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Major bleeding events in octagenarians associated with drug interactions between dabigatran and P-gp inhibitors

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Abstract

Background   The direct oral anticoagulant dabigatran does not require any routine therapeutic drug monitoring. Yet, concerns about possible drug interactions susceptible to increase its inherent bleeding risk, especially in very elderly patients, have been raised recently. The aim of our study was to evaluate to what extent the co-prescription of P-gp inhibitors with dabigatran may increase its plasma levels and lead to bleeding complications, in usual conditions of care of the very elderly. **Methods**   Fifty-eight patients over 85 years old with non valvular atrial fibrillation receiving dabigatran were included in a prospective cohort. Prescriptions were screened for the presence of P-gp inhibitors (Group A) or not (Group B). **Results**   Patients from Group A had increased dabigatran mean plasma concentrations as compared with patients from Group B (A *vs.* B: 182.2 ± 147.3 *vs.* 93.7 ± 64.9 ng/mL). One third of the patients from Group A had dabigatran concentrations that were deemed "out of range" versus none in Group B ($P = 0.05$). This was associated with more frequent bleeding complications in Group A (A: 30.4%, B: 8.6%, $P = 0.04$). **Conclusion**   In our cohort of very elderly patients, at least, the co-prescription of dabigatran with P-gp inhibitors in usual conditions of care resulted in higher dabigatran plasma concentrations and more frequent bleeding occurrences.

1   Introduction

The prevalence of non valvular atrial fibrillation (AFib) increases substantially with age and concerns up to 9% of patients 85 years of age or older.[1] Anticoagulants, such as vitamin K antagonists (VKA) are keystone to prevent stroke and systemic embolism in elderly patients with AFib.[2,3] However, the emergence of direct oral anticoagulants (DOACs) such as the direct thrombin inhibitor dabigatran, and different factor Xa inhibitors such as rivaroxaban, are appealing due to convenient oral dosing and the absence of routine laboratory monitoring and have changed the therapeutic landscape for stroke prevention in the elderly.[4] However, their better efficacy/safety ratio is being currently challenged.[5–9] As conflicting opinions regarding their

safety are ongoing, the European Medicines Agency (EMA) is currently reviewing their bleeding risk in normal conditions of use.[5] Dabigatran, approved by the FDA to prevent stroke and systemic embolism in patients with AFib with a recommended dose at 300 mg/day, had previously raised postmarketing concerns as serious events had emerged, involving life-threatening bleedings in the elderly.[10-12] Indeed, a study nested within the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY®) pivotal study has observed that the risk of bleeding, extra-cranial particularly, increased with age and surpassed that of warfarin in the elderly.[13] Dabigatran has also been considered as one of the most frequently involved drugs for the occurrence of drug adverse-effects.[14] In the elderly, cases of dabigatran-induced bleedings stirred discussion in mainstream media.[15–20] Risks factors such as a low body weight (< 50 kg), kidney disease and pharmacodynamics drug interactions were found to increase the occurrence of bleedings leading to a reduction of the recommended dose at 220 mg/day in patients over 75 years, with moderate renal impairment, or small body weight. A direct relationship between high dabigatran plasma concentrations and the oc-

currence of bleedings has even been suggested.[21,22] Surprisingly, drugs interfering with the pharmacokinetics of DOACs are prescribed up to the astounding level of 60% in real conditions of use.[5] Bleedings related to pharmacokinetics interactions between dabigatran and P-glycoprotein (P-gp) inhibitors have been reported.[23–26] Conversely, to other DOACs, *in vitro* studies have not revealed major inferences of CYP450 isoenzymes on dabigatran pharmacokinetics. Yet, dabigatran etexilate, the prodrug of dabigatran, is a substrate of P-gp which could modulate its intestinal absorption and dabigatran is contraindicated with potent P-gp inhibitors such as ketoconazole, ciclosporin, itraconazole or dronedarone.[27,28] However, according to dabigatran summary of product characteristics (SmPC), caution only must prevail with mild to moderate P-gp inhibitors such as amiodarone, verapamil or digoxin.[28] Although these P-gp inhibitors have shown to induce changes in dabigatran plasma concentrations, no clinical consequence could be assessed in clinical trials, hence in usual conditions of care.[6]

The aim of our study was to evaluate in very elderly patients with AFib, who are often frail, polymedicated and suffering from renal insufficiency, whether a concomitant prescription of P-gp inhibitors could be associated with increased dabigatran plasma concentrations and higher occurrences of bleeding.

