Treatment of Peptic Ulcer Disease: Yesterday, today and tomorrow

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The edict “No Acid, No Ulcer” (Schwarz Beit Clin Chir 1910, led to efforts in the twentieth century to inhibit acid secretion. The most successful early intervention was vagotomy (Dragsted et al PSEBM 1943) which was then superseded by H₂ antagonists (Black et al Nature 1972). These show uniform tolerance and short duration of action making them relatively ineffective but still were a major breakthrough in treatment. They were then replaced by PPIs that are acid activated covalent inhibitors of the gastric H,K ATPase (Fellenius et al Nature 1981) that show long duration of action and no tolerance. Omeprazole binds to cys813 and cys892 in the proton pathway (Besancon et al JBC 1997). However, the need for acid activation and a short plasma half-life restricts their efficacy even at bid dosing. The first potassium competitive inhibitor (PCAB) of the gastric H,K ATPase, SCH28080, had liver toxicity and was an imidazopyridine with a short plasma half-life and rapid dissociation (Wallmark et al JBC 1987) and many other imidazopyridine were tested and dropped. Recently a pyrrolopyridine (vonoprazan Hori et al JPET 2011) is on the market and others are in development with relatively long half-lives and immediate onset of action that likely will supersede PPIs. This compound's N-methylmethanamine (pK_a9.2) binds at glu343 blocking K binding and ATPase activity (Abe et al Nature 2018). It is now clear that infection by *Helicobacter pylori* is responsible for most peptic ulcer diseases where 1% of infected individuals succumb to the disease a rate 10 times higher than non-infected people and therefore eradication of the infection could be a new modality of treatment. Antibiotic resistance has made eradication difficult and generally unpredictable without measurement of antibiotic resistance. However, it appears that lengthy acid inhibition (pH >5.0 24hrs per day) stimulates bacterial division and hence amoxicillin sensitivity (Marcus et al APT 2012) and amoxicillin resistance is rare compared to resistance to other antibiotics. However, *H. pylori* expresses beta-lactamase so resistance may appear. Elevation of the organism's periplasmic pH is essential for acid survival and urease and periplasmic carbonic anhydrase are essential for this to occur. The elevation of periplasmic pH has been shown directly by measurement of eGFP fluorescence (Wen et al J Bact 2018) Expression of this carbonic anhydrase remains high at pH 3.0 in contrast to urease (Marcus et al *Helicobacter* 2018) suggesting its importance for gastric survival. An attractive eradication strategy would be then to use a long lasting carbonic anhydrase inhibitor with twice a day dosing to provide an antibiotic free means of eradication and this inhibitor is already available in the form of Diamox sequels. Treatment with Diamox resulted in a recurrence rate of 6% similar to that found after eradication of *H. pylori* compared to 43% following conventional medical therapy and with hindsight this is likely due to eradication of the infection (Puscas ANYAS 1984). It has indeed been shown that its periplasmic carbonic anhydrase is important for gastric survival of *H. pylori* and is required for neutralization of periplasmic pH in acid (Marcus et al J Bact 2005). So, today, the dictum might become “No Hp, no ulcer”.