The Future of Acid Inhibition

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ABSTRACT

There are many unmet needs with current gastric acid suppression with proton pump inhibitors (PPIs). Recommended prescription of one standard morning dose for all patients and for all medical conditions must be scientifically inappropriate and far from individualized personal medicine. For several diseases, especially gastroesophageal reflux disease and Barrett esophagus, more intense, more prolonged diurnal acid suppression is indicated. Especially inhibition of nocturnal acid secretion with our current delayed-release PPIs turns out to be difficult. This overview summarizes the actual attempts to improve the control of acid secretion, which is necessary to adapt the degree of acid inhibition to the individual patient needs. To be discussed are: immediately release PPIs, extended PPI formulations, PPIs with a much longer half-life, potassium competitive acid blockers, gastrin antagonists, etc. Future studies have to proof that those novel drug approaches indeed contribute to reduce the unmet needs.

***Keywords**: acid secretion, PPI, nocturnal acid secretion*

ABSTRAK

Pada saat ini banyak kebutuhan yang tidak terpenuhi dalam upaya menekan produksi asam lambung dengan menggunakan penghambat pompa proton. Rekomendasi pemberian satu dosis standar di pagi hari untuk semua pasien dan semua kondisi medis seharusnya merupakan hal yang tidak sesuai secara ilmiah dan jauh dari pemenuhan kebutuhan pasien secara individu. Untuk beberapa penyakit, terutama penyakit refluks gastroesofageal dan esofagus Barrett, diindikasikan dengan penggunaan supresi asam diurnal yang lebih intensif dan waktu kerja lebih panjang. Dengan obat penghambat pompa proton lepas lambat yang digunakan saat ini, inhibisi sekresi asam nokturnal dirasa sulit. Artikel ini merangkum usaha aktual untuk meningkatkan kontrol sekresi asam yang diperlukan untuk mengadaptasi tingkat inhibisi asam sesuai dengan kebutuhan pasien. Beberapa hal yang akan didiskusikan antara lain: penghambat pompa proton lepas langsung, penghambat pompa proton dengan formulasi ekstensi, penghambat pompa proton dengan waktu paruh yang jauh lebih panjang, penghambat asam kompetitif dengan kalium, antagonis gastrin, dan lain-lain. Studi selanjutnya perlu dilakukan untuk membuktikan bahwa pendekatan terhadap obat-obatan tersebut berkontribusi dalam mengurangi kebutuhan yang belum terpenuhi.

***Kata kunci:** sekresi asam, penghambat pompa proton, sekresi asam nokturnal*

INTRODUCTION

Anti-acid secretory therapy has greatly advanced since the introduction of H2-receptor antagonist and especially proton pump inhibitors (PPIs). Yet there remain unmet needs, especially in the treatment of gastroesophageal reflux disease (GERD). This overview will discuss some of the possibilities that are being explored to remedy the unmet needs where an antisecretory treatment with rapid onset of action and sustained antisecretory effect would be desirable.[1]

TRADITIONAL DELAYED RELEASE PROTON PUMP INHIBITORS (DRPPIS)

The Traditional Proton Pump Inhibitors

Omeprazole, lansoprazole, pantoprazole, rebeprazole, esomeprazole are prodrugs and need to

be converted to be a sulfonamide form in the acid space of secretory canacilus. Activated PPIs then establish a covalent disulphide bond with cysteines of the proton pump, blocking the H/K exchange path. The speed of activation of a delayed release proton pump inhibitor (drPPI) in the acidic medium depends on the pKa, which varies between the various PPIs. Esomeprazole, the S-isomer of omeprazole, has an improved pharmacokinetic profile with higher bioavailability and less inter-individual variability.[2] All drPPIs are acid labile and need to be protected from acid breakdown when passing the stomach through enteric coating. Another limitation of drPPIs is their short plasma half-life of about 1-1.5 hour, when compared to the half-life of activation and synthesis of H/K-ATPase of about 24-hour.

