Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Administration Matters: Successful Management of Ticagrelor Resistance Challenges in a High-Risk Patient

Ashley Schuler

ashley.schuler@ohiohealth.com

Riverside Methodist Hospital https://orcid.org/0009-0006-0988-7164

Connie Yoon

Riverside Methodist Hospital

Anna Sahlstrom Drury

Riverside Methodist Hospital

Nirav Vora

Riverside Methodist Hospital

Research Article

Keywords:

Posted Date: October 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11039449/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

We present the case of a 33-year-old South Asian woman with immune thrombocytopenia during pregnancy, recent right medullary stroke secondary to vertebral artery dissection complicated by dysphagia requiring percutaneous endoscopic gastrostomy (PEG) tube placement, and a new left vertebral artery dissection with pseudoaneurysm formation. She presented for planned left vertebral artery flow diversion embolization of the pseudoaneurysm. She was initiated on aspirin and P2Y12 inhibition with ticagrelor two weeks prior to the procedure and reported adherence with regimen. A steady-state VerifyNow PRU (P_2Y_{12} reaction units) Test obtained before the procedure resulted at 179 PRU (goal <180 PRU), prompting re-loading with ticagrelor 180 mg. The post-load level resulted at 231 PRU, and the patient was subsequently started on a cangrelor infusion due to concern for ticagrelor nonresponse.

Main Text

Case

We present the case of a 33-year-old South Asian woman with immune thrombocytopenia during pregnancy, recent right medullary stroke secondary to vertebral artery dissection complicated by dysphagia requiring percutaneous endoscopic gastrostomy (PEG) tube placement, and a new left vertebral artery dissection with pseudoaneurysm formation. She presented for planned left vertebral artery flow diversion embolization of the pseudoaneurysm. She was initiated on aspirin and P2Y12 inhibition with ticagrelor two weeks prior to the procedure and reported adherence with regimen. A steady-state VerifyNow PRU (P_2Y_{12} reaction units) Test obtained before the procedure resulted at 179 PRU (goal <180 PRU), prompting re-loading with ticagrelor 180 mg. The post-load level resulted at 231 PRU, and the patient was subsequently started on a cangrelor infusion due to concern for ticagrelor nonresponse.

What is contributing to ticagrelor "failure" and risks? Questions to ask when facing unexpected medication monitoring values.

Despite her taking the ticagrelor orally, the patient's history of dysphagia and PEG- tube placement raised concern that absorption may have been affected. Incidence of inadequate response to P_2Y_{12} inhibitors due to medications that delay gastric emptying, like morphine, have been reported in the literature. Sikora and colleagues evaluated overcoming delayed absorption due to morphine by utilizing metoclopramide.[1] As ticagrelor is primarily absorbed in the small intestine, this increase in gastric emptying with metoclopramide could assist in improved delivery of ticagrelor to its site of absorption.[2] By administering metoclopramide along with ticagrelor in patients receiving morphine, mean ticagrelor plasma concentrations were significantly higher than in patients who were not co-administered metoclopramide.[1]

Compared to ticagrelor, clopidogrel has a higher bioavailability, making it an attractive alternative agent for an inadequate response to ticagrelor. Despite the higher bioavailability, clopidogrel has its own pharmacokinetic challenges with efficacy. Clopidogrel is a prodrug that must be metabolized by the liver via the cytochrome P450 enzyme CYP2C19 into its active metabolite.[3] CYP2C19 is a polymorphic allele, and those with alleles with reduced CYP2C19 function have been shown to have a lower degree of platelet inhibition, increasing the risk of thrombosis.[3] Additionally, frequency of CYP2C19 alleles can vary widely based on ethnicity, andup to 35% of patients may be low metabolizers and need alternative P2Y12 inhibitor therapy. [4]

In this case, while changing ticagrelor to clopidogrel was a consideration, this patient's CYP2C19 allele was unknown, and testing was not available. Additionally, when considering ethnicity and likelihood of CYP2C19 polymorphisms, there was potentially a higher risk that she might have a polymorphism for CYP2C19 requiring alternative therapy.

Treatment Decision Reached and Monitoring Plan

Cangrelor was titrated based on an institutional specific algorithm with a goal PRU range of 50-150. Due to inability to obtain therapeutic PRUs while receiving cangrelor up to 1.7 mcg/kg/min, the decision was made to discontinue cangrelor and administer crushed ticagrelor 180 mg and aspirin 81 mg. Two hours after ticagrelor 180 mg was crushed and administered via G-tube, the post-load PRU resulted as 140 PRU, meeting the goal of < 180 PRU.

