Oral trans-mucosal administration of ticagrelor: is this really the future?

Fabiana Rollini; Francesco Franchi; Dominick J. Angiolillo
University of Florida College of Medicine-Jacksonville, Jacksonville, Florida, USA

The combination of aspirin and an adenosine diphosphate (ADP) P2Y12 receptor antagonist represents one of the strongholds for the prevention of thrombotic events in patients with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI) (1–3). Ticagrelor is a first-in-class cyclopentyltriazolopyrimidine which inhibits the P2Y12 receptor with direct and reversible binding properties (4, 5). Ticagrelor has been approved for clinical use as a 180 mg loading dose (LD) and 90 mg twice a day maintenance dose oral regimen (4, 5). Ticagrelor has consistently shown to be associated with more prompt and potent antiplatelet effects compared with clopidogrel (6), which in turn translates into reduced ischaemic event rates and overall better clinical outcomes, including reduced cardiovascular mortality (7). However, in high-risk ACS patients undergoing PCI there is a delay in the onset of action of oral P2Y12 receptor inhibitors, including ticagrelor, and more than 2 hours (h) are required to exert full antiplatelet effect, thus exposing these high-risk patients to an increased risk of early thrombotic complications (8–10).

The origin of this delayed onset of antiplatelet effect in high-risk ACS settings is likely multifactorial and affects the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of any drug, including ticagrelor, and translate into delayed absorption (11–14). These observations underscore the need to identify strategies associated with improved drug absorption. Crushing tablets of P2Y12 receptor inhibitors has shown to be associated with faster absorption and onset of antiplatelet effect compared with whole tablets (15, 16). However, crushing tablets may be technically challenging in the emergency setting of primary PCI. Chewing ticagrelor tablets has recently been proposed as an easier strategy to improve absorption by 1) mechanical “fractioning” of the tablets, 2) initiation of enzymatic metabolic degradation of the tablets in the mouth due to the prolonged contact of the drug with the saliva, and 3) enhanced oral transmucosal absorption of the drug (17). In this issue of Thrombosis and Haemostasis, Asher et al. (18) and Niezgoda et al. (19) report the results of two studies exploring the pharmacological profile of chewed ticagrelor administration: the CHEERS (Chewing versus Swallowing Ticagrelor to Accelerate Platelet Inhibition in Acute Coronary Syndrome) study and the Crushed sublingual versus oral ticagrelor administration strategies in patients with unstable angina – a pharmacokinetic/pharmacodynamic study, respectively.

CHEERS is a randomised PD study investigating the effects of chewing tablets compared with traditional tablet swallowing of ticagrelor LD in patients (n=25 in each group) with non-ST segment elevation myocardial infarction (NSTEMI) (18). Platelet reactivity was assessed by VerifyNow at baseline and 1 and 4 h after the LD. Patients randomised to chewed ticagrelor were asked to chew, but not swallow, the tablets until nothing was left in the mouth and everything was absorbed via the buccal mucosa. The authors found that chewed ticagrelor was associated with significantly lower P2Y12 reaction units (PRU) and high on treatment platelet reactivity (HPR) rate (defined as PRU > 208) at 1 h, and numerically lower PRU and HPR at 4 h (18).

Niezgoda et al. randomised in a 1:1:1 fashion patients with unstable angina to: 1) crushed tablets of ticagrelor LD administered sublingually (n=15), 2) crushed tablets of ticagrelor LD in 10 mL suspension in tap water administered orally (n=17) and 3) integral ticagrelor LD tablets administered orally (n=17) (19). All patients who were administered ticagrelor sublingually were advised to keep the drug in the mouth as long as possible before swallowing it. This was a PK and PD study, in which plasma concentrations of ticagrelor and its major active metabolite (AR-C124900XX) were evaluated using liquid chromatography mass spectrometry and platelet reactivity was assessed using multiple electrode aggregometry (MEA) performed with the Multiplate analyzer. HPR was defined as AUC>46 units (U). Both, PD and PK samples were collected at nine time points: before the administration of ticagrelor LD and 15 minutes (min), 30 min, 45 min, 1 h, 2 h, 3 h, 4 h, 6 h post LD. Platelet inhibition was more effective after oral administration of crushed tablets as compared with sublingual administration of crushed tablets at 30 and 45 min. HPR was significantly lower in the crushed oral administration group at 15, 30 and 45 min. Accordingly, the exposure to ticagrelor and its metabolite were higher in the crushed oral administration. The tested ticagrelor sublingual administration strategy showed no superiority over the orally administered crushed formulation in terms of PK and PD profile (19).