All drPPIs have relatively slow onset of pharmacological action and may require several doses to achieve maximum acid suppression and symptom relief, possibly limiting their usefulness in on-demand treatment. The time of dosing and ingestion of meals may also influence the pharmacokinetics of drPPIs. Moreover they fail to provide full 24-hour suppression of gastric acid production because all allow nocturnal acid recovery, defined as a drop of intragastric pH under 4 for more than 1-hour, even with twice-daily dosing.[3]

NOVEL DEVELOPMENT AND FUTURE EXPECTATIONS

New PPIs formulations, recently introduced in clinical practice or under development and new avenues such as competitive K antagonism or blockade of CCK2 receptors will be explored in this section.

Immediate-release (Ir) Proton Pump Inhibitor or Ir-omeprazole

This formulation consists of pure, non enteric coated omeprazole powder along with sodium bicarbonate. The antisecretory effect of immediate release (ir)-omeprazole is quicker compared to drPPIs. The early increase in intragastric pH is likely due to the neutralizing effect of sodium bicarbonate, which may also accelerate and enhance the absorption of omeprazole, whose increased bioavailability may translate in more profound acid suppression. The rapid rise of intragastric pH may also facilitate gastrin release, enhancing activation proton pumps, available or inhibition. This new formulation provide sustained control of intragastric pH at steady and when dosed at bedtime, may be effective in improving control of nocturnal pH and treating night-time GERD.[4-6]

Extended Release Formulations of drPPIs

Extended-release formulations may well become an important strategy to inhibit nocturnal acid recovery because of their controlled and sustained release.

AGN 201904 is the acid stable sodium salt of sulfonamide of omeprazole, designed to delay absorption and to prolong the plasma residence time and thereby increase the number of proton pumps that might be inhibited. The drug was shown to provide faster and more profound acid auppression, including the nocturnal period.[7]

TAK-390MR is an extended release version of dexlansoprazole with a dual-peaked pharmacokinetic profile. TAK-390MR has shown prolonged acid inhibition across all dose levels compared to the parent compound. The drug has been shown to be highly efficacious in inducing and maintaining healing of erosive esophagitis.[8,9]

Novel Proton Pump Inhibitors with Prolonged Half-Life

Tenatoprazole, unlike the traditional drPPIs, has an imidazopyridine backbone, which is responsible for the prolonged half-life of 7 to 8 hours. Also tenatoprazole is a prodrug (pKa 4.04), converted to the active sulfonamide by acid in the secretory canaliculus. The active species binds to luminqally accessible cysteine 813 and 822 of the pump, resulting in disulfide formation and blockage of the proton transport pathway. The increase of intragastric pH with tenatoprazole 40 mg daily up to 7 days is significantly higher compared to esomeprazole 40 mg. Particular the improvement of nocturnal acid secretory control is impressive.[10,11] Tenatoprazole is a racemic mixture of two steroisomers, which derive from the chiral nature of the sulphur atom of the sulphinyl group. The bioavailability of S-tenatoprazole sodium salt hydrate is almost twice that of free S-tenatoprazole, which was selected for further development. So far no clinical trials are available.

Potassium-competitive Acid Blockers or Acid Pump Antagonists

Acid pump antagonists (APAs) are potassium competitive inhibitors of H/K- ATPase, interfering with the potassium-binding region of the pump. Potassium-competitive acid blockers (PCABs) are lipophilic weak bases with high pKa values and stable at low pH. PCABs with a pKa of 6 would theoretically be expected to be 100,000-fold higher in the acid space of the parietal cell than in the plasma. On entering the acidic

space, PCABs are instantly protonated and compete for the potassium-binding site of the pump, resulting in more rapid and stronger acid inhibition compared to drPPIs. Because of these characteristics, PCABs were considered superior for on-demand therapy. Unfortunately, superiority to drPPIs (esomeprazole) with AZD0865 could not be seen, neither in erosive-, nor in non-erosive GERD.[12,13] In addition, transient, dose-related rise in transaminases was observed. It is currently impossible to predict whether this class of drugs will ever become available for clinical use.

Gastrin (CCK2) Antagonists

Gastrin is a major endocrine regulator of acid secretion, thought to be responsible for up to 90% of postprandial acid secretion. Gastrin receptors are identical to CCK2-receptors, present on parietal and enterochromaffin-like cells. Selective CCK2-receptor antagonists offer a potential approach to regulate acid production. Compounds like itriglumide have been shown to inhibit gastrin-stimulated acid secretion in a dose dependent manner. Theoretically, CCK2 receptor antagonist could antagonize the effects of drPPI-induced hypergastrinemia on parietal and ECL-cell hyperplasia.[14] Whether CCK2-receptor antagonists will ultimately become available for the treatment of acid and gastrin-related disorders is uncertain at present.