Metoclopramide 5 mg was administered orally 30 minutes prior to subsequent ticagrelor doses. A PRU was checked 30 minutes after the first maintenance ticagrelor 90 mg dose and resulted at 173 PRU. There was concern this level was too early to be accurate, so a subsequent PRU was checked 6 hours after the same dose and resulted at 181 PRU. The decision was made to obtain a 2-hour PRU level after the second maintenance ticagrelor 90 mg dose for confirmation, which resulted as 176 PRU. Due to repeated testing within goal, it was decided to continue therapy with ticagrelor upon discharge.

The patient was counseled on taking metoclopramide 30 minutes prior to ingesting crushed ticagrelor tablets orally on discharge. It was recommended to repeat PRU during outpatient follow up to ensure compliance with administration protocols and consider CYP2C19 allele testing in the event an alternative agent was needed.

Discussion

Our patient highlights an uncommon but clinically important scenario: apparent ticagrelor failure in a patient with a high risk stent-associated thrombosis. Although ticagrelor is often selected due to the uncertain response rate of clopidogrel due to CYP2C19 mutations, inadequate platelet response can still occur. Current neurointerventional literature describes rare cases of ticagrelor non-response and highlights the utility of platelet function testing and evaluation of absorption when the consequences of thrombotic failure are high.[5] In this patient, an elevated steady-state PRU despite reported adherence,

coupled with elevated post-load levels after the procedure, required a broader evaluation of contributors, rather than assuming irreversible ticagrelor resistance.

Our patient's history of dysphagia, subsequent PEG tube placement, and lack of ticagrelor response led to the suspicion of issues with medication delivery or absorption. While most of the current evidence focus on impaired absorption due to opioid co-administration, the impaired absorption principle could apply to many other patients in the inpatient setting, including those with dysphasia, feeding tubes, critical illness, postoperative ileus, gastroparesis, or other concomitant medications that can decrease gastric emptying.

To overcome our patients' absorption issues, two strategies were implemented. The first was to increase the drug delivered to the small bowel by decreasing dissolution time and crushing the ticagrelor tablet. Pharmacokinetic trials have demonstrated faster ticagrelor absorption, earlier peak concentrations, and greater platelet inhibition early on when ticagrelor is administered as crushed or dispersed tablets.[2,6-9] In a systematic review by Serenelli, et al., crushed/chewed ticagrelor loading doses resulted in a mean difference of −59.24 PRU (25%) when compared to 1 hour post dose PRUs with whole tablet administration.[6] While these studies were conducted in patients receiving ticagrelor orally, critically ill patients frequently require enteral administration via a nasogastric (NG) tube due to impaired oral access, introducing factors that may affect drug absorption, bioavailability, and platelet inhibition.

Delivery of ticagrelor via nasal gastric (NG) tube resulted in sufficient platelet inhibition and comparable serum concentrations when compared to healthy volunteers in an alternative trail.[2,10] In one case presented by Laurent, et al., tube feeds were held with NG tube administration, resulting in increased response to ticagrelor and in a 19% drop in PRU.[5] Despite the evidence to support tube administration and holding tube feeds, we choose to administer the crushed tablet orally without regard to nutrition to re-create long term administration conditions, as our patient had PEG tube removal scheduled prior to her discharge. In our case, this alone resulted in a significant reduction in PRU post oral administration of a crushed tablet.

Our second strategy was to focus on improving gastric emptying time, theoretically allowing more medication to be delivered to the small bowel without being inactivated in low pH gastric secretions. Metoclopramide has been used as a potential strategy to mitigate delayed ticagrelor absorption.[1,5] Although not extensively studied, there is a reasonable rationale for considering modifying the motility with metoclopramide, which is relatively safe in most patients. This consideration is increasingly relevant as more of our patients are receiving medications that slow gastric emptying, including glucagon-like peptide-1 receptor agonists (GLP-1s), and as our neurologically injured patients frequently have impaired gastrointestinal transit issues from opioid administration and gastric tube placement.

In high-risk neuroendovascular procedures, our case supports a pragmatic approach to ticagrelor non-response: platelet function testing when clinically necessary, interpreting PRU results in the context of patient specific pharmacokinetic factors, and considering alternative administration when absorption is

a plausible contributor to inadequate platelet inhibition. Clinicians can consider crushed administration up front, in patients with decreased absorption risk factors, rather than waiting for inadequate response, theoretically decreasing the risk of thrombosis post procedures.

Lessons Learned (Summary)

1. Unlike clopidogrel, where resistance may be related to CYP polymorphisms, ticagrelor resistance is likely related to absorption. Ticagrelor resistance may be overcome through administration as a crushed tablet and/or increasing gastric motility.

2. While PRU testing is not typically completed in patients on ticagrelor, it may be considered in patients receiving high risk neuroendovascular stents.