2 Methods

2.1 Study setting and Sample

This is an exposed/unexposed non-interventional, prospective and monocentric study that was conducted at the University Medical Center of Nice, France from July 2015 to October 2018 in a cohort of elderly patients treated with dabigatran. All very elderly ($\geq$ 85 years) patients admitted to the Medical Center, benefitting from treatment with dabigatran and known from the department of pharmacology, were included in this study. The inclusions were carried out during the usual activity, whether weekly visits in the different departments, regular interrogation of the "emergency terminal" (computerized management tool of the emergency department room) or spontaneous notifications from health care professionals of the University Hospital.

To be consistent with previous studies, we only included patients over 85 years, treated with dabigatran for prevention of stroke and systemic embolism in non valvular AFib, and having achieved steady-state plasma concentrations (treated for at least three days).[6,29] Of the 61 included patients over 85 years, 58 were included in the analysis. Two patients had another indication for dabigatran (one for deep vein thrombosis and one for pulmonary embolism) and one patient had received dabigatran for 1 day only.

2.2 Data collection

The patients renal function was evaluated by the Cockcroft and Gault formula, since drug doses are adjusted to it.[30] Two risk scores assessed the patients' thromboembolic and hemorrhagic risks. The CHA_2DS_2-VASc score evaluated the thromboembolic risk: a higher score confers a higher risk of presenting a thromboembolic event. A score of 4 corresponds to an embolic risk of 4.0% per year, whereas a score of 9 coincides with a risk of 15.2% per year.[31] The HAS-BLED hemorrhagic score assessed the hemorrhagic risk of AFib patients. A HAS-BLED score $\geq$3 qualified a high risk of bleeding.[32]

The usual treatment, prescription for acute management and self-medication if ever, were listed upon inclusion of each patient. The total number of concomitant treatments was calculated to assess the level of "polypharmacy".[33] The level was "minor" for prescriptions containing 2–4 drugs and "major" for prescriptions of five different drugs or more. Antiplatelet drugs, known to increase the hemorrhagic risk, were also screened for.

2.3 Assessment of drug interactions

Neither dabigatran etexilate nor dabigatran are metabolized by the cytochrome P450 system, nor do they affect drugs metabolized by this system.[34] Prescriptions were screened for the following known potent and moderate inhibitors of P-gp: verapamil, amiodarone, dronedarone, digoxin, quinidine, ticagrelor, clarithromycin, ketoconazole, itraconazole and protease inhibitor (ritonavir alone or in combination).[35] According to the presence or absence of a known P-gp inhibitor in their concomitant treatments, the patients were classified as "exposed" in the Group A or "unexposed" in the Group B.

2.4 Assessment of bleeding events

The bleeding events and their severity were carefully assessed according to the classification of The International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC).[36] Briefly, fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells were considered as a "major bleeding" whereas "minor bleeding" lacked any of these criteria.

Table 1. Dabigatran plasma concentrations at the upper 95% CI.

Dabigatran prescription	220 mg/day		300 mg/day	
Dabigatran concentrations at the upper normal range (95% CI)	Peak	Trough	Peak	Trough
	328.7 ng/mL	185.0 ng/mL	457.7 ng/mL	257.0 ng/mL

Dabigatran plasma concentration beyond the upper bounds of the 95% CI obtained under the conditions of the RE-LY study.[6]

2.5 Assessment of dabigatran plasma concentrations

Total dabigatran plasma concentrations were determined at peak or trough, when felt necessary by the physicians, by a validated high-performance liquid chromatography tandem mass spectrometry (LC/MS-MS). "Trough" concentrations were ascribed to samples collected within 10 to 14 h following the previous dabigatran dosing. Similarly, "peak" concentrations were defined by samples collected within 2 to 4 h after dosing. Dabigatran plasma concentrations beyond the upper bounds of the 95% confidence interval (CI) yielded in the pivotal study RE-LY® defined an abnormally "high" concentration for peak or trough (Table 1).[6]

2.6 Statistical analysis

All data were collected and introduced into a single database. Continuous variables are given as mean ± SD. Categorical variables were presented as frequencies and percentages.

Significance between groups was assessed by the Student *t* test for continuous variables and Chi square or Fisher's exact test for categorical variables.

A multivariate logistic regression analysis [odds ratio (OR) and 95% CI], was performed to assess the occurrence of bleeding. The best-fit model was defined based on the Akaïke Information Criterion.[37] The impact of the covariates body mass index, creatinine clearance (Cl_{creat}), HAS-BLED score, concomitant drugs and P-gp inhibitor were investigated.

A two-sided *P*-value < 0.05 indicated statistical significance between the predicted and observed event rates. All statistical analyses were performed with the statistics software package "R" (R Development Core Team, version 3.3.3, Vienna, Austria).

3 Results

3.1 Population characteristics

Fifty-eight very elderly patients were successively included (F: 55%, *n* = 32; M: 45%, *n* = 26), with a mean age of 88 ± 3 years. Their estimated Cl_{creat} was 48 ± 13 mL/min. Their mean CHA_2DS_2-VASC score was at 5.0 ± 1.5 and HAS-BLED score at 1.9 ± 0.8. At the inclusion, 7 patients presented with a thromboembolic event (7 ischemic strokes).

