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Impact of morphine versus methoxyflurane on platelet activity and myocardial reperfusion in patients with acute coronary syndrome (ACS) loaded with ticagrelor and aspirin, a randomized clinical trial.

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Streszczenie w języku angielskim

Introduction: Oral antiplatelet drugs, including aspirin and P2Y12 receptor inhibitors, together with heparin and percutaneous coronary angioplasty, are currently the standard of care for acute coronary syndromes. According to the guidelines of the European Society of Cardiology, among P2Y12 receptor inhibitors, ticagrelor and prasugrel are preferred. In order to relieve angina symptoms in patients with acute coronary syndrome, morphine is administered. An adverse impact of this opioid on the pharmacokinetic and pharmacodynamic profile of all oral P2Y12 receptor-acting antiplatelet agents has been demonstrated, and data on the influence of morphine on the clinical results of treatment in patients with acute coronary syndrome are inconsistent. Therefore, caution should be exercised when using morphine in this patient group and alternative pain management methods should be sought. Studies conducted so far have not allowed us to identify an optimal way of treating pain in acute coronary syndromes. A suitable candidate seems to be methoxyflurane, which due to its mechanism of action should not affect the pharmacological profile of anti-aggregation drugs.

Aim: To evaluate the impact of methoxyflurane treatment compared to morphine on the pharmacokinetic and pharmacodynamic profile of ticagrelor, platelet reactivity, and myocardial reperfusion in patients with acute coronary syndrome who are administered loading doses of antiplatelet agents: ticagrelor and aspirin.

Methodology: The study was designed as a multicenter, randomized, open-label phase IV clinical trial including patients with unstable angina and persistent chest pain. Patients were randomized at a 1:1:1 ratio to one of 3 groups: 1) receiving 180mg ticagrelor and 3mg

methoxyflurane; 2) receiving 180mg ticagrelor and 5mg morphine intravenously; and 3) receiving 180mg ticagrelor alone. In order to evaluate the pharmacokinetic and pharmacodynamic profile, within 6 hours of administration of 180mg ticagrelor, platelet reactivity by multiple electrode aggregometry and the concentration of ticagrelor and its metabolite AR-C124910XX were measured. Selected patients were assessed for microcirculation function using the Corovenis CoroFlow CardioVascular System.

Results: In the analysis, 48 patients with unstable angina were included. At 45 minutes of the study, the number of patients with low platelet reactivity in the morphine group was significantly lower than in the ticagrelor group (N=10 vs. N=16, p=0.0177) and showed a trend towards statistical significance when comparing morphine with methoxyflurane (N=10 vs. N=16, p=0.0755). The median serum concentrations of ticagrelor at 15, 45 and 60 minutes in patients treated with ticagrelor alone were higher compared to patients receiving morphine (respectively: Me_{15}: 14.54 vs. 11.06 ng/mL, p_{15}=0.0231; Me_{45}: 227.18 vs. 125.76 ng/mL, p_{45}=0.0578; Me_{60}: 359.63 vs. 226.39 ng/mL, p_{60}=0.0312). At 45 and 60 minutes, the median serum concentrations of ticagrelor in patients treated with methoxyflurane were higher than in the morphine group (Me_{45}: 289.82 vs. 125.76 ng/mL, p_{45}=0,0418; Me_{60}: 401.57 vs. 226.39 ng/mL, p_{60}=0.0418). The median serum concentrations of ticagrelor in patients treated only with ticagrelor and ticagrelor with methoxyflurane did not differ significantly during the first two hours of the study. The median peak serum concentrations of ticagrelor in patients treated with morphine in addition to ticagrelor compared to patients not receiving morphine showed a trend of statistical significance (Me: 428.11 vs. 570.70 ng/mL, p=0.0552). There were no significant differences between the median peak ticagrelor concentration and median time to peak ticagrelor concentration in blood serum in patients treated with ticagrelor alone and ticagrelor with methoxyflurane. The median time to peak ticagrelor concentration was higher among patients receiving morphine compared with methoxyflurane (Me 180.0 vs. 120.0 min., p=0.0014) and not receiving pain medications (Me 180.0 vs. 120.0 min., p=0.0179).

The median concentration of the AR-C124910XX metabolite in the blood serum of patients treated with ticagrelor alone was significantly higher than in the morphine group at 45 and 60 minutes of the study (Me_{45}: 60.51 vs. 44.01 ng/mL, p_{45}=0.0854; Me_{60}: 108.04 vs. 53.26 ng/mL, p_{60}=0.0855). Similarly, at 45, 60 and 120 minutes of the study, the median

concentration of the AR-C124910XX metabolite was higher in the methoxyflurane group compared to morphine (Me_{45}: 73.76 vs. 44.01 ng/mL, p_{45}=0.0282; Me_{60}: 132.96 vs. 53.26 ng/mL, p_{60}=0.0255; Me_{120}: 273.54 vs. 204.69 ng/mL, p_{120}=0.0721). No differences were found when comparing the median AR-C124910XX metabolite concentrations in patients treated with ticagrelor alone and ticagrelor with methoxyflurane. Median peak serum concentrations of AR-C124910XX did not differ significantly in all groups. Median time to peak AR-C124910XX metabolite concentration was higher in the morphine group compared with methoxyflurane (Me 180.0 vs. 120.0 min., p=0.0122). No differences were found between patients treated with ticagrelor alone and ticagrelor with methoxyflurane.

Conclusions: Morphine has an adverse impact on the pharmacokinetic and pharmacodynamic profile of ticagrelor in patients with unstable angina, and methoxyflurane does not have such an effect.

Keywords: morphine, methoxyflurane, ticagrelor, ACS, acute coronary syndrome