3. Timing of PRU testing can have a significant impact. PRU should be measured 1-2 hours after administering crushed ticagrelor, when maximal plasma concentrations are achieved from the parent drug and its active metabolite.

Declarations

This manuscript complies with all instructions to the authors.

Author Contributions

- **Ashley Schuler, PharmD, BCCCP**
  Conceptualization; Investigation; Data Curation; Formal Analysis; Literature Review; Writing – Original Draft; Writing – Review & Editing; Visualization; Project Administration. Dr. Schuler identified the educational value of the case, performed the literature review, interpreted relevant pharmacotherapy and platelet function testing data, drafted the initial manuscript, incorporated coauthor feedback, and coordinated manuscript preparation and submission.
- **Connie Yoon, PharmD, BCPS, BCCCP**
  Conceptualization; Investigation; Formal Analysis; Writing – Review & Editing. Dr. Yoon contributed to case interpretation, provided expertise in critical care pharmacotherapy and antiplatelet management, assisted with development of the clinical teaching points, and critically reviewed and revised the manuscript for intellectual content
- **Anna Sahlstrom Drury, PharmD, BCEMP, BCCCP**
  Investigation; Formal Analysis; Writing – Review & Editing. Dr. Drury contributed clinical expertise regarding neurocritical care and acute management considerations, participated in interpretation of the case findings and lessons learned, and critically reviewed and revised the manuscript.
- **Nirav Vora, MD**
  Conceptualization; Investigation; Resources; Supervision; Writing – Review & Editing. Dr. Vora contributed expertise in neurovascular disease and neurointerventional management, provided

clinical oversight and case-specific procedural context, assisted in interpretation of findings, and critically reviewed and revised the manuscript for important intellectual content.

- **All Authors**
  All authors contributed to manuscript development, reviewed and approved the final version of the manuscript, agreed to be accountable for all aspects of the work, and approved submission to *Neurocritical Care*.

The manuscript has not been published previously and is not under consideration by another journal.

Patient consent has been obtained and ethical considerations have been addressed in accordance with journal requirements

The authors have no conflicts of interest or funding to report.

No AI was used in any part of the manuscript development or editing.

References

1. Sikora J, Niezgoda P, Barańska M, et al. METoclopramide Administration as a Strategy to Overcome MORPHine-ticagrel Or Interaction in PatientS with Unstable Angina. Thromb Haemost. 2018;118(12):2126–33. 10.1055/s-0038-1675605.
2. Teng R, Maya J. Absolute bioavailability and regional absorption of ticagrelor in healthy volunteers. J Drug Assess. 2014;3:43–50. 10.3109/21556660.2014.946604.
3. Mega JL, Close SL, Wivicott SD, et al. Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360:354–62. 10.1056/NEJMoa0809171. https://www.nejm.org/doi/.
4. Scott SA, Sangkuhl K, Shuldiner AR, et al. PharmGKB summary: very important pharmacogene information for cytochrome P450, family 2, subfamilyC, polypeptide 19. Pharmacogenet Genomics. 2012;22(2):159–65. 10.1136/neurintsurg-2021-017638.
5. Laurent D, Dodd WS, Small C, et al. Ticagrelor resistance: a case series and algorithm for management of non-responders. J Neurointerv Surg. 2022;14(20):179–83.
6. Serenelli M, Pavasini R, Vitali F, et al. Efficacy and safety of alternative oral administrations of P2Y12-receptor inhibitors: systematic review and meta-analysis. J Thromb Haemost. 2019;17(6):944–50. 10.1111/jth.14434.
7. Alexopoulous D, Barampoutis B, Gkizas V, et al. Crushed versus integral tablets of ticagrelor in ST-segment elevation myocardial infarction patients: a randomized pharmacokinetic/pharmacodynamic study. Clin Pharmacokinet. 2016;55:359–67. 10.1007/s40262-015-0320-0.
8. Perla HT, Thomson VS, Attumalil TV, et al. Randomized, Double-Blind, Active Comparator Pharmacodynamic Study of Platelet Inhibition with Crushed and Integral Formulations of

Clopidogrel and Ticagrelor in Acute Coronary Syndrome. Am J Cardiovasc Drugs. 2023;23(4):455–66. 10.1007/s40256-023-00591-8.

9. Venetsanos D, Sederholm Lawesson S, Swahn E, Alfredsson J. 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. Thromb Res. 2017;149:88–94. 10.1016/j.thromres.2016.10.013.
10. Ratcovich H, Sadjadieh G, Andersson HB, et al. The effect of TIcagrelor administered through a nasogastric tube to COMAtose patients undergoing acute percutaneous coronary intervention: the TICOMA study. EuroIntervention. 2017;12(14):1782–8. 10.4244/EIJ-D-16-00398.