Dabigatran trough concentrations in very elderly patients

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ABSTRACT

Objectives The aim of this observational study was to explore dabigatran concentrations in elderly and very elderly patients in a real-life population. Patients aged >75 years receiving dabigatran have a significantly higher risk of gastrointestinal bleeding compared withthose receiving warfarin. High trough concentrations have an important impact on this bleeding risk.

Methods We measured dabigatran trough concentrations in 75 patients with atrial fibrillation, divided into age categories <75, ≥75 to 84 and ≥85 years. The most important exclusion criteria were use of interacting medication and severe renal failure. We analysed absolute trough concentrations and concentrations normalised for dose.

Results Trough concentrations were considerably higher in the highest age category. Dose-normalised medians were 0.66, 0.83 and 1.20 ng/mL/mg in the <75, ≥75–84 and ≥85 age groups, respectively (p=0.004).

Conclusion Clinicians should be aware of higher dabigatran concentrations in elderly patients despite dose reduction.

What this paper adds

What is already known about this subject?

- The efficacy of dabigatran is preserved in patients aged >75 years, but the risk of gastrointestinal bleeding in this age group is higher in patients taking dabigatran than in those taking warfarin.
- Dabigatran concentrations are higher in elderly patients.
- The risk of gastrointestinal bleeding increases substantially if trough concentrations are above 150 ng/mL.

What this study adds

- 40% of patients aged ≥85 years in this study population had trough concentrations above 150 ng/mL.
- Patients aged ≥85 years had 33% higher trough levels than patients aged <75 years, despite using a reduced dose of dabigatran.

INTRODUCTION

The incidence of atrial fibrillation increases with age, as do other risk factors of ischaemic cerebrovascular events.[1] Therefore, many geriatric patients need oral anticoagulants.

Dabigatran is a direct oral anticoagulant. The efficacy of dabigatran in reducing cerebrovascular events is preserved in patients aged >75 years. The 150 mg dose has been shown to be superior to warfarin and the 110 mg dose is non-inferior to warfarin, just as in younger age categories.[2] In contrast, the risk of gastrointestinal bleeding is significantly higher in elderly patients receiving dabigatran. The relative risk in patients aged >75 years receiving dabigatran compared with warfarin is 1.39 and 1.79 for patients taking 110 mg tablets and those taking 150 mg tablets, respectively.[3]

Previous studies have shown a relation between age and high dabigatran concentrations, and a relation between the dabigatran trough concentration and risk of bleeding.[4 5] The bleeding risk rises substantially if the plasma trough concentration is above 150 ng/mL.[4] We also know that inter-patient variation in dabigatran concentrations is high. Since there is no established indication for routinely measuring plasma concentrations of dabigatran, it is difficult to predict the bleeding risk for an individual patient.

The aim of this observational pilot study was to explore dabigatran concentrations in elderly and very elderly patients with atrial fibrillation in our hospital, to take a step towards bridging the gap between trial data and clinical practice.

METHODS

We compared dabigatran concentrations in this pilot study in three age categories: <75, ≥75–84 and ≥85 years, with 25 patients in each group. All patients were selected by their cardiologist or geriatrician and provided written informed consent. Patients used dabigatran because of atrial fibrillation and had been using it for at least 1 week. They used a dose of 150 mg twice daily or 110 mg twice daily, depending on age and other clinical characteristics as advised in the SmPC. Exclusion criteria were use of other anticoagulants or antiplatelet agents and use of medication with pharmacokinetic interactions by P-glycoprotein (P-gp) inhibition. Other exclusion criteria were estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, transaminase elevation above two times upper limit of normal, actual malignancy and body weight <50 kg or >110 kg.

Blood samples were taken just before the next dose. eGFR and transaminase levels were measured directly and the plasma samples used for measuring the dabigatran concentration were stored at −80°C and analysed later using the UPLC-MS/MS method.[6] There were no missing data and there was no loss to follow-up since there was only one study visit.

