ACCP Cardiology PRN Journal Club

American College of Clinical Pharmacy
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Mentor Bio

Dr. Craig Beavers graduated from the University of Kentucky (UK) College of Pharmacy and completed a PGY1 pharmacy practice residency and a PGY2 cardiology pharmacy residency at UK Albert B. Chandler Hospital in Lexington, Kentucky. He is the cardiovascular clinical pharmacy coordinator at UK Healthcare and assistant adjunct professor with the University of Kentucky College of Pharmacy. Dr. Beavers is also the immediate past-chair of the Cardiology PRN.
Effect of Intravenous Fentanyl on Ticagrelor Absorption and Platelet Inhibition Among Patients Undergoing Percutaneous Coronary Intervention [PACIFY]

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Disclosures

I or Dr. Beavers have no financial interest or affiliation with the manufacturer or any marketed product herein.
• 2011 ACCF/AHA/SCAI Guidelines for PCI Recommendations
  • Minimal (anxiolysis) or moderate (depressed consciousness with ability to respond purposefully to verbal commands) sedation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Effects</th>
<th>Dose</th>
<th>Onset (min)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Sedation, Anxiolysis</td>
<td>0.5-1mg IV, then titrated</td>
<td>2 - 3</td>
<td>45 - 60</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Analgesia</td>
<td>50mcg IV. May repeat every 3 minutes, titrate to effect</td>
<td>3 - 5</td>
<td>30 - 60</td>
</tr>
<tr>
<td>Etomidate</td>
<td>Sedation, Anxiolysis</td>
<td>0.1mg/kg IV, repeat if inadequate response</td>
<td>&lt;1</td>
<td>5 - 15</td>
</tr>
<tr>
<td>Propofol</td>
<td>Sedation, Anxiolysis</td>
<td>Load 1mg/kg IV; administer additional 0.5mg/kg doses as needed to enhance sedation</td>
<td>&lt;1</td>
<td>5 - 15</td>
</tr>
</tbody>
</table>

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; SCAI, Society of Cardiovascular Angiography and Interventions
Sedation, Analgesia, and Anaesthesia Variability in Laboratory-based Cardiac Procedures: An International Survey

Type of Anesthesia Reported by Cardiologists (n=151)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>None</th>
<th>Sedation</th>
<th>General Anesthesia</th>
<th>Not Done</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary angiography or PCI</td>
<td>32.5%</td>
<td>66.9%</td>
<td>0.7%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Physician Beliefs: Radial vs. Femoral Access

<table>
<thead>
<tr>
<th>Belief</th>
<th>Radial Access</th>
<th>Femoral Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventional Cardiologist believes more sedation should be given</td>
<td>29.4%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

## Background

**Previous clinical trials**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>- Double-blind RCT</td>
<td>- Double-blind, placebo-controlled RCT</td>
<td>- Double-blind, cross-over RCT</td>
</tr>
<tr>
<td>- n = 24</td>
<td>- n = 70</td>
<td>- n = 12</td>
</tr>
<tr>
<td>- Healthy volunteers</td>
<td>- Subjects with acute MI</td>
<td>- Healthy volunteers</td>
</tr>
<tr>
<td>- Clopidogrel PO 600mg + Morphine IV 5mg</td>
<td>- Morphine 5mg IV followed by ticagrelor 180mg</td>
<td>- Prasugrel 60mg + Morphine IV 5mg</td>
</tr>
<tr>
<td>- Clopidogrel absorption delayed</td>
<td>- Ticagrelor + active metabolite AUC by ↓ 36% and 37%, delay in C_{max} by 2 hours</td>
<td>- Prasugrel AUC and absorption unaffected</td>
</tr>
<tr>
<td>- ↓ active metabolite AUC by 34%</td>
<td></td>
<td>- Reduced C_{max} of active metabolite by 31%, 10min delay in onset of maximal platelet inhibition</td>
</tr>
<tr>
<td>- Slowed and diminished antiplatelet effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fentanyl</strong></td>
<td><strong>Ticagrelor</strong></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>• <strong>MOA:</strong> μ-opioid agonist</td>
<td>• <strong>MOA:</strong> Reversible inhibitor of platelet P2Y&lt;sub&gt;12&lt;/sub&gt; ADP-receptor to prevent signal transduction of platelet activation</td>
<td></td>
</tr>
<tr>
<td>• <strong>Onset:</strong> 1-2 min</td>
<td>• <strong>Equipotent active metabolite</strong></td>
<td></td>
</tr>
<tr>
<td>• <strong>Peak:</strong> 3-5 min</td>
<td>• <strong>T&lt;sub&gt;max&lt;/sub&gt;:</strong> 1.5h (1.0-4.0)</td>
<td></td>
</tr>
<tr>
<td>• <strong>Duration:</strong> 30-60 min</td>
<td>• <strong>T&lt;sub&gt;max&lt;sub&gt;active metabolite&lt;/sub&gt;:</strong> 2.5h (1.5-5.0)</td>
<td></td>
</tr>
<tr>
<td>• Reduction in GI motility</td>
<td>• <strong>Sites of absorption</strong></td>
<td></td>
</tr>
<tr>
<td>• Increase in smooth muscle tone in antrum of stomach and duodenum</td>
<td>• Small bowel</td>
<td></td>
</tr>
<tr>
<td>• Digestion is decreased in small intestine and propulsive contractions are decreased</td>
<td>• Ascending colon</td>
<td></td>
</tr>
<tr>
<td>• Reduced gastric secretions</td>
<td>• <strong>Offset:</strong> 24-48 hours</td>
<td></td>
</tr>
</tbody>
</table>

