Dual acid pump blocking as a novel therapeutic approach to the treatment of acid-related digestive diseases

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Conflict of interest: none

Funding statement: funding not received for the study

Introduction

1. Dual treatments are frequently used:

dual antiplatelet treatment (aspirin + clopidogrel, NOAC)

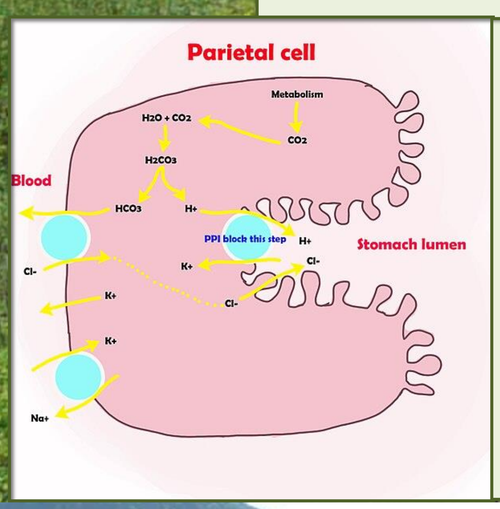
dual incretins (twincretins (GLP1 + GIP)

2. PPIs were introduced in the late 1980's-1990's, having a more profound acid inhibitory effect than the agents used earlier. Potasium-competitive acid blockers PCABs were recently introduced in the management of GERD, PUs and eradication of H. pylori infections in the hope of avoiding the unmet needs of PPI's. Although Eastern Asian results were excellent proving their superiority or non-inferiority as compared to PPI, in Western regions they achieved less acceptable results (Graham, DY, Dig.Dis.Sci- 2023, https://doi.org/10.1007/s10620-023-07886-5

Hypothesis

Having in view the different chemical structure, mechanism of action, pharmacologic profile of PPIs and P-CABs, one might suppose that their combined administration would further increase the intragastric pH and improve the clinical efficacy of these drugs in treating GERD, PU's and eradicating H. pylori infection. Such a combination has not been proposed so far.

Evaluation of hypothesis



Proton pump and potassium channel are genetically different structures

Proton pump: GATA DNA-binding protein gene (Chr. 10)

Potassium channel ancillary subunit (Chr 21)

(knockout mice experiments)

Pharmacological differences

Comparison of pharmacological properties

Pharmacology	Proton pump inhibitors	Poassium-competitie acid blockers
Chemistry	Substituted benzimidazoles	Imadazolpyridine derivatives
Steady state	3-5 days	8-17 h
Plasma half life	1-2 hs	8-17 h
CYP450 polymorphism	CYP2C19-dependent metabolism	CYP3A4: no influence
Proton pump activation	necessary	not necesasary
24h intragastric pH>4	46-68%	82.9-85.9%
Nocturnal acid breakdowns	possible	none
Effect on H. pylori	inhibition of urease	inhibition of urease
Effect on breath test	DOB‰ ↓	DOB‰↓
Effect of food	Acid inhibiton ↓	No influence

Physiological evaluation

a) The degree and rate of healing of eroive esophagitis is correlated with the reduction of esophageal acid exposure and inhibition of acid secretion, proven by 24h esophageal and gastric pH monitoring (H_2 histmaine receptor blockers, PPIs, P-CABs)

b) The degree of acid suppression is related to the rate of healing of both gastric and duodenal ulcers

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Susceptibility of antibiotics

-the effect of antibiotics is dependent on intragastric pH

-susceptibility of *H. pylori* to antibiotics is increased at pH> 4

-dual acid inhibition could achieve intragastric pH > 5, thus increasing sensitivity of antimicrobials

Conclusion

If the hypothesis above will be validated in practice, combined administration of PPIs and P-CABs will lead to a more profound and prolonged inhibiton of acid secretion than that obtained by either of these agents given alone. This can be of clinical benefit by improvement of reflux symptoms, healing of erosive oesophagitis and peptic ulcers and increasing eradication rates of *H. pylori* infection.