Abstract

Monitoring the effect of sarcopenia parameters on plasma concentrations of direct oral anticoagulants I

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Introduction: Direct oral anticoagulants (DOACs) are hydrophilic substances whose plasma concentrations are dependent on body composition. As skeletal muscle decreases, their distribution in muscle decreases while plasma concentration increases. Sarcopenic patients with low muscle mass may potentially experience an increase in plasma DOAC concentrations above the therapeutic range.

Aim: The aim of this study was to determine the effect of sarcopenia parameters (maximum handgrip strength, appendicular muscle mass, and walking speed) on plasma concentrations of dabigatran, apixaban, and rivaroxaban. In addition, to evaluate the drug interactions of these drugs and their potential effect on DOAC plasma concentrations.

Methods: The study included patients over 65 years or older, who were using DOACs (dabigatran, apixaban, or rivaroxaban) for at least one month for atrial fibrillation or maintenance treatment of deep vein thrombosis, with a creatinine clearance (CrCl) ≥ 15 ml/min, and who agreed to participate in the study. Sarcopenia diagnostic parameters included appendicular muscle mass (ASMM) (measured using the BODYSTAT QuadScan 4000), maximum handgrip strength (using the Jamar dynamometer), and 4 m walking speed. Plasma concentrations of DOACs were measured before DOAC administration (minimum plasma concentration) and 2–4 hours after DOAC administration (peak plasma concentration). Patients completed the validated The Medication Adherence Report Scale (MARS-CZ) questionnaire focusing on adherence to DOAC treatment and an additional questionnaire to identify potential risk factors affecting DOAC plasma concentrations.

Results: A total of 43 patients were included in the study (30.2% female; average age 74 ± 6.3 years). Supratherapeutic plasma concentrations of DOACs were found in 23.3% of patients. No statistically significant correlation was found between sarcopenia parameters and plasma concentrations of DOACs (maximum handgrip strength ($P = 0.158$), ASMM ($P = 0.102$), 4 m walking speed ($P = 0.963$)). Sarcopenia was not diagnosed in any patient. In contrast, CrCl

(P = 0.028), hemoglobin (P = 0.018), and phase angle (P = 0.010) values were statistically significantly different between groups of patients with therapeutic and supratherapeutic plasma DOAC concentrations. Among the most clinically relevant drug interactions, interactions with amiodarone (in five patients), carbamazepine (in one patient) and rifampicin (in one patient) were found in the patients' medication. Only one patient taking a risky drug combination (apixaban and amiodarone) had DOAC plasma concentration outside the therapeutic range.

Discussion and Conclusion: The effect of sarcopenia parameters on DOAC plasma concentrations could not be demonstrated due to the absence of patients with a confirmed diagnosis of sarcopenia. A study in a larger cohort of patients with a sufficient representation of sarcopenic subjects is needed to validate the present findings. Significant drug interactions were found in the patients' medications (e.g., with amiodarone, rifampicin, carbamazepine), but only one interaction affected DOAC plasma concentrations.

Keywords: DOAC, sarcopenia, plasma concentration, muscle mass, drug interactions