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BRIEF REPORT

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Peak plasma concentration of direct oral anticoagulants in obese patients weighing over 120 kilograms: A retrospective study

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Abstract

Background: Due to a paucity of data on the efficacy and safety of direct oral anticoagulants (DOACs) in patients with a body mass index >40 kg/m^2 or a weight >120 kg, the use of DOACs in this group is not recommended.

Objectives: To determine the proportion of obese patients with body weight >120 kg with a peak plasma concentration of DOACs lower than the expected median trough level derived from population pharmacokinetic studies for each DOAC.

Methods: Patients with body weight >120 kg taking DOACs for any indication underwent a peak drug concentration measurement at steady state.

Results: 38 patients were included in the analysis. The mean age was 64 ± 11 years, and 30 (79%) were males. The median body weight was 132.5 kg (interquartile range [IQR] 127-146.5). The median peak concentrations (IQR) were 148 ng/mL (138-240), 138 ng/mL (123-156.5), 215 ng/mL (181-249) for apixaban, dabigatran, and rivaroxaban, respectively. Two patients (5%, 95% confidence interval [CI]: 0.5%-18%) had a peak plasma concentration lower than the median trough and eight (21%, 95% CI: 11%-37%) had a peak plasma concentration below the fifth percentile (10th percentile for dabigatran) peak concentration.

Conclusions: Most patients in our study had peak plasma concentration higher than the median trough level for each of the three DOACs. However, 21% had a peak plasma concentration that was below the usual on-therapy range of peak concentration for the corresponding DOAC.

KEYWORDS

anticoagulants, laboratories, obesity, pharmacology, thrombosis

Essentials

- Use of direct oral anticoagulants in >120-kg patients is not recommended by recent guidelines.
- We retrospectively examined the peak plasma direct oral anticoagulant concentration in >120-kg patients.
- 95% of patients had a peak plasma concentration higher than the expected median trough level.
- 21% had a peak plasma concentration at the low end of reported on-therapy range of peak concentration.

1 | INTRODUCTION

Nearly 30% of the world's population is either obese or overweight.[1] With obesity predisposing to thromboembolic disease,[2] the need for anticoagulation in this subpopulation is growing. Four direct oral anticoagulants (DOACs), dabigatran, rivaroxaban, apixaban, and edoxaban have been shown to be as effective as warfarin in prevention of stroke in atrial fibrillation and treatment and secondary prevention of venous thromboembolism (VTE) in phase III randomized trials.[3-11] However, patients weighing ≥100 kg were underrepresented and accounted for <20% of patients enrolled in these trials. Furthermore, it is unclear what proportion of this group is >120 kg or at the extreme of obesity. Consequently, there is uncertainty about the efficacy of DOACs in obesity since the latter may predispose to drug underexposure due to an increased volume of distribution and an enhanced drug clearance. Based on these considerations, the Scientific and Standardization Subcommittee of the International Society on Thrombosis and Haemostasis issued a guidance document recommending against the use of DOACs in patients with a body mass index (BMI) >40 kg/m^2 or a weight >120 kg unless drug-specific peak or trough levels fall within the usual on-therapy range.[12]

Our aim was to determine the proportion of obese patients (with body weight [BW] >120 kg) taking DOACs who have drug underexposure.

2 | MATERIALS AND METHODS

2.1 | Inclusion and exclusion criteria

Adult patients (≥18 years) with BW >120 kg taking any of the DOACs apixaban, dabigatran, edoxaban, or rivaroxaban for any indication for at least 3 days, and who had a measurement of peak drug concentration after at least 3 days of DOAC use, were included. The measurement was part of the routine clinical practice at the discretion of the thrombosis physician. A retrospective chart review was performed of these patients, who had been seen at the anticoagulation clinics at Hamilton Health Sciences between June 2017 and February 2018. Patients taking a reduced dose were not included unless the drug was given based on labeled criteria for dose reduction. Patients were informed to take higher doses of rivaroxaban (≥15 mg) with food. Ethics approval for retrospective chart review was obtained from the Hamilton Integrated Research Ethics Board. We also accessed de-identified data from two prospective studies examining the variability of dabigatran[13] and rivaroxaban levels (data unpublished) in unselected patients taking these drugs with permission from the investigators (NC and VB). The latter data were added to the analysis.

