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, P2Y12
- ✓ Platelet P2Y12 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 von Willebrand factor (vWF) which are responsible and essential for platelet crosslinking and aggregation

Clopidogrel non-responders

- ✓ Multiple mechanisms are speculated for why certain individuals do not receive adequate antiplatelet effects when appropriately dosed clopidogrel
- ✓ Most 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.

References:

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5. Patel TV, Shah JS, Patel CN. Ticagrelor: A new antiplatelet drug for acute coronary syndromes. Ann Trop Med Public Health 2013;6:14-9

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral, Specialist Link and through RAAPID. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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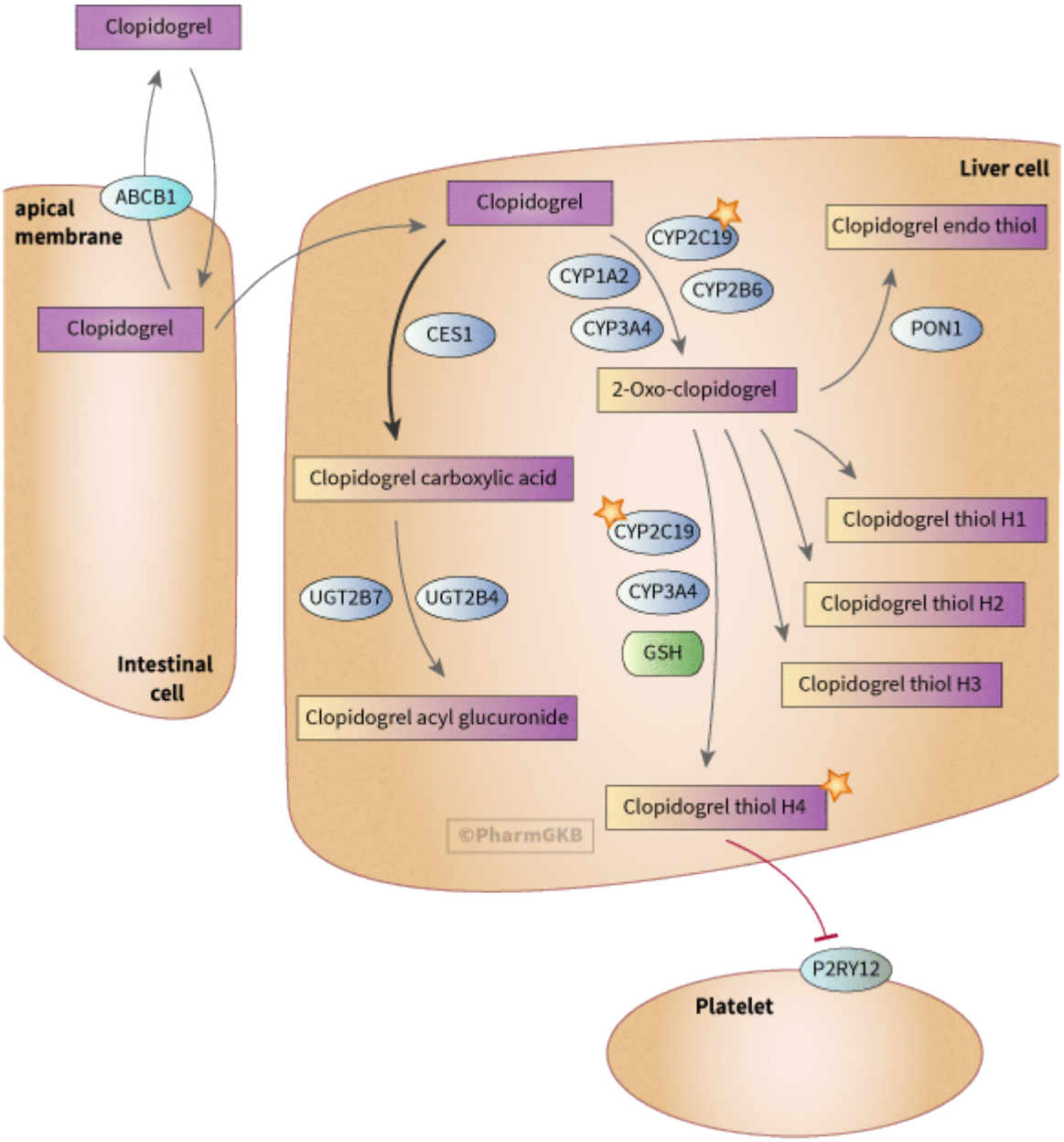

Clopidogrel metabolism. From Pharm GKB. https://www.pharmgkb.org/pathway/PA154424674