Drugs for Peptic Ulcer Disease Basheerahmed AM What is peptic ulcer?Substitution of antibiotics (that is, do not substitute "ampicillin for amoxicillin" or "doxycycline for tetracycline"). Recommended duration of therapy 10 – 14 days H2–Receptor Antagonists The receptor–mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases. The kinases stimulate the proton pumps to secrete hydrogen ions in exchange for K+ into the lumen of the stomach. These agents reduce the secretion of gastric acid by competitively blocking the binding of histamine to H2 receptors. Thy inhibit ? basal, ? food–stimulated, and ? nocturnal secretion of gastric acid by about 90%. Cimetidine, the first histamine H2–receptor antagonist, is rarely used due to a wide range of drug– drug interactions. o o Therapeutic Uses Peptic Ulcers: All agents are equally effective in promoting healing. If H. pylori infection is present, use in combination with antibiotics. PPIs are more effective in treating NSAID–induced ulcers. Selectivity of H2–receptor antagonists No effect on H1 receptors Selective for H2 receptors Therapeutic Uses Acute stress ulcers can develop in patients admitted to intensive care units, such as, critically ill surgical patients, or patients with sepsis, respiratory failure etc. Some of these patients may be unconscious. Intravenous drugs are administered to manage stress ulcers. PPIs are more effective because tolerance may develop to H2 receptor antagonists. Gastroesophageal Reflux Disease (GERD) Low–dose H2 receptor antagonists are effective for GERD in only 50% of patients. Onset of action: 45 minutes, therefore, antacids relieve heartburn more quickly. PPIs are preferred ? ? ? Pharmacokinetics Route of Administration: Oral, IV Absorption and Distribution: Well absorbed orally and distributed widely throughout the body: Use in pregnancy: Available data shows no increased risk of congenital malformations, or low infant birth weight: Excretion: urine Intravenous formulations: Cimetidine Ranitidine Famotidine. Half–life: Increased in patients with renal dysfunction, and dosage adjustments are needed. ? ? Adverse Effects In general, the H2 antagonists are well tolerated. Cimetidine is a nonsteroidal antiandrogen. It can produce the following effects Gynecomastia and Galactorrhea (discharge of milk). The other agents do not produce the antiandrogenic and prolactin–stimulating effects of cimetidine. Elderly patients may experience confusion after IV administration. ? ? ? Adverse Effects Cimetidine can interfere with the metabolism of Warfarin Phenytoin Clopidogrel All H2 receptor antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as ketoconazole. Cimetidine inhibits several cytochrome P450 isoenzymes Proton Pump Inhibitors (Inhibitors of H+/K+–ATPase – "The hydrogen/potassium pump" also called "The Proton Pump") IN Flow won't stop if you shut any one of the inlets IN But if you block the outlet, there will be no flow THE FINAL COMMON PATHWAY CLOSED IN IN OU T Actions of PPIs PPIs are prodrugs with an acid–resistant enteric coating to prevent them from premature activation by gastric acid.It forms a stable "covalent" bond with H+/K+ ATPase. The proton pump is permanently inactivated. PPIs are weak bases At therapeutic doses, PPIs inhibit both basal and mealtime acid secretion by more than 90% (please note these patients have hyperacidity, they still have enough acid to activate pepsin during meals). PPIs need an hour for onset of acid suppression. For faster action, an oral preparation containing omeprazole and sodium bicarbonate is available in the market. Pharmacokinetics All of these agents are effective orally. For maximum effect, PPIs should be taken 30 to 60 minutes before breakfast or the largest meal of the day. Although the plasma half–life of these agents is only a few hours, they have a long duration of

action due to covalent bonding with the H+/K+– ATPase enzyme. Excretion: Metabolites of these agents are excreted in urine and feces. Dexlansoprazole has a dual delayed release formulation and can be taken without regard to food. Dual release multi– particulates IV formulations ? Esomeprazole ? Pantoprazole ? Lansoprazole are also available in intravenous formulations. Adverse Effects of PPIs (Clopidogrel is an antiplatelet drug) Because clopidogrel is a prodrug. it is converted to active form by CYP–2C19. PPIs inhibit this enzyme. Vitamin B12 deficiency: Because an acidic environment is required for "B12 and intrinsic factor" complex formation Absorption of calcium carbonate decreases.H. pylori Infection H. pylori are invariably found in ulcer craters 50% of world population is infected with H. pylori What Causes Peptic Ulcer Disease o Helicobacter Pylori (H. pylori) – Most ulcers are the result of infection with H. pylori – Not all of those infected with H. pylori develop ulcers – H. pylori MAY result in a weakening of the mucosal defense systems, allowing for development of ulcer subsequent to acid/pepsin aggression; 3/24/2022 13 Role of H. pylori in Peptic Ulcer Disease o Diagnosis: – The majority cases of peptic ulcer disease are related to H. pylori.– The diagnosis of H. pylori infection must be confirmed prior to initiation of therapy (histology and culture) – Urea breath test 3/24/2022 14 Figure 28.2 (still) 3/24/2022 15 Chapter 28 MENU > Urease Urease Urease Urease Urease Urease Urea H2O Urease Urease Urease Urease Urease Ammonia cloud Urease Urease 3/24/2022 Urease Urease Urease Urease Type IV secretion system 16 Urease Urease Urease NH3 2CO 2 NH3 cloud is formed by the action of urease enzyme H. pylori produces large amounts of the enzyme urease, molecules of which are localized inside and outside of the bacterium.Pathogenesis o In normal acid/pepsin attack is balanced by mucosal defences o Increased attack by hyperacidity o Weakened mucosal defence – the major factor (H. pylori related) 3/24/2022 5 o o What Causes Peptic Ulcer Disease o NonSteroidal AntiInflammatory Drugs (NSAIDs) Long term use of nonsteroidal anti–inflammatory drugs.o It is defined as mucosal erosions equal to or greater than 0.5 cm. o As many as 70–90% of such ulcers are associated with Helicobacter pylori, a rod–shaped bacterium that lives in the 3/24/2022 2 Gram negative bacterium Figure 28.3 (still) 3/24/2022 3 Chapter 28 MENU > o The two main causes of peptic ulcer disease are infection with gram–negative Helicobacter pylori and the use of nonsteroidal anti–inflammatory drugs (NSAIDs).Mucosal Protective Agents Bismuth subsalicylate Brief Review of Pathophysiology Components involved in providing gastroduodenal mucosal defense and repair HCO3 HCO3 HCO3 HCO3 3/24/2022 9 If patients are unable to tolerate the above therapies, neutralizing .gastric acid with nonabsorbable antacids is an option.Bismuth compounds ????2.3.4.1.2.3.2.3.4.1.??2