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Adherence in patients with atrial fibrillation treated with dabigatran

Brief title: Adherence in patients with atrial fibrillation

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INTRODUCTION

According to the definition given by the World Health Organisation in 2003, adherence is the degree to which a patient’s behaviour follows the medical recommendation obtained from a healthcare professional. This is an active process, where the patient is a partner in the creation of a therapy plan [1]. Failure to follow the physician’s instructions is a serious health hazard for the patient, as well as a source of an increased costs in the healthcare system. It is particularly difficult to maintain adherence in chronic and asymptomatic diseases [2–4].
Measuring the drug’s blood concentration is the most dependable method to verify the patients’ declarations. In the case of the new oral anticoagulants however, it is an expensive method and applicable only in several scientific facilities in the country. There is also the risk of inaccurate evaluation of adherence due to individual variation in metabolism rates and possible drug interactions that influence the drug’s plasma concentrations [3, 5].

Atrial fibrillation (AF) is one of the most common heart arrhythmias. It increases the risk of death due to cardiovascular causes and other risks, predominantly stroke. The first-choice drugs for the prevention of thromboembolic events are the new oral anticoagulants, dabigatran among others [6]. The lack of objective, easily accessible treatment verification method, makes adherence particularly important.

METHODS

Forty consecutive patients with AF treated with dabigatran, were enrolled to the study. Plasma concentrations of dabigatran were determined in Department of Pharmacology and Therapeutics Collegium Medicum, Nicolaus Copernicus University in Bydgoszcz, by the thrombin time in dilute plasma, using a Hemoclot thrombin inhibitors assay of Hyphen BioMed. Descriptive statistics were performed using StatSoft Inc. (2014). STATISTICA.

RESULTS AND DISCUSSION

All patients qualified to the research declared taking dabigatran in 2 × 110 mg (n = 13) or 2 × 150 mg (n = 27) doses. The mean age of patients was 70.45 ± 13.28 years, 72.5% were men, 67.5% of the study population was admitted to hospital as planned. The average number of points obtained in CHA²DS²VASc score was 3.95 ± 1.78, and in HAS-BLED score was 2.28 ± 1.13. Estimated glomerular filtration rate, according to Modification of Diet in Renal Disease formula, was 71.63 ± 21.99 mL/min/1.73 m². The concentration of dabigatran in the tested group ranged from 0 ng/mL to 481.78 ng/mL (median 119.86 ng/mL, the average concentration of 131.11 ± 118.54 ng/mL). In 27.5% dabigatran plasma levels were below the optimal therapeutic concentration (i.e. less than 40 ng/mL). The optimal therapeutic concentration, that is 40–200 ng/mL was observed in 50% of patients. Dabigatran concentrations above this range, but unrelated to a clear increase in the risk of bleeding complications, i.e. 201–400 ng/mL was noticed in 17.5% of patients. Dabigatran
concentrations above 400 ng/mL, which is causing a significant increase in the risk of bleeding complications, occurred in 5% of patients. 27.5% of patients that showed dabigatran concentrations lower than 40 ng/mL were qualified to the non-adherent group, because failure to take the drug is the only explanation of such low dabigatran concentrations in plasma.

Similar results were obtained in several recent studies, assessing the level of adherence for new oral anticoagulants in patients with AF. The retrospective analysis by Xiaoxi Yao et al. [7], included a population of 6461 American citizens with AF, treated with warfarin (59.1%), dabigatran (15.7%), rivaroxaban (19.1%) or apixaban (6.0%). The researchers tested the proportion of days covered (PDC) and in the case of PDC at $\geq 80\%$, the patients were qualified as adherent. The study showed that the percentage of adherent patients during the initial six months of the observation, estimated less than a half of all patients: 47.5% for new oral anticoagulants versus 40.2% for warfarin ($p < 0.001$)

Furthermore, in a study by Shore et al. [8], including 5376 patients with non-valvular AF, 27.8% of the group were non-adherent in the first year of dabigatran therapy.

A similar result was shown in a retrospective study by Borne et al. [9], including 2882 patient with non-valvular AF and CHA$_2$DS$_2$VASc score of two or more. Those patients were tested for adherence within a year of introducing dabigatran (72.7%), rivaroxaban (19.8%) or apixaban (7.5%). The percentage of non-adherent patients (PDC < 80%) estimated 27.6% for the entire group.

In the study by Maur et al. [10], that included a population of 22,267 French patients with non-valvular AF, treated with dabigatran (11,141 people) or rivaroxaban (11,126 people) and spanned over a year, the percentage of adherent patients estimated only 53.3% for dabigatran and 59.9% for rivaroxaban.

The reasons for non-adherence in patients with AF treated with new oral anticoagulants are caused by among others misunderstanding medical recommendations, side-effects of therapy or the fear thereof, economic considerations or the lack of the patient’s conviction that the therapy is indeed necessary [3, 4].

In the case of new oral anticoagulant therapy, higher adherence can be expected for rivaroxaban, which is taken once a day as opposed to dabigatran and apixaban that require taking every 12 h; just as it is the case in other long-term cardiovascular therapies [11, 12].
Andrade et al. [13] in their study were assessing the preferences of Canadian doctors (n = 178) and patients (n = 266) on new oral anticoagulant therapies and their cooperation in this treatment. The research showed better compliance for the drugs taken once a day (rivaroxaban and varfarin). Patients taking apixaban and dabigatran, the drugs dosed twice a day, were missing their doses during the seven preceding days and 30% on average were taking the drugs erroneously, i.e. once a day [13].

Good patient-doctor communication is the key to improve adherence. It boils down to clear explanation of the gist of the disease and the need for treatment, as well as learning about the patient’s way of life, their physical and financial capabilities and preferences. The decision about anticoagulation therapy should be made mutually with the patient, which leads to a better understanding and acceptance of the therapy goals [2, 11].

Improving adherence for new oral anticoagulants is a great challenge for medical staff in the years to come, since those drugs have become the drugs of choice in thromboembolic prophylaxis in patients with non-valvular atrial fibrillation.

**Conflict of interest:** Prof. Grzegorz Grześk received honoraria for the lectures from Boehringer Ingelheim. The rest of the authors declare no conflict of interests.

**References**