They were subject to a "major" polypharmacy in 59% of the cases with an average of 5.7 ± 2.9 drugs per patient. The sociodemographic and clinical characteristics as well as their prescriptions did not reveal any significant difference between groups A and B (Table 2).

Twenty three out of 58 patients (39.7%) had one P-gp inhibitor amidst their usual treatment (Group A) and 35 patients had none (60.3%, Group B). The main P-gp inhibitor involved was amiodarone, prescribed in 96% of the cases. One patient only was taking another one: verapamil (2%). No other patient was treated with any other known P-gp inhibitor.

Table 2. Baseline characteristics of patients included.

	Group A $N = 23$	Group B $N = 35$	*P*-value
Sociodemographic criteria			
Males	10 (43.5%)	16 (45.7%)	1.00
Female	13 (56.5%)	19 (54.3%)	
Age, yrs	89 ± 3	88 ± 3	0.85
Clinical criteria			
Weight, kg	65 ± 11	64 ± 14	0.76
[a]Cockcroft CL_{creat}, mL/min	47 ± 11	49 ± 14	0.69
[b]HAS-BLED score	2.1 ± 0.8	1.8 ± 0.7	0.09
[c]CHA_2DS_2-VASc score	4.4 ± 1.3	5.1 ± 1.6	0.11
[d]Dabigatran prescription			
Conformity, 220 mg/day	23 (100%)	31 (88.6%)	0.41
Co-prescription			
Average number of concomitant treatment	5.7 ± 2.8	6 ± 3.0	0.96
Major polypharmacy	15 (65.2%)	19 (54.3%)	0.43
Minor polypharmacy	8 (34.8%)	16 (45.7%)	
[e]Pharmacodynamics interactions	7 (30.4%)	8 (22.9%)	0.55

Data are presented as mean ± SD or *n* (%). [a]Cockcroft Cl_{creat} equation = (140 − age) × (weight, kg) × (0.85 if female)/(72 × serumCreat).[30] [b]HAS-BLED score: hypertension, abnormal renal/ liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (> 65 years), drugs/alcohol concomitantly (1 point each).[32] [c]CHA_2DS_2-VASc score = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke or transient ischaemic attack or systemic embolism (doubled), Vascular disease, Age 65–74, and Sex (female).[32] [d]Following Pradaxa®.[28] For both prevention of stroke and blood clots in patients with non-valvular AFib, a lower dose (220 mg/day) should be used in patients aged 80 or above. [e]Including: platelet antiaggregant and derivatives (acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor, ticlopidine, dipyridamole and anti-GPIIbIIIa), NSAIDs and other anticoagulants.

Table 3. Influence of P-gp inhibitors on dabigatran plasma concentrations.

Group Number of patients	Group A N = 10		Group B N = 15		*P*-value
Dabigatran concentrations > the upper normal range (95CI)	3	30%	0	0	0.05

The 95% CI was defined under the conditions of the RE-LY study.[6]

3.2 Influence of P-gp inhibitors on dabigatran plasma concentrations

The available dabigatran plasma concentrations of the control patients from Group B (15 out 35) were all within the pre-defined normal range (that is < 328.7 ng/mL for peak, < 185.0 ng/mL for trough), whereas almost thirty percent of patients from Group A with available dabigatran concentrations were beyond the upper bound of the defined "normal range" (> 400 ng/mL, *P* = 0.05) (Table 3).

The dabigatran mean concentrations from group A (182.2 ± 147.3 ng/mL) were higher than those from group B (93.7 ± 64.9 ng/mL).

3.3 Influence of P-gp inhibitors on dabigatran-associated bleeding occurrence

Seven patients from Group A (30.4%) and 3 patients from Group B (8.6%) experienced a hemorrhagic adverse event (*P* = 0.04). Four patients from Group A suffered from a gastrointestinal bleeding (one fatal digestive hemorrhage and three melena, one of which required a two unit blood transfusion), two intracranial bleedings (leading to death in one case) and one hematuria. In Group B, one patient presented with an epistaxis, one suffered from a gastrointestinal bleeding (melena) and one from an intracranial bleeding (hematoma with no further complication) (Table 4).

