Thrombosis Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Chewed ticagrelor tablets provide faster platelet inhibition compared to integral tablets
The inhibition of platelet aggregation after administration of three different ticagrelor formulations (IPAAD-Tica) study, a randomised controlled trial

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ARTICLE INFO

Article history:
Received 27 June 2016
Received in revised form 20 September 2016
Accepted 14 October 2016
Available online xxxx

Keywords:
Pharmacodynamic
Chewed
Crushed
VerifyNow
Platelet
Aggregation

ABSTRACT

Aims: To provide pharmacodynamic data of crushed and chewed ticagrelor tablets, in comparison with standard integral tablets.
Methods: Ninety nine patients with stable angina were randomly assigned, in a 3:1:1 fashion, to one of the following 180 mg ticagrelor loading dose (LD) formulations: A) Integral B) Crushed or C) Chewed tablets. Platelet reactivity (PR) was assessed with VerifyNow before, 20 and 60 min after LD. High residual platelet reactivity (HRPR) was defined as >208 P2Y12 reaction units (PRU).
Results: There was no significant difference in PRU values at baseline. PRU 20 min after LD were 237 (182–295), 112 (53–238) and 84 (29–129) and 60 min after LD, 56 (15–150), 51 (18–85) and 9 (7–34) in integral, crushed and chewed ticagrelor LD, respectively ($p < 0.01$ for both). Chewed ticagrelor tablets resulted in significantly lower PRU values compared to crushed or integral tablets at 20 and 60 min. Crushed ticagrelor LD resulted in significantly lower PRU values compared to integral tablets at 20 min whereas no difference was observed at 60 min. At 20 min, no patients had HRPR with chewed ticagrelor compared to 68% with integral and 30% with crushed ticagrelor LD ($p < 0.01$).
Conclusion: With crushed or chewed ticagrelor tablets a more rapid platelet inhibition may be achieved, compared to standard integral tablets. We also show that administration of chewed tablets is feasible and provides faster inhibition than either crushed or integral tablets.
CLINICAL TRIAL REGISTRATION: European Clinical Trial Database (EudraCT number 2014-002227-96).

1. Introduction

Platelets play a fundamental pathophysiological role in patients with acute coronary syndrome. Following an atherosclerotic plaque rupture or erosion, platelet aggregation leads to thrombus formation and an acute ischemic event. [1] Ticagrelor is a direct acting and reversibly binding P2Y12 receptor inhibitor that is highly recommended in clinical guidelines for treatment of patients with acute coronary syndrome (ACS). [2–4] In patients with stable angina pectoris (SAP), administration of 180 mg loading dose (LD) of ticagrelor resulted in a more rapid and stronger inhibition of platelet reactivity (PR) compared to clopidogrel. Within 30 min, ticagrelor administration led to the same degree of inhibition of PR as that achieved 8 h after a 600 mg LD of clopidogrel. [5] However, in patients with ST segment elevation myocardial infarction (STEMI), where fast and effective platelet inhibition is even more important, a delayed onset of action of platelet inhibitors, and a wider variability of drug response has been demonstrated. Beside the higher baseline PR in STEMI patients, a limited or delayed intestinal absorption of orally administered drugs is another major contributor to this observation [6–8].

Previous pharmacokinetic studies have demonstrated that chewable aspirin and crushed clopidogrel administration increased the rate of drug absorption compared to integral tablets, when administered orally. [9,10] Recently, crushed ticagrelor tablets, administered orally or via a naso-gastric tube, have been shown to be feasible and resulted in increased plasma concentration of ticagrelor and its active metabolite at an earlier time point compared to integral tablets [11,12]. As the plasma concentration of ticagrelor and its active metabolite is linearly associated with the degree of platelet inhibition, [2] administration of crushed or chewed ticagrelor may provide a more rapid onset of drug action. Nevertheless, limited pharmacodynamic data of novel methods of

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http://dx.doi.org/10.1016/j.thromres.2016.10.013
0049-3848/

ticagrelor administration exist and data regarding chewed ticagrelor have not been reported.

Thus, the aim of our study was to provide pharmacodynamic data of two novel ways of ticagrelor administration, crushed and chewed tablets, in comparison with the standard, integral tablets administration.

2. Material and methods

2.1. Study design and population

This was a single center, open-label, randomised, investigator initiated, pharmacodynamic study. Patients > 18 year of age, with stable angina pectoris, scheduled for outpatient coronary angiography, were randomly assigned, at least 90 min before the intervention, in a 3:1:1 fashion (according to a computer generated randomisation list) to one of the following treatment modalities: A) Integral ticagrelor tablets, 180 mg LD B) Crushed ticagrelor tablets, 180 mg LD or C) Chewed ticagrelor tablets, 180 mg LD. The allocation sequence was concealed from the researcher enrolling and assessing participants in sequentially numbered, sealed envelopes. Exclusion criteria were: pregnancy or lactation, known allergy to the study medication, chronic therapy with ticagrelor, prasugrel, clopidogrel or ticlopidine, treatment with warfarin or new oral anticoagulants (NOAC) within 4 days before admission, active bleeding, bleeding diathesis or coagulopathy, history of gastrointestinal or genitourinary bleeding in the last 2 months, history of intracranial bleeding, major surgery in the last 4 weeks, known relevant hematological deviation (severe anemia, severe thrombocytopenia), known severe liver disease or severe renal failure, increased risk of bradycardia or inability to chew tablets.