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Brilinta® [package insert]. AstraZeneca LP, Wilmington, DE; 19850.
VerifyNow® PRUTest P2Y₁₂ Assay
Platelet Reactivity Test

% inhibition = \[ \frac{\text{Baseline PRU} - \text{Post-treatment PRU}}{\text{Baseline PRU}} \times 100 \]

Response to P2Y₁₂ Therapy Reference

<table>
<thead>
<tr>
<th>PRU: P2Y₁₂ Reaction Units</th>
<th>NORMAL PLATELET REACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 ± 10%</td>
<td>200 ± 10%</td>
</tr>
<tr>
<td>↓ PLATELET REACTIVITY</td>
<td></td>
</tr>
</tbody>
</table>
**Study Design**

<table>
<thead>
<tr>
<th>Objective</th>
<th>To assess if fentanyl has adverse outcomes in patients undergoing PCI</th>
</tr>
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<tbody>
<tr>
<td>Design</td>
<td>Single-center randomized clinical trial</td>
</tr>
<tr>
<td>Study Population</td>
<td>Elective coronary angiography</td>
</tr>
</tbody>
</table>
Inclusion & Exclusion Criteria

**Inclusion**
- Clinically-indicated elective coronary angiography
- No receipt of P2Y\textsubscript{12} inhibitors for 14 days prior to enrollment

**Exclusion**
- Pre-procedural treatments with oral anticoagulants or opiates
- Platelet count <100,000/mm\textsuperscript{3}
- Renal dysfunction
- Hepatic dysfunction

Baseline Characteristics

- Mean age: 63 years
- Female: 27%
- Race majority: White

In the Cath Lab

All participants: lidocaine + midazolam

PCI indicated

n = 70

Ticagrelor 180mg at conclusion of angiography

PCI not indicated

n = 142

No ticagrelor

n = 212

mITT

Patients + Outcomes Assessors = blinded
Treating providers = not blinded

Intervention

PCI indicated

(+) Fentanyl
Ticagrelor 180mg

(-) Fentanyl
Ticagrelor 180mg

Blood sampling

Baseline
Ticagrelor 180mg
0.5 h 1 h 2 h 4 h 24 h

Outcomes

Primary
- Ticagrelor concentration during the 24 hours after loading (AUC$_{0-24}$)

Secondary
- Platelet inhibition assessed by VerifyNow PRU at 2 hours
- Platelet inhibition assessed by aggregometry (% change from baseline with ADP) at 2 hours
- Self-reported maximum pain experienced during the procedure (0 to 10 numeric scale)

Statistical Analysis
- Between-group comparisons, categorical: Fisher's exact test
- Between-group comparisons, continuous: Wilcoxon rank-sum test
- Significance: p<0.05 (2-sided)
Results