The authors need to be congratulated for these studies (18, 19). The major
strength of these investigations is that for the first time chewed administration of ticagrelor has been tested in sizable cohorts of patients with ACS. In addition, the study by Niezgoda et al. included both PK and PD analysis assessed at several time points at close intervals (19). Although the CHEERS study has the limitation of using integral tablets as a comparator, Niezgoda et al. included an arm of patients receiving crushed ticagrelor (18, 19). A common limitation to both studies is the use of a single platelet function assay, whereas the use of additional tests would have allowed to corroborate the study findings (18, 19).

In addition, the clinical setting where the absorption of oral P2Y12 receptor inhibitors is known to be mostly impaired (and thus where faster onset of ticagrelor PD effects needed) is STEMI (8–16). Therefore, performing the study in primary PCI patients would have been the best approach, and whether these results can be reproduced in patients with STEMI is unknown. Importantly, the two studies seem to provide conflicting results. In fact, in the study from Asher et al. drug absorption through the oral mucosa appeared to be more effective than the standard oral administration of whole tablets, whereas in the study by Niezgoda et al. the strategy of oral mucosa absorption was not associated with better (actually often times worse) PK and PD profiles compared with the orally administered crushed as well as the whole tablets formulations (18, 19). However, this might be related to the different methods of administration: in CHEERS, ticagrelor tablets were actively chewed by patients, whereas in the study by Niezgoda et al. tablets were crushed in advance and then administered sublingually to the patients.

The oral transmucosal system allows for a more rapid absorption into the blood stream as compared with oral administration to the gastrointestinal tract and consequently offers an alternative means of drug administration, which therefore could be more effective in settings, such as STEMI, where gastrointestinal absorption is impaired (8–16). Of note, the oral cavity comprises the lips, cheeks, tongue, hard palate, soft palate and the floor of the mouth and the lining of the oral cavity is referred to as the oral mucosa, which includes the buccal, sublingual, gingival, palatal and labial mucosa (20). The permeability of different regions of the oral cavity is considerably different because of the diverse structures and functions of the different oral mucosa. In general, the permeability of the oral mucosa decreases in the order of sublingual > buccal > palatal, which is based on the relative thickness and degree of keratinisation of these tissues (20). Therefore, the way of administration and the site within the mouth where the drug is absorbed can create high interindividual variability, especially in case of chewing tablets created for standard oral administration. In addition, drugs for oral transmucosal delivery must have the necessary physicochemical properties, including penetration enhancers that promote permeation of drugs throughout epithelial barriers (20).

In conclusion, although the idea of trans-oral mucosa absorption is potentially appealing to accelerate the absorption of ticagrelor and obtain a faster platelet inhibition in acute settings, the efficacy and safety of this strategy need to be determined. Moreover, studies conducted in the appropriate clinical setting and using an ad hoc formulation specifically designed for oral-trans mucosal absorption are warranted.

Conflicts of interest
Dominick J. Angiolillo has received payment as an individual for: (a) consulting fees or honoraria from Sanofi, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Merck, Abbott Vascular, Amgen, Bayer, Pfizer, Chiesi, Biosensors, and PLx Pharma; (b) participation in review activities from CeloNova, Johnson & Johnson, and St. Jude Medical. Institutional payments for grants received from GlaxoSmithKline, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Janssen Pharmaceuticals, Inc., Osprey Medical, Inc., Novartis, CSL Behring, and Gilead. Fabiana Rollini and Francesco Franchi have no disclosures to report.

References