2.2 | Baseline characteristics

Patient demographics, clinical characteristics, and laboratory data were collected. The demographics included patient's age, sex, and BW. Clinical characteristics included were a previous history of bariatric surgery, the use of antiplatelet drugs (aspirin and/or clopidogrel), strong inducers of P-glycoprotein or of cytochrome P450 3A4; and parameters related to treatments: type, dose, and the indication for anticoagulation. The laboratory parameters included the baseline creatinine and the peak plasma concentration of DOACs. Peak plasma concentration of apixaban and rivaroxaban was measured once 2-3 hours after taking the drug, using specifically calibrated anti-factor Xa assay (Diagnostica Stago STAr-Evolution, Asnieres, France). The lowest limit of detection of the assay is 20 and 25 ng/mL for rivaroxaban and apixaban, respectively. Peak plasma concentration of dabigatran was measured once 2-3 hours after taking the drug using dilute thrombin time, which has a lower limit of detection of 20 ng/mL (Hemoclot Thrombin Inhibitors Hyphen BioMed, Neuville sur Oise, France). Patients from the variability studies had repeated measurements of the peak concentrations. The average of these results for the respective patient was calculated. The creatinine clearance was calculated using the Cockcroft-Gault formula.

2.3 | Outcomes

We examined the proportion of patients with peak plasma concentrations of apixaban, dabigatran, and rivaroxaban falling below the median trough level for the respective drug as obtained from population pharmacokinetic (PK) studies in non-obese patients.[14-17] In other words, in cases of such a low peak concentration, it would be very likely that the exposure to the drug is inadequate during most of the dosing interval. If the peak plasma concentration is below the median trough level, this outcome would be a specific but not a sensitive marker of underexposure throughout the dosing interval. We acknowledge that there are different methods of performing this analysis. However, there is no official recommendation available as to how to verify adequate drug exposure from plasma concentrations.

We also examined the proportion of patients who had a plasma peak concentration of apixaban, or rivaroxaban below the fifth percentile or plasma peak concentration of dabigatran below the 10th percentile

(the lowest percentile reported in the literature for dabigatran);[14-17] the proportion of patients who were switched to warfarin based on the discretion of the treating physician; and the proportion of patients with recurrent VTE and/or stroke during the study follow-up since the peak concentration was measured. The latter two outcomes were assessed in 22 patients from the anticoagulation clinics. We were unable to assess the clinical outcomes in patients who were in the variability studies because those studies did not collect clinical outcome data.

2.4 | Statistical analysis

Results are presented with mean and standard deviation for variables with a normal distribution and with median and interquartile range (IQR) for skewed distributions. The 95% confidence intervals (CI) for a proportion were calculated using the modified Wald method. Student two-tailed t-test and Mann-Whitney U test were utilized to compare means and medians, respectively.

3 | RESULTS AND DISCUSSION

A total of 252 patients were referred to our center from June 2017 to February 2018, 34 were >120 kg, and 26 from the latter group were taking a DOAC. Of the 26 patients, 22 were included in the study. Of the four patients excluded, two had completed therapy and two patients refused drug level measurement. In the variability studies, there were 18 eligible patients but two patients from the dabigatran variability study were excluded for taking the drug at a reduced dose not indicated by renal function or age. Thus, a total of 38 patients were included and analyzed. The baseline characteristics of the patients are listed in Table 1. The median peak plasma concentrations, the proportion of patients with a peak plasma concentration below the population PK median trough, and the proportion of patients with a peak plasma concentration below the fifth percentile (10th percentile for dabigatran) peak concentration for each of the DOACs are listed in Table 2. There were only two patients with peak plasma concentrations below the median trough level from PK studies (5%, 95% CI: 0.5%-18%). Both patients were taking dabigatran. Peak plasma concentrations were below the usual on-treatment range for the peak in eight patients (21%, 95% CI: 11%-37%) (Table 2). Six (29%) were taking rivaroxaban and two patients (20%) were taking dabigatran. Outcome data for each DOAC are presented in Figure 1. One patient from the anticoagulation clinic (4%) was switched to warfarin and none had a recurrence VTE and/or stroke. The median study follow-up since the peak concentration was measured was 4 months (range one to eight).

