Clinical Pharmacology & Toxicology Pearl of the Week

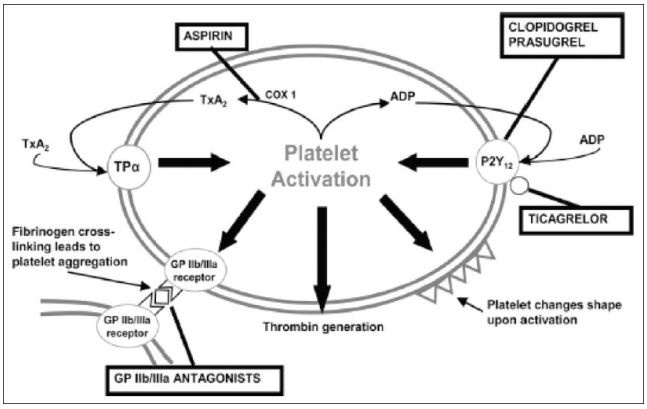
Clopidogrel and Clopidogrel non-responders

Pharmacokinetics of clopidogrel

- ✓ Clopidogrel is rapidly absorbed orally and metabolized to its active metabolite by CYP2C19
  - Peak active metabolite concentration within 30-60 minutes
- ✓ Peak antiplatelet effects after 600 mg loading dose occurs within 2-5 hours
- ✓ Peak antiplatelet effect after daily 75 mg dosing only occurs within 5-7 days
- ✓ Clopidogrel and its metabolites are eliminated 50/50 by the kidney and in the stool
- ✓ Half-life of parent clopidogrel compound is 6 hours
- ✓ Half-life of active –thiol metabolite is 45 minutes

Mechanism of action of clopidogrel

- ✓ Clopidogrel is an irreversible selective inhibitor of the platelet low-sensitivity adenosine diphosphate receptor: $P2Y_{12}$.
- ✓ Platelet $P2Y_{12}$ is responsible for potentiating platelet activation and activation of glycoprotein IIb and glycoprotein IIIa
  - GPIIIa/IIB are responsible for recruitment and binding to fibrinogen and vWB factor which are responsible and essential for platelet crosslinking and aggregation



Patel et al. 2013

Clopidogrel non-responders

- ✓ Multiple mechanisms are speculated for why certain individuals do not receive adequate antiplatelet effects when appropriately dosed clopidogrel
- ✓ Most commonly implicated is a genetic polymorphism in CYP2C19 activity making the individual a **poor or intermediate metabolizer of clopidogrel to its active metabolite**
  - A US based study found up to 30% of patients can be poor or intermediate metabolizers
  - Another study found the polymorphisms to be most common in Chinese participants, followed by African descent, then Caucasians.
- ✓ Another factor to consider is co-administration of strong CYP2C19 inhibitors
  - These include PPIs (most notably omeprazole), antifungals (most notably fluconazole), and fluoxetine
- ✓ Further epidemiological studies highlight that poorly controlled diabetics and obese patients may be at higher risk of being a non-responder, though mechanisms are unclear

What next?

- ✓ Suspect clopidogrel non-response in patients with recurrent thrombotic events or in-stent thrombosis post-PCI
- ✓ Laboratory testing for CYP2C19 polymorphisms more readily available
- ✓ Avoid CYP2C19 inhibitors in patients on clopidogrel
- ✓ If clopidogrel non-response is suspected, or a strong CYP2C19 inhibitor can't be avoided, consider the indication for clopidogrel, risk of inadequate platelet inhibition, and consider another antiplatelet agent such as ticagrelor. Ticagrelor has a similar mechanism of action but does not need to be activated through metabolism.

My patient is on clopidogrel and is bleeding!

- ✓ Consider activated charcoal if this is an acute ingestion/overdose
- ✓ Achieve local control of bleeding if possible
- ✓ Consider desmopressin (DDAVP) to mobilize vWF and aid with platelet aggregation and function
- ✓ Reserve platelet transfusion for critically ill patients with severe bleeding. Studies are small but show empiric platelet transfusion is potentially harmful.
- ✓ Consult your local hematology services
- ✓ No role for dialysis due to short serum half-life with prolonged therapeutic effect, along with higher risks of iatrogenic complications from catheter placement.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

References:

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