<table>
<thead>
<tr>
<th></th>
<th>(+) Fentanyl</th>
<th>(-) Fentanyl</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC$_{[0-24]}$</td>
<td>2,107 vng ml$^{-1}$ h</td>
<td>3,301 vng ml$^{-1}$ h</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hour PRU (SD)</td>
<td>112 ± (95)</td>
<td>78 ± (72)</td>
<td>0.09</td>
</tr>
<tr>
<td>ADP response</td>
<td>39.3% ± 18.7</td>
<td>27.5% ± 14.4</td>
<td>0.04</td>
</tr>
<tr>
<td>2 hour HPR PRU</td>
<td>20%</td>
<td>6%</td>
<td>0.07</td>
</tr>
<tr>
<td>2 hour HPR aggregometry</td>
<td>33%</td>
<td>5%</td>
<td>0.03</td>
</tr>
<tr>
<td>4 hour PRU</td>
<td>55</td>
<td>50</td>
<td>0.73</td>
</tr>
<tr>
<td>Self-reported maximal intra-procedural pain, mean</td>
<td>1.5/10</td>
<td>2.3/10</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean (SD) Troponin-I level at 2 hours</td>
<td>12.1 ± (9.5) ng/L</td>
<td>6.7 ± (4.2) ng/L</td>
<td>0.02</td>
</tr>
<tr>
<td>Thrombotic events, n</td>
<td>2</td>
<td>0</td>
<td>NR</td>
</tr>
</tbody>
</table>

ADP, adenosine diphosphate; HPR, high platelet reactivity; NR, not reported
Primary Outcome: Ticagrelor concentration

Plasma Concentrations of Ticagrelor (means) after a 180mg load, according to fentanyl randomization

- 0
- 0.5
- 1
- 2
- 4
- 24

Ticagrelor plasma concentration (ng/mL*h)

0 0.5 1 2 4 24

P=0.06 P=0.07 P=0.04 P=0.43 P=0.41

High Platelet Reactivity: 2h after Ticagrelor

High Platelet Reactivity %

Author’s Conclusions

• Fentanyl administration lowers plasma concentrations of ticagrelor and delays its antiplatelet effects

• Routine use of fentanyl should be discouraged during PCI in the absence of pain
  • Particularly when P2Y_{12} agents are loaded near the time of opioid administration
  • Radial versus femoral access

• The use of fentanyl did not provide significant evidence of improvement in subjective comfort
Critique

Patient population of interest
Utilization of VerifyNow and platelet aggregometry
Proof of concept as gateway to larger study

All subjects received lidocaine prior to procedure
Dosing of all sedation medications left to physician discretion
No dosing described
Sample size
Did not measure active metabolite levels
Femoral versus radial approach not stated
Clinical Practice Implications

1. Administration of fentanyl may delay ticagrelor absorption up to 4 hours. 
   Is this clinically significant?

2. Clinical relevance for stent thrombosis unknown, therefore strongly recommended changes in practice are not warranted currently.

3. Decision to use opioids for minimally invasive procedures in the cath lab. 
   Use as needed, avoid where possible.
   Less sedation required with femoral access.
   Use local anesthesia ± midazolam.

4. Crushing of ticagrelor could provide a plausible solution.
The Effect of Intravenous Cangrelor and Oral Ticagrelor on Platelets, the Microcirculation and Myocardial Damage in Patients Admitted With STEMI Treated by Primary Percutaneous Coronary Intervention: A Randomized Controlled Pilot Trial

| Enrollment | 100 subjects presenting with STEMI and eligible for PCI |
| Study Design | Open-label, randomized |
| Where | United Kingdom |
| Primary Outcome | Degree of platelet inhibition measured by VerifyNow Rapid platelet function analyzer VASP flow cytometry at infarct vessel open time |
| Timeframe | July 2016 – February 2019 |

https://clinicaltrials.gov/ct2/show/NCT02733341
References


Acknowledgements

• Craig Beavers, PharmD, FAHA, AACC, BCPS-AQ Cardiology, CACP
• Zachary Noel, PharmD, BCPS
• Thomas Szymanski, PharmD
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