Most patients (95%; 95% CI: 82%-99%) in our study had a plasma concentration higher than the median trough level for each of the three DOACs, and 79% (95% CI: 63%-89%) of patients had levels within the usual on-therapy range. In addition, the median peak concentrations in our study were similar to those reported in PK studies of the respective DOACs (Table 2). Of the eight patients with peak levels below the usual on-treatment range, six were taking rivaroxaban and two were taking dabigatran. The latter two patients were from the dabigatran variability cohort and had a normal creatinine clearance. Furthermore, six of the 21 patients (29%) that were taking rivaroxaban had a peak concentration that was below the fifth percentile peak rivaroxaban concentration obtained from PK studies. There was no significant difference in the mean BW or the median creatinine clearance between these six patients and the rest of the patients taking rivaroxaban. There was a trend towards these six patients being younger (mean 55 vs 66 years old, $P = 0.06$). The clinical implication of a peak level below the fifth or 10th percentile of peak level distribution is unclear since unlike trough level,[15,18,19] data supporting a correlation between peak levels and clinical outcome are lacking, and the lower threshold of peak concentration associated with an elevated risk of thromboembolic events is unknown.

TABLE 1 Baseline characteristics

Characteristic	Result
Age, years, mean ± *SD*	64 ± 11
Males (N; %)	30 (79)
Anti-platelet use (N; %)	6 (16)
P-gp or CYP3A4 inducer use (N; %)	0 (0)
Previous bariatric surgery	2 (5)
Body weight, kg, median (IQR)	132.5 (127-146.5)
BMI[a], kg/m^2 (IQR)	41 (37.6-47.6)
Indication for anticoagulation (N; %)	
Atrial fibrillation	22 (58)
VTE	14 (37)
Atrial fibrillation and VTE	1 (3)
Other	1 (3)
Type of anticoagulant (N; %)[b]	
Apixaban	7 (18)
Dabigatran	10 (26)
Rivaroxaban	21 (55)
Laboratory parameters	
Creatinine, μmol/L, mean (SD)	92 (25)
Creatinine clearance, mL/min, mean (SD)	147 (48)

BMI, body mass index; CYP3A4, cytochrome P450 3A4; IQR, interquartile range; N, number of patients; P-gp, P-glycoprotein; SD, standard deviation; VTE, venous thromboembolism.
[a]Based on data available for 29 patients, missing height in 9 patients.
[b]None of the patients were taking a reduced dose oral anticoagulant or were on edoxaban.

There is emerging evidence from the literature that DOACs are effective and safe in obesity. Two retrospective studies, reported in abstract form, have examined the use of DOACs in obese patients >120 kg or a BMI >40 kg/m^2.[20,21] A retrospective analysis of 390 patients with a BMI >40 kg/m^2 compared the efficacy and safety of apixaban with warfarin.[20] Of the 181 patients that were taking apixaban, only one each had a recurrent VTE (1.7%) or stroke (0.8%),[20] rates which were comparable to one (1.1%) and three (2.4%) of the 209 patients who were taking warfarin.[20] The authors concluded that safety and efficacy of apixaban and warfarin in patients with

TABLE 2 Peak Plasma Concentration for Each of the Direct Oral Anticoagulants

DOAC	N	Median trough concentration from PK studies (ng/mL)[14-17]	Median peak concentration from PK studies (ng/mL)[14-17]	Median peak plasma concentration ng/mL (IQR)	Peak plasma concentration below the median trough (N, %)	Peak plasma below the 5th percentile (10th percentile for dabigatran) peak concentration (N, %)
Apixaban	7	63.2 (59-67.9)	130 (5th-95th percentile range 59-302)	148 (138-240)	0 (0)	0 (0)
Dabigatran	10	93	184 (10th-90th percentile range 74-383)	138 (123-156.5)	2 (20)	2 (20)[a]
Rivaroxaban	21	60	249 (5th-95th percentile range 184-343)	215 (181-249)	0 (0)	6 (28)[b]
Overall	38	NA	NA	NA	2 (5)	8 (21)

DOAC, direct oral anticoagulant; IQR, interquartile range; N, number of patients; NA, not applicable; PK, pharmacokinetics.
[a]The body weight of these two patients and the corresponding plasma concentration in parenthesis were 133 kg (69.5 ng/mL) and 173 kg (39 ng/mL).
[b]The body weight of these 6 patients and the corresponding plasma concentration in the parenthesis were 123 kg (168 ng/mL), 124 kg (152 ng/mL), 140 kg (63 ng/mL), 143 kg (164 ng/mL), 145 kg (181 ng/mL), and 152 kg (166 ng/mL).

