

20.201 Mechanisms of Drug Action

Lecture #21: Omeprazole Case Study

November 9, 2005

Gastric physiology

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Images of Acetylcholine Pathways, Gastrin Pathways, Histamine Pathways removed due to copyright restrictions.

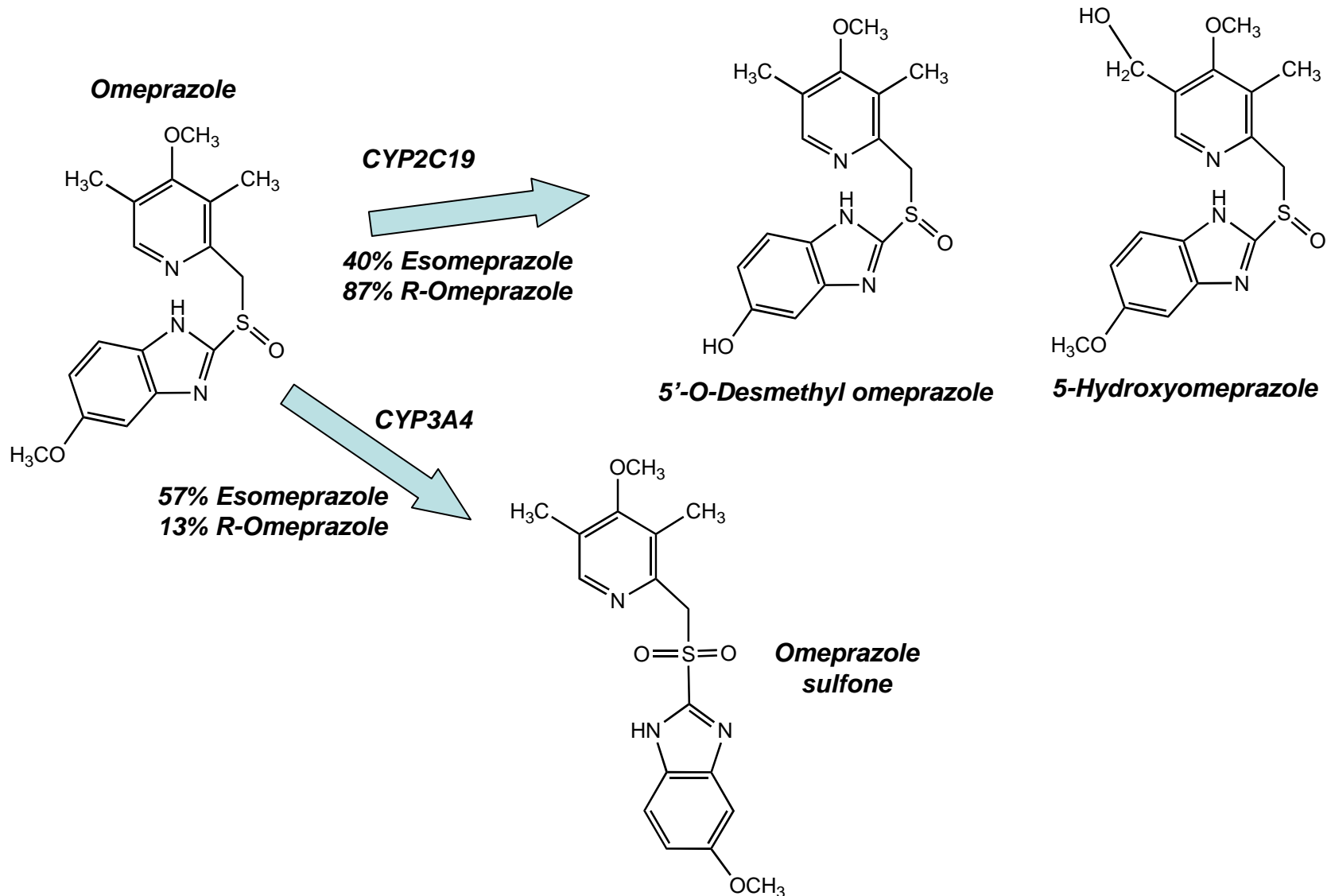
Acid Secretion Pathways

http://hopkins-gi.org/multimedia/database/intro_247_Parietal.swf

PKs of Omeprazole vs. Esomeprazole

	<i>R/S-Omeprazole</i> (20 mg)	<i>Esomeprazole</i> (20 mg)
V_d	0.34 L/kg	16 L
Plasma $t_{1/2}$	0.7 hr	1.2 hr
Albumin binding	95%	97%
Peak Conc. (C_{max})	EM = 0.6-0.7 μM PM = 3.5 μM	"EM" = 1.7 μM
CL_{total}	7.5 $\text{ml}\cdot\text{min}^{-1}\cdot\text{mg}^{-1}$	
CL_{int} (liver microsomes)	42.6	14.6
Oral availability	53%	89%
Urinary Excretion	<1%	<1%
5 d \uparrow in AUC	49%	111%

Metabolism of omeprazole and esomeprazole



In vitro Microsomal Metabolism Studies
(metabolism in units of clearance ($\mu\text{L}/\text{min}/\text{mg}$))