Table 1 Characteristics of patients (n=75) and results (percentages are shown as percentage within one age group)

	<75 years (n=25)	≥75–84 years (n=25)	≥85 years (n=25)	
Age, median (min–max)	68 (55–74)	77 (75–83)	88 (85–94)	
Sex, n (%) male	16 (64%)	19 (76%)	11 (44%)	
eGFR*				
30–44 mL/min	0 (0%)	2 (8%)	3 (12%)	
45–59 mL/min	5 (20%)	12 (48%)	9 (36%)	
≥60 mL/min	20 (80%)	11 (44%)	13 (52%)	
Dose				
Patients on 110 mg	0 (0%)	15 (60%)	24 (96%)	
Patients on 150 mg	25 (100%)	10 (40%)	1(4%)†	
Dabigatran concentration, ng/mL Median (min–max)	99 (29–214)	108 (33–327)	132 (36–324)	p=0.20
Dose-normalised dabigatran concentration, ng/mL/mg Median (min–max)	0.66 (0.19–1.43)	0.83 (0.24–2.97)	1.20 (0.33–2.95)	**p=0.004**
Patients with trough concentrations >150 ng/mL, n (%)	4 (16%)	8 (32%)	10 (40%)	p=0.17

*eGFR was estimated by using the modification of diet in renal disease (MDRD) formula.
†Dabigatran trough concentration of this specific 85-year-old patient who was using 150 mg twice daily was 120 ng/mL.
eGFR, estimated glomerular rate.

We compared trough concentrations per age category using the Kruskal–Wallis test. Trough concentrations were also compared after normalisation for dose in order to make comparison possible between patients taking 150 mg and 110 mg tablets. These normalised concentrations are presented as ng/mL/mg. The prevalence of patients with absolute concentrations above 150 ng/mL was compared using the Fisher's exact test. Regression analysis was used to examine the impact of renal function on the differences between the age groups. For each statistical test, significance was set at p>0.05. SPSS Version 25 was used for all statistical analyses.

RESULTS

Between August 2017 and May 2019, 50 patients aged ≥75 years were included in the study. A total of 155 patients aged ≥75 years were eligible, of which 105 patients did not participate for personal reasons. Dabigatran concentrations of the 25 patients aged <75 years were previously measured in our hospital under the same conditions and were used anonymously.

Patient characteristics are shown in table 1. The reduced dose of dabigatran was used in the majority of patients aged 75 years. Ten patients aged ≥75–79 years were treated with 150 mg twice daily, in all cases conforming to the SmPC dosage advice. One patient aged 85 years was treated with 150 mg twice daily because of specific high thrombotic risk factors. The number of patients with renal failure was higher in the two upper age groups, but did not differ significantly between these two groups.

Median dabigatran concentrations are shown in table 1. The median trough concentration was 9% higher in patients aged ≥75 to 85 years and 33% higher in patients aged ≥85 years compared with those aged <75 years, despite the fact that most elderly patients use the reduced dose of dabigatran. Dose-normalised concentrations were significantly higher in patients in the oldest age group (p=0.004).

Trough concentrations above 150 ng/mL were 2.5 times more prevalent in patients aged ≥85 years than in those aged <75 years, with a prevalence of 40% and 16%, respectively (p=0.059).

Univariate regression analysis showed a significant association between age and trough concentrations, which was preserved in multivariate analysis with eGFR as a covariate (p=0.002).

When comparing median concentrations in all patients using 110 mg tablets versus those using 150 mg tablets, regardless of age, median absolute concentrations in the 110 mg group were 27% higher than in the 150 mg group (133 ng/mL vs 105 ng/mL).

DISCUSSION

This pilot study adds to the knowledge about real-life dabigatran trough concentrations in elderly patients. This helps to bridge the gap between information gained from selected populations in trials and our own patients in daily practice.