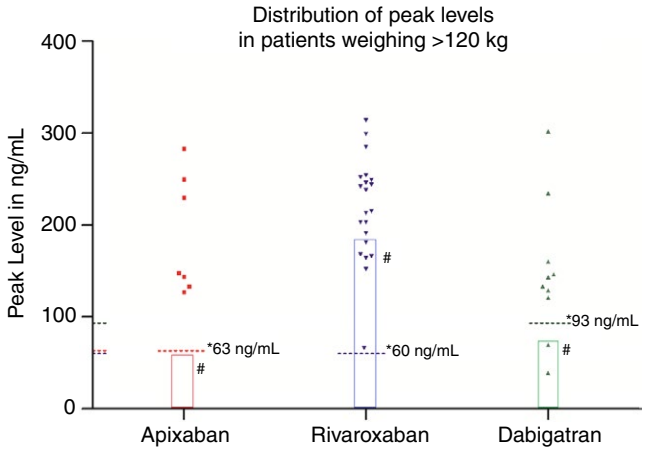

FIGURE 1 Dot plot of the peak concentration of each of the direct oral anticoagulants. *Median trough level from population pharmacokinetics studies. #Below 5th percentile peak plasma concentration (10th percentile for dabigatran) from population pharmacokinetics studies

a BMI >40 kg/m^2 are similar.[20] A retrospective study of 17 patients >120 kg on rivaroxaban for the treatment of venous thromboembolism found that the majority of the patients (16 of 17; 94%) had a peak concentration within the expected range and none had a recurrent thromboembolic event.[21] A subgroup analysis of the ARISTOTLE trial based on BW reported that higher BW and BMI were associated with lower all-cause mortality rate and lower risk of stroke or systemic embolism.[22] A pharmacokinetic study of healthy volunteers taking rivaroxaban reported that the area under the curve (AUC) was unaffected by BW,[23] the volume of distribution was moderately influenced by BW in patients taking rivaroxaban,[24] and a mean increase in BW of 83% resulted in a limited 23% decrease of the AUC in healthy volunteers taking apixaban.[25] A large prospective study of real-life patients receiving DOACs for treatment of atrial fibrillation or VTE, which included 98 patients with BMI >40 kg/m^2, did not find any indication that high BMI is associated with reduced DOAC efficacy or safety.[26] Lastly, a pharmacokinetic study of 101 patients taking rivaroxaban for prevention or treatment of VTE (six patients had a BMI ≥ 40 kg/m^2) reported that BW alone did not significantly affect rivaroxaban pharmacokinetics.[27]

Our study has limitations. First, due to the retrospective design of our study, the results may be subject to selection bias. For example, we cannot exclude the possibility that the primary care physician, cardiologist, or neurologist did not have obese patients >120 kg taking DOACs who were not referred to our center. We cannot assess the magnitude of this bias since we do not have data on drug levels of the other obese patients taking DOACs. Second, there are no defined therapeutic ranges available for DOAC drug concentrations but usual on-therapy ranges are available. Third, the DOAC peak concentration was measured 2-3 hours after intake. This time interval may be too short for some patients due to the inter-individual variability of DOAC absorption. The administration of the last dose of the DOAC was exactly documented. Fourth, we combined the data from different sources, thus there may be differences in the data quality excluding the timing of sampling or the laboratory analysis. Unlike the variability studies, drug levels in patients of the retrospective cohort were performed based on a clinical decision. Fifth, our study was not designed to examine clinical outcomes with recurrent thromboembolic complications. The median duration of follow-up was limited.

In conclusion, we found that most patients with weight >120 kg had a peak drug concentration higher than the expected median trough level. However, 21% of our cohort had a peak plasma concentration that was below the usual on-therapy range of peak concentration for the corresponding DOAC.

RELATIONSHIP DISCLOSURES

SS reports receiving consulting fees from Boehringer Ingelheim, Bristol-Myer-Squibb, Bayer and Daichii and grant support from Boehringer Ingelheim, Baxter, and Octapharma without any relationship to this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the preparation of the manuscript and met the required conditions for authorship. SP designed the study, collected, analyzed, and interpreted the data, and wrote the manuscript. HT collected and analyzed the data. NC and VC interpreted and analyzed the data and provided vital reviews of the manuscript. SS designed the study, interpreted the data, and provided vital reviews of the manuscript.

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