PPI제제와 Prokinetics 제대로 사용하기

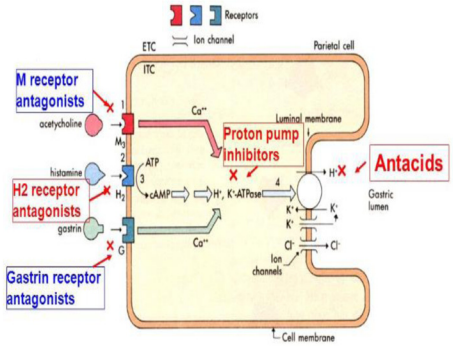
이 준 형
일산백병원

연수강좌

PPI 작용기전

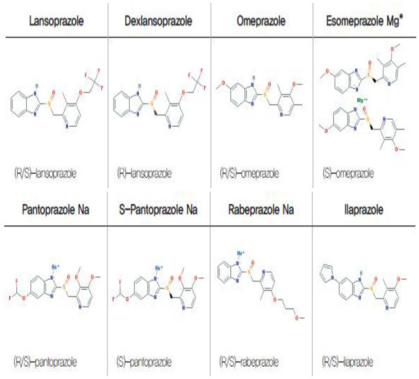
- 위산 분비 세가지 경로
  - histamine 에 의해 히스타민2 수용체 (histamine2 receptor , H2 Rc)가 활성화 됨
  - acetylcholine 에 의해 무스카린3 수용체 (muscarinic3 receptor, M3 Rc) 가 활성화 됨
  - gastrin 에 의해 CCK2 수용체가 활성화 됨
- 세가지 경로의 활성화를 통해서 위산 분비의 최종 단계인 proton pump 가 작동

PPI 작용기전



Current indications of proton pump

Generation of PPI

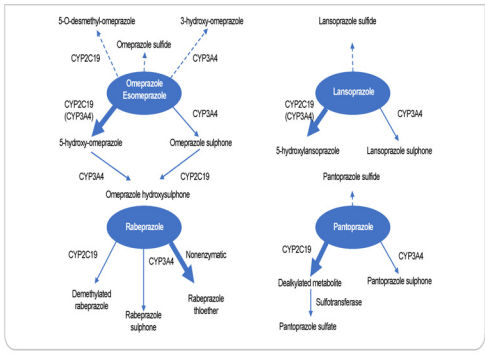


Comparison of pharmacokinetics and pharmacodynamics of PPIs

Parameters	Omeprazole 20 mg/day	Pantoprazole 40 mg/day	Lansoprazole 30 mg/day	Rabeprazole 20 mg/day	Esomeprazole 40 mg/day	Ilaprazole 10 mg/day
C_{max} (μg/ml)	0.08 - 0.8	1.1 - 3.3	0.6 - 1.2	0.41	1.6	NA*
T_{max} (h)	1 - 3	2 - 4	1.3 - 2.2	3.1	1.5	3.4 - 3.7
AUC (μg h/ml)	0.2 - 1.2	2 - 5	1.7 - 5	0.8	3.9	1.8 - 2.2
$t_{1/2}$ (h)	0.6 - 1	0.9 - 1.9	0.9 - 1.6	1	1.2	8.1 - 10.1
Metabolism by CYP2C19	++	++	++	+	++	-
Metabolism by CYP3A4	+	+	++	+	+	++
Nonenzymatic metabolism	-	-	-	++	-	+
% Time pH > 4‡	49.16	41.94	47.98	50.53	58.43	68.9
Mean 24-h pH‡	3.54	3.33	3.56	3.70	4.04	4.8

Nicola B. et. al. The pharmacokinetics of ilaprazole for gastro-esophageal reflux treatment. Expert Opin. Drug Metab. Toxicol. (2013) 9(10):1361-1369

Metabolic Pathways of PPIs



17. Marelli S and Pace F. Expert Rev. Gastroenterol. Hepatol. 2012;6:423-435

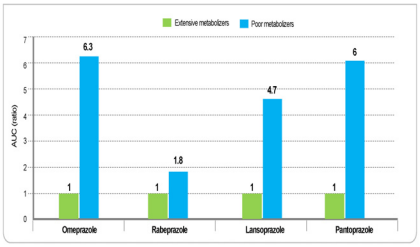
pKa values of PPIs

- PPI는 혈액과 같은 중성 pH에서는 수소화되지 않다가 자체의 pKa보다 낮은 pH를 가진 산성 환경에 들어가면 수소를 얻어 활성화 됨
- PPI 를 지속적으로 사용하여 위내 환경이 약산으로 변하면 활성이 떨어질 수 있음

Proton pump inhibitor	pKa1	pKa2
Omeprazole/esomeprazole	4.06	0.79
Lansoprazole	3.83	0.62
Pantoprazole	3.83	0.11
Rabeprazole	4.53	0.62
Ilaprazole	5.10	