2.2. Administration of the different ticagrelor formulations

All three groups received two tablets of ticagrelor (180 mg) and 150 mL of water. In the first group (A), two integral ticagrelor tablets were administered as an oral dose, followed by 150 mL of water. In the second group (B), two ticagrelor tablets (180 mg) were placed in a point-of-care (POC) crushing device and crushed. The total content of the crushed tablets was transferred to a dosing cup, 50 mL of water was added and the suspension was mixed before drinking. Afterwards, 100 mL of water was administered. In the third group (C), the patient was instructed to chew two tablets of ticagrelor for at least 10–15 s followed by oral administration of 150 mL of water.

2.3. Blood sampling for platelet aggregation measurements

Platelet aggregation assessment was performed at three timepoints: before administration of ticagrelor (baseline, sample 1) 20 ± 5 min (sample 2) and 60 ± 10 min (sample 3) after administration of ticagrelor. In all cases, the blood samples were drawn from a recently inserted venous catheter for repeated sampling or by direct venipuncture. The first 2–3 mL of blood was discarded to avoid platelet aggregation and then blood was collected in 3.2% citrated tubes. Platelet aggregation was measured with the VerifyNow P2Y12 (Accumetrics Inc., San Diego, CA) POC test. The test has been described in detail earlier [13]. Briefly, VerifyNow is a turbidimetric test which measures agonist-induced aggregation as an increase in light transmittance. The system contains a lyophilised preparation of human fibrinogen-coated beads, which causes a change in light transmittance by agonist-induced platelet aggregation.

Platelet reactivity (PR) results are reported in arbitrary P2Y12 reaction units (PRU). The percent inhibition of platelet reactivity (IPR) was defined as: [(PRU baseline − PRU sample 1 or 2) / PRU baseline] × 100. Based on a recently published consensus document, high residual platelet reactivity (HRPR) was defined as PR > 208 PRU (non-responders) [14]. Patients with PR values ≤ 208 were considered as responders to the drug.

2.4. Outcome

We report residual platelet reactivity, percent IPR and proportion of patients with HRPR at baseline, 20 and 60 min.

Safety outcomes include TIMI major, minor or minimal bleeding within 24 h after randomisation.

2.5. Sample size calculation

In the ONSET/OFFSET study [5], around 50% of patients had HRPR 30 min after LD ticagrelor (integral tablets). A recent study [15] has shown that administration of crushed ticagrelor tablets resulted in a mean plasma concentration of ticagrelor that was four to five times higher at 30 min compared with plasma concentration after administration of integral tablets. We assumed that chewed ticagrelor tablets would have at least as fast uptake as crushed ones. Given the antiplatelet effect of ticagrelor is linearly related to the blood concentration of ticagrelor [2], we also assumed that 20% of patients with the novel ways of ticagrelor administration (crushed and chewed) would have HRPR 20 min after administration of LD. A sample of 100 patients (60 patients in the integral, 20 patients in the crushed and 20 patients in the chewed group) would give an 80% power to detect statistically significant differences in the HRPR rates.

2.6. Study population

Between November 2014 and July 2015, 102 patients were included in the study. Three patients were excluded due to technical reasons (e.g. inability to run the VerifyNow assay). Ninety nine eligible patients were included in the final analysis.

2.6.1. Ethics

The study was approved by the local ethical review board (Dnr 2014/334-31) and was conducted according to the declaration of Helsinki. All patients provided written informed consent before enrollment. The study has been registered at the European Clinical Trial Database (EudraCT number 2014-002227-96).

2.7. Statistical analysis

Continuous variables are presented as median and interquartile range. Categorical variables are presented as counts and percentages. The Kolmogorov-Smirnov test was used to test for normality of the distribution of PR values. Baseline characteristics were compared according to randomised treatment by Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. Friedman's test was used for within group comparisons of PR over time. PR and IPR of the three groups of patients were compared using Kruskal-Wallis test. Pairwise comparisons of the groups were performed with Mann Whitney *U* test. Percentage of HRPR in the three groups was compared using Chi-squared test. Pairwise comparisons were also performed using the same test. A p-value < 0.05 was considered to indicate statistical significance. Due to the relatively small number of hypotheses being tested under the pairwise comparison, the likelihood of type I error was estimated as low and adjusted p values were not used. A forward stepwise binary logistic regression analysis was used to identify independent predictors of HRPR at 20 min after administration of ticagrelor. Known and potential predictors of HRPR were included in the model, in accordance with previous studies. [16,17] Variables included in the model were age, gender, diabetes, Body Mass Index (BMI), smoking status, estimated glomerular filtration (eGFR) by the MDRD formula, platelet count, treatment with beta blockers or diuretics, PR at baseline and randomisation group as a dichotomous variable (integral tablets versus crushed or chewed tablets) [16,18].. Odds ratios (OR) with 95% confidence intervals (CI) are presented for the significant predictors.

Please cite this article as: D. Venetsanos, et al., Chewed ticagrelor tablets provide faster platelet inhibition compared to integral tablets, Thromb Res (2016), http://dx.doi.org/10.1016/j.thromres.2016.10.013