Severity of bleeding showed no statistical difference, although two patients died and one required blood transfusion in Group A, whereas no patient suffered any complication further than bleeding in Group B. The presence of a P-gp inhibitor was identified as a risk factor for bleeding (*P* = 0.04). In the multivariate analysis, elderly patients co-medicated with a P-gp inhibitor had about a six-fold risk to bleed [5.79 (1.04, 32.11)] as compared with patients with

Table 4. Influence of P-gp inhibitors on dabigatran bleeding occurrence and severity

	Group A N = 23	Group B N = 35	*P*-value
Bleeding occurrence	7 (30.4%)	3 (8.6%)	0.04*
Major bleeding	4 (57.0%)	1 (33.0%)	0.49
Minor bleeding	3 (43.0%)	2 (67.0%)	

Data are presented as *n* (%). Bleedings are classified according to the classification of The International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions.[36]

no such drug. In this limited cohort, a high HAS-BLED score, a low weight, an impaired creatinine clearance, a concomitant medication with antiplatelet drugs and a major polypharmacy did not appear as significant risk factors for bleeding though.

4 Discussion

In people older than 85 years, the combination of dabigatran with a P-gp inhibitor significantly augments the risk of bleeding. This result raises concern since few studies, if any, have shown an over-incidence of hemorrhagic events with P-gp inhibitors in usual conditions of use.[22] Our observation may result from the considerably older age of our patients (88 years of age in average) than those from the pivotal study RE-LY® (mean age: 71 years).[22] We focused on patients aged over 85, as they represent an important population suffering from AFib in our departments. They still benefit from DOACs, even though fragile, polymedicated, and with more risks to bleed.[1,38–40] It is also possible that elderly patients who had P-gp inhibitors prescribed might bear a greater risk of bleeding because of their inherent condition. We cannot provide other biomarkers, unfortunately, as high sensitivity troponin and natriuretic peptides, to evaluate this drug-independent confounder. As underlined by guidelines from scientific societies, available data on DOACs are rather scant in the elderly. We feel that this cohort in usual conditions of care, gathers a very elderly, fragile, polymedicated and polypathological geriatric population. A way larger European cohort of more than 180,000 patients with DOACs is currently being screened by the EMA and should be soon available, since preliminary data confirm that such co-prescriptions occur.[5]

We found amiodarone as a main drug of concern, which represents over 95% of the co-prescribed P-gp inhibitors in our study. It had been previously found that amiodarone was the most common inhibitor involved in pharmacokinetic interactions.[41] This is not surprising given its wide use in AFib, for rhythm as well as for rate control in clinical practice. Calcium channel blockers (verapamil and diltiazem) and digoxin are less implicated because of either contraindications or poor tolerance, at that age.

We also found that P-gp inhibitors significantly increased dabigatran plasma concentrations (when available) beyond

their "normal" range. Interactions of dabigatran with P-gp inhibitors have already been associated with extremely high levels of dabigatran, with up to 22% of patients exceeding the expected range for drug levels.[41] Reports have been published of increased bioavailability of dabigatran by 23% and steady-state exposure by 12% when co-prescribed with verapamil and amiodarone respectively.[6,42,43] Administration of dabigatran with a single oral dose of 600 mg amiodarone increases dabigatran exposition by 50%.[6] After discontinuing amiodarone, and because of its long half-life, a potential interaction persists for several weeks. Similarly, when dabigatran etexilate (150 mg) is co-administered with oral verapamil, both concentration of, and exposition to dabigatran are increased readily from the first dose and up to 180%. This led the FDA to limit the use of dabigatran to smaller doses in case of CrCl 30–50 mL/min and avoid it altogether in case of CrCl 15–30 mL/min or prescription of dronedarone or systemic ketoconazole when deemed necessary.[44] In our cohort, one third of patient plasma concentrations are considered out of range, even by the quite conservative methodology (upper 95th percentile) that we used. We used high-performance liquid chromatography (HPLC) with tandem mass spectrometry for the plasma determination of dabigatran over standard hematology techniques, because of past discrepancies of DOACs assays that we had observed.[45]

Our study has limitations though. In relation to the real conditions of care, the methodology of our cohort study has an inevitable selection bias, as patients were recruited in a context of hospitalization suggesting more "serious" patients and dabigatran blood concentrations could not be assessed in all patients but in these deemed necessary by their healthcare physician. Finally, as assessed by the lack of significance of "standard" bleeding risk factors like impaired renal function, lack of power may have a role in this small cohort and hinders extrapolation.

In conclusion, dabigatran benefits number of patients suffering from AFib. These also include very elderly frail patients with polypathology, polypharmacy and chronic kidney disease. Our findings showed that coadministration of P-gp inhibitors to dabigatran may expose these patients to higher dabigatran plasma concentrations and are associated with an increased bleeding occurrence in hospital conditions of use. Health professionals should be aware of these interactions since amiodarone and verapamil are very commonly used to control rhythm and heart rate disorders in AFib, and amiodarone bears a long half-life. Some kind of therapeutic drug monitoring of dabigatran might therefore be of special interest in this population.

Conflicts of Interest

Authors have no conflict of interest to report.

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