The dabigatran concentrations we measured in the youngest two age groups are in line with the outcomes of the RE-LY data, but concentrations in our patients aged ≥85 years are much higher.[4] A large proportion (40%) of the patients aged ≥85 years had trough concentrations above a level of 150 ng/mL. Previous studies have shown that, across the very wide range of trough concentrations, only very small differences are seen in the reduction of stroke risk but a much larger difference is seen in the risk of bleeding, which rapidly rises from trough levels about 150 ng/mL and above.[4 5]

In contrast to previous study data, dose reduction to 110 mg tablets for most elderly patients in our study did not lead to mean concentrations that are equal to those of patients using 150 mg tablets. Patients receiving 110 mg tablets in our study had concentrations that were on average 27% higher. These higher levels despite dose reduction were also found by Bolek *et al*.[7] In the RE-LY data the opposite was found: patients receiving 110 mg tablets had lower trough concentrations. The probable explanation for this difference is the random assignment of the dose in the RE-LY trial rather than dosing based on clinical characteristics. In a study by Chan *et al*, similar drug exposure was found in both dosage groups although dosage was based on patient characteristics, but in this study the average age was lower than that of the patients in our study.[8]

Regression analysis showed a significant association between age and trough concentrations which was preserved in multivariate analysis with eGFR as a covariate. Although the value of this regression analysis is limited in this relatively small population, previous studies have also shown that higher levels in elderly patients are not only caused by reduced renal clearance.[7]

The effort for the participants to visit the hospital for the study may have caused selection bias, since the most frail elderly patients were not able or willing to come to the hospital for the

study. This may have led to an underestimation of the differences in trough concentrations between the age categories.

Another limitation of this study is the variation in time between the last dose and the blood test. Most patients take dabigatran at breakfast and at dinner time, which is not an exact 12-hour interval. All blood samples were taken just before the next dose but, among patients aged ≥75 years, more trough concentrations were measured in the afternoon because of difficulties for elderly patients to reach the hospital early in the morning.

More research is needed to determine whether concentration monitoring or extra dose adjustment should be considered in very elderly patients. The scarcity of elderly patients willing to participate in studies makes this difficult. Concentration monitoring as part of usual care in the oldest patients could be of great value to gain more information about the impact of higher concentrations on the risk of gastrointestinal bleeding in this age group.

In conclusion, despite the fact that concentration monitoring and dose adjustment protocols have not been clinically validated, clinicians should be aware of unexpectedly high dabigatran concentrations and an associated relatively high risk of bleeding in very elderly patients, despite a reduction of the dose.

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REFERENCES

1 Heeringa J, van der Kuip DAM, Hofman A, *et al*. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949–53.
2 Sharma M, Cornelius VR, Patel JP, *et al*. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis. *Circulation* 2015;132:194–204.
3 Eikelboom JW, Wallentin L, Connolly SJ, *et al*. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial. *Circulation* 2011;123:2363–72.
4 Reilly PA, Lehr T, Haertter S, *et al*. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol* 2014;63:321–8.
5 Šinigoj P, Malmström RE, Vene N, *et al*. Dabigatran concentration: variability and potential bleeding protection In "real-life" patients with atrial fibrillation. *Basic Clin Pharmacol Toxicol* 2015;117:323–9.
6 Boonen K, Schmitz E, Rozestraten F, *et al*. Real life dabigatran and metabolite concentrations, focused on inter-patient variability and assay differences in patients with atrial fibrillation. *Clin Chem Lab Med* 2017;55:2002–9.
7 Bolek T, Samoš M, Škorňová I, *et al*. Dabigatran levels in elderly patients with atrial fibrillation: first post-marketing experiences. *Drugs Aging* 2018;35:539–44.
8 Chan NC, Coppens M, Hirsh J, *et al*. Real-world variability in dabigatran levels in patients with atrial fibrillation. *J Thromb Haemost* 2015;13:353–9.