; [5]Haematology Service, Hospital San Jorge de Huesca, Spain; and [6]Department of Anaesthesia and Intensive Care Medicine, Hotel-Dieu and Cochin University Hospitals; Université Paris Descartes; Assistance Publique, Hôpitaux de Paris, Paris, France

Correspondence: mquintana.hulp@salud.madrid.org
doi:10.3324/haematol.2013.092767

Key words: dabigatran, prothrombin complex concentrate, bleeding, reversal.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. European Medicines Agency [Internet]. Pradaxa dabigratan etexilate. London: The Association EMA Science Medicines Health [Update 2013 Jan 16; cited Jul 22]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fincludes%2Fmedicines%2Fmedicines_landing_page.jsp&searchkwByEnter=false&quickSearch=pradaxa&spanFlag=0&keywordSearch=Submit
2. Cao YB, Zhang JD, Shen H, Jiang YY. Rivaroxaban versus enoxaparin for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. 2010;66(11):1099-108.
3. Pradaxa monograph. Boehringer-Ingelheim [Internet]. Ingelheim-Germany [update 2012 Dec 12; cited 2013 Feb 23]. Available from: ttp://www.boehringer-ingelheim.ca/en/Home/Human_Health/
4. vanRyn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, et al. Dabigatran etexilate-a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010;103(6):1116-27.
5. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52.
6. Kansal AR, Sorensen SV, Gani R, Robinson P, Pan F, Plumb JM, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. Heart. 2012;98(7):573-8.
7. van Ryn J, Baruch L, Clemens A. Interpretation of point-of-care INR results in patients treated with dabigatran. Am J Med. 2012;125(4):417-20.
8. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.
9. Pragst I, Zeitler SH, Doerr B, Kaspereit FJ, Herzog E, Dickneite G, et al. Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model. J Thromb Haemost. 2012;10(9):1841-8.
10. Lambourne MD, Eltringham-Smith LJ, Gataiance S, Arnold DM, Crowther MA, Sheffield WP. Prothrombin complex concentrates reduce blood loss in murine coagulopathy induced by warfarin, but not in that induced by dabigatran etexilate. J Thromb Haemost. 2012;10(9):1830-40.
11. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate. A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects. Circulation. 2011;124(14):1573-9.
12. Clemenes A, van Ryn J, Sennewald R, Yamamura N, Stangier J, Feuring M, et al. Switching from enoxaparin to dabigatranetexilate: pharmacokinetics, pharmacodynamics, and safety profile. Eur J Clin Pharmacol. 2012;68(5):607-16.
13. Lillo-Le Louët A, Wolf M, Soufir L, Galbois A, Dumenil AS, Offenstadt G, et al. Life-threatening bleeding in four patients with an unusual excessive response to dabigatran: Implications for emergency surgery and resuscitation. Thromb Haemost. 2012;108(3):583-5.