

20.201 Mechanisms of Drug Action

Lecture #22: Omeprazole Case Study

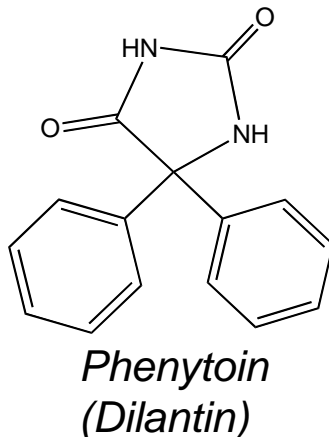
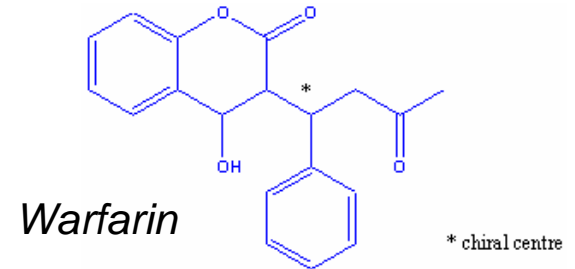
November 14, 2005

Other drugs metabolized by CYP2C19

- Diphenylhydantoin -
 - ~ antiepileptic
 - ~ 10-20% of the metabolism
 - ~ CYP2C9 accounts for bulk
- Diazepam -
 - ~ anxiolytic
 - ~ prolonged sedation in mutants
- Proguanil - antimalarial
- Citalopram - antidepressant
(selective serotonin reuptake inhibitor)
- Some barbiturates

Polymorphisms in CYP2C9

- Rarer than CYP2C19 polymorphisms
- Arg₁₄₄ to Cys₁₄₄:
 - ~ diminished activity
 - ~ 8% Caucasians; absent in Asians
- Ile₃₅₉ to Leu₃₅₉:
 - ~ higher K_m /lower V_{max}
 - ~ Homozygous 0.3% Caucasians; Hetero 6%
- Major effect, though, due to metabolism of drugs with narrow therapeutic windows:
 - ~ Warfarin - anticoagulant
 - ~ Glipizide - type II diabetes
 - ~ Tolbutamide - type II diabetes
 - ~ Phenytoin - antiepileptic (80-90%)

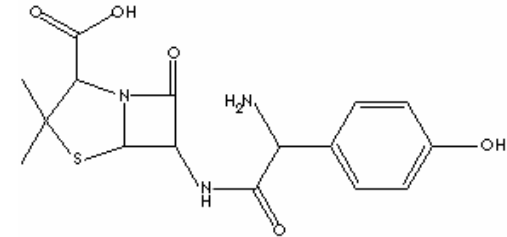


Name	R	R1
Tolbutamide	-CH ₃	-CH ₂ CH ₂ CH ₂ CH ₃
Glipizide		

H. Pylori treatment and CYP2C19 Polymorphisms

Furuta et al. *Annals Int. Med.* 129: 1027-1030, 1998

- H. pylori infection associated with ulcers and high risk of gastric cancer
- Previous ulcer treatments focused solely on the acid production
- Now add antibiotic regimen to ulcer treatment
- Furuta et al. used combination of amoxicillin and omeprazole to treat H. pylori infection in Japanese patients displaying range of CYP2C19 polymorphisms



Amoxicillin

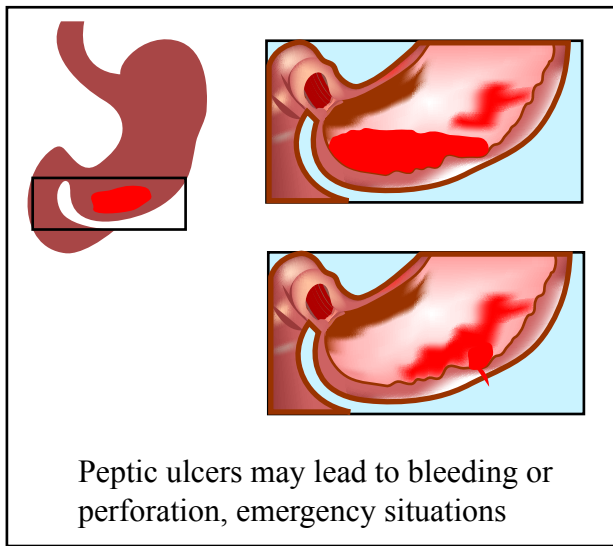
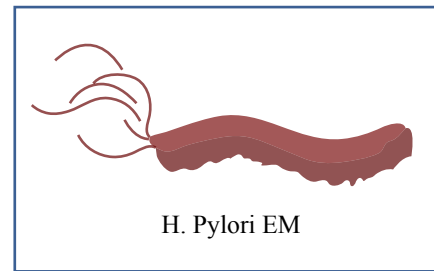


Figure by MIT OCW.



H. Pylori EM

Figure by MIT OCW.

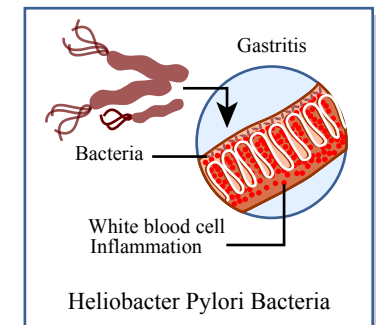


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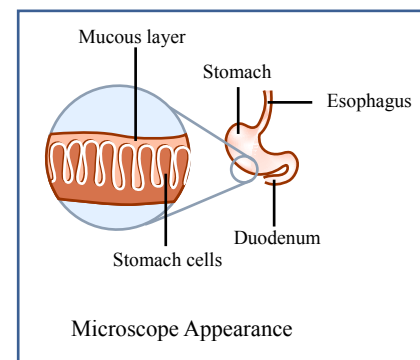


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Image of H. Pylori immunostaining in stomach lining removed due to copyright restrictions.