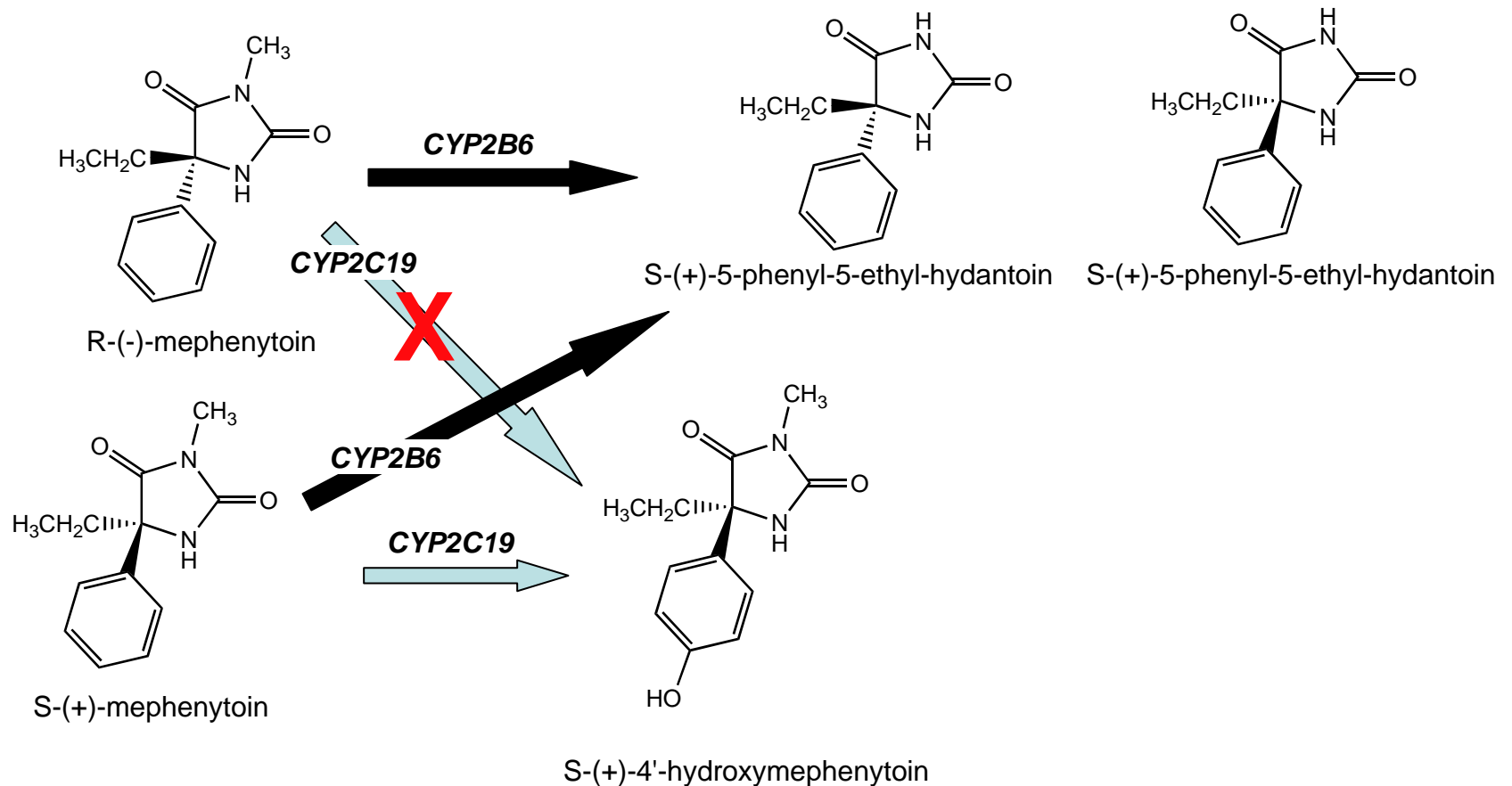
		<i>S-Omeprazole</i>	<i>R-Omeprazole</i>
<i>2C19</i>	<i>5-OH</i>	<i>4</i>	<i>40</i>
	<i>Desmethyl</i>	<i>6.7</i>	<i>1.8</i>
<i>3A4</i>	<i>Sulfone</i>	<i>3.9</i>	<i>0.8</i>
	<i>CL_{int} $\mu\text{L}/\text{min}/\text{mg}$</i>	<i>14.6</i>	<i>42.6</i>

Main points of the Chang et al. paper

- Genetic polymorphisms in the metabolism of omeprazole lead to variations in its pharmacokinetics and in the stimulation of gastrin production
- Rapid, intermediate and slow metabolizers showed relative omeprazole AUC's of 1:4:20
- Omeprazole may serve as a better probe of CYP2C19 function than mephenytoin

Mephenytoin metabolism

- Mephenytoin is an antiepileptic agent used as a probe of CYP2C19
- Stereospecific metabolism:
 - ~ Only S-isomer metabolized by CYP2C19
 - ~ Both S- and R-isomers demethylated by CYP2B6



Other drugs metabolized by CYP2C19

- Diphenylhydantoin - antiepileptic
- Diazepam - anxiolytic
- Proguanil - antimalarial
- Citalopram - antidepressant
(selective serotonin reuptake inhibitor)
- Some barbiturates