Genetic Variations in CYP2C19 Effect on PPI AUC

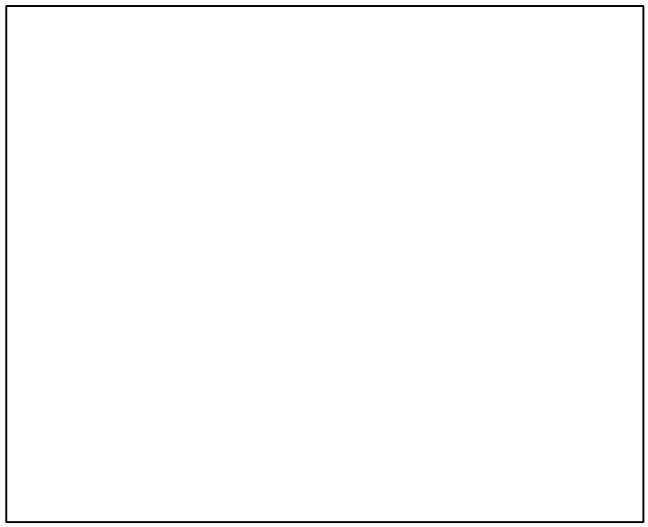
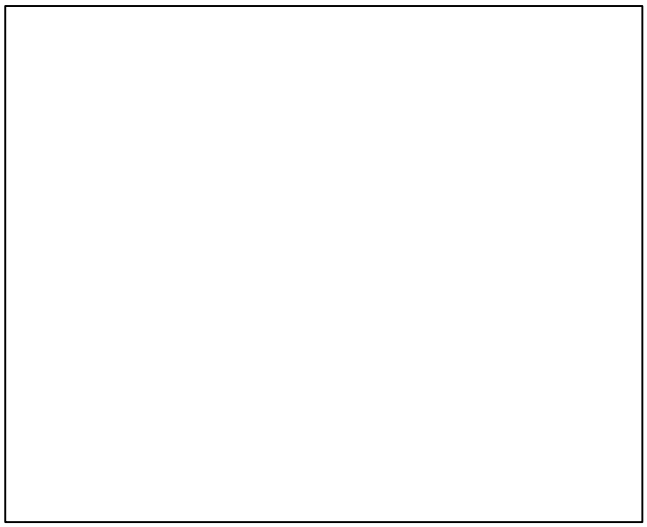
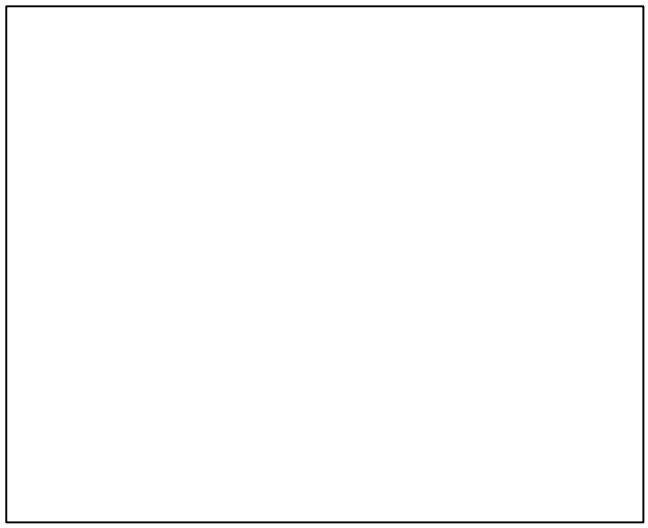
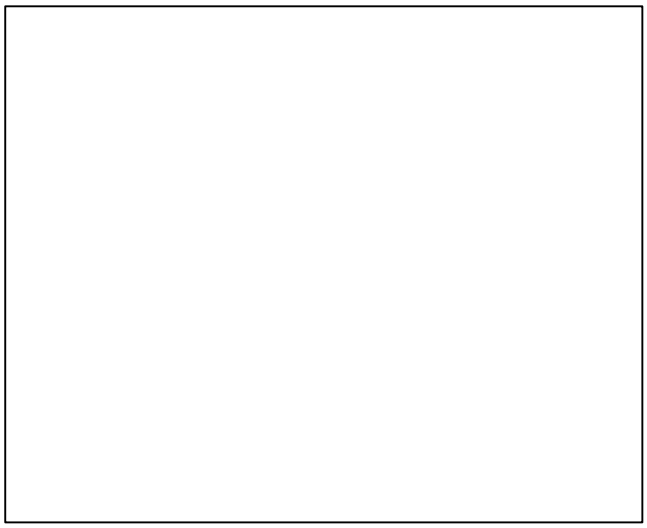
- Single Dose Studies



Comparison of the mean values for area under the plasma concentration–time curve after one oral dose of omeprazole, rabeprazole, lansoprazole and pantoprazole in extensive metabolizers versus poor metabolizers.

*AUC0 expressed as the ratio of extensive extensive metabolizers (reference value 1.0) : poor metabolizers

Marelli S and Pace F. Expert Rev. Gastroenterol. Hepatol. 2012;6:423-435

Long-term side effects of PPI

Potential adverse effect	Relative risk	Absolute excess risk
Chronic kidney disease	10% to 20% increase	0.1% to 0.3% per patient/year
Dementia	4% to 80% increase	0.07% to 1.5% per patient/year
Bone Fracture	30% to 4-fold increase	0.1% to 0.5% per patient/year
Myocardial infarction	No association in RCTs	
Small intestinal bacterial overgrowth	2-fold to 8-fold increase	Unable to calculate
Campylobacter or Salmonella infection	2-fold to 6-fold increase	0.03% to 0.2% per patient/year
Spontaneous bacterial peritonitis	50% to 3-fold increase	3% to 16% per patient/year
Clostridium difficile infection	No risk to 3-fold increase	0% to .09% per patient/year
Pneumonia	No association in RCTs	
Micronutrient deficiencies	60% to 70% increase	0.3% to 0.4% per patient/year
Gastrointestinal malignancies	No association in RCTs