CONCLUSION

Obviously the synthesis of drPPIs has been a major breakthrough in the treatment of acid related disorders. Yet over the years limitations and shortcomings were recognized, justifying the search for novel possibilities for full control of acid secretion. Several of those novel pathways were alluded above. Unfortunately progress has been slow and often disappointing and frustrating. This explains to some extent the catastrophic and rapid lost of interest of the biopharmaceutical industry for acid related disorders and gastroenterology in general. The impact of acid related disorders in clinical medicine is substantial and will in all probability increase worldwide this by itself justifies more interest from the biomedical industry. Hopefully some of the new avenues will mature and ultimately become clinically available for improved care of the gastrointestinal patients.

REFERENCES

1. Schubert ML, Peuro DA. Control of gastric acid secretion in health and disease. Gastroenterology 2008;134:1842-60.
2. Scarpignato C, Pelosini I, Di Mario F. Acid suppression therapy: where do we go from here? Dig Dis 2006;24:11-46.
3. Hunt RH. The unmet needs in delayed-release proton pump inhibitor therapy in 2005. Aliment Pharmacol Ther 2005;22 (suppl 3):10-19.
4. Castell D, Bagin R, Goldlust B, Major J, Hepburn B. Comparison of the effects of immediate release omeprazole powder for oral suspension and pantoprazole delayed-release tablets on nocturnal acid breakthrough in patients with symptomatic gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2005;21:1467-74.
5. Katz PO. Putting immediate-release proton-pump inhibitors into clinical practice-improving nocturnal acid control and avoiding the possible complications of excessive acid exposure. Aliment Pharmacol Ther 2005;22 (suppl 3):31-8.
6. Katz PO, Koch FK, Ballard ED, Bagin RG, Gautille TC, Checani GC, et al. Comparison of the effects of immediate-release omeprazole oral suspension, delayed-release lansoprazle capsules and delayed-release esomeprazole capsules on nocturnal gastric acidity after bedtime dosing in patients with night-time GERD symptoms. Aliment Pharmacol Ther 2007;25:197-205.
7. Hunt RH, YuanY, Yaghoobi M. GERD: new strategies and new failures. J Clin Gastroenterol 2007;25:197-205.
8. Sharma P, Shaheen NJ, Perez MC, Pilmer B, Lee M, Peura Da. TAK-390MR, a proton pump inhibitor (PPI) with a novel dual delayed release (DDR) formulation is highly effective in the healing of erosive esophagitis. Gastroenterology 2008;134 (suppl 1):A-171.
9. Metz DC, Howden CW, Perez MC, Larsen LM, O'Neil JM. TAK-390MR, a proton pump inhibitor (PPI) with a novel dual delayed release (DDR) formulation maintains healing and controls heartburn in GERD patients with healed erosive esophagitis. Gastroenterology 2008;134 (suppl 1):A-171.
10. Kahrilas PJ, Dent J, Luritsen K, Malfertheiner P, Denison H, Franzén S, et al. A randomized, comparative study of three doses of AZD0865 and esomeprazole for healing of reflux esophagitis. Clin Gastroent Hepatol 2007;5:1385-91.
11. Dent J, Kahrilas PJ, Hatlebakk J, Vakil N, Denison H, Franzen S, et al. A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with non-erosive reflux disease. Am J Gastroenterol 2008;103:20-6.
12. Galmische JP, Des Varanes BS, Ducrotte P, Sacher-Havelin S, Vavasseur F, Taccoens A, et al. Tenatoprazole, a novel proton pump inhibitor with a prolonged half-life: effects on intragastric pH and comparison with esomaprazole in healthy volunteers. Aliment Pharmacol Ther 2004;19:655-62.
13. Yuan Y, Chen Y, Hunt RH. Dose-effect of S-tenatoprazole–Na in healthy volunteers: a meta-analysis of individual subject data from four pharmacodinamic studies. Gastroenterology 2008;134 (suppl 1):S1093.
14. Lehmann FS, Hildebrand P, Beglinger C. New molecular targets for treatment of peptic ulcer disease. Drugs 2003;63:1785-97.

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