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EDITORIAL

Potassium-Competitive Acid Blockers (P-CABs): Are They Finally Ready for Prime Time in Acid-Related Disease?

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The need for new acid suppressing agents with improved pharmacology and superior antisecretory effects to address unmet clinical needs in acid-related disorders has been evident for over a decade. Recent new antisecretory drugs (IR-omeprazole and MR-dexlansoprazole) only provide a small incremental advance in control of acid secretion over the delayed-release proton pump inhibitors. Vonoprazan (a new potassium-competitive acid blocker) displays more potent and extended 24 h acid suppression and preliminary Japanese trials translate this into meaningful clinical benefits in gastro-esophageal reflux disease and *Helicobacter pylori* eradication. We review the vonoprazan information to date and the indications, benefits, and concerns of more effective therapeutic control of acid secretion.
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The need for new acid suppressing drugs with improved pharmacology and superior antisecretory effects has been clear for more than a decade, as evidenced by papers addressing unmet needs in acid-related disorders.[1–4] These unmet needs initially focused on non-erosive reflux disease (NERD), severe grades of erosive esophagitis, extra-esophageal reflux disease, non-*Helicobacter pylori,* non-steroidal antiinflammatory drug (NSAID) ulcer, but also included non-variceal upper gastrointestinal (GI) bleeding, the prevention of stress-related mucosal bleeding and the potential to improve and simplify *H. pylori* eradication treatment. All these conditions continue to reflect significant challenges in clinical practice.[1,2,5]

Some of these issues have been clarified by a better understanding of the definitions of gastro-esophageal reflux disease (GERD), NERD, and functional heartburn (FH).[6,7] The Montreal GERD Workshop and the Vevey NERD Task Force concluded that intra-esophageal acidity was not a factor in FH and that proton pump inhibitors (PPIs) are not indicated. However, the role of weakly acidic reflux in generating or perpetuating symptoms in patients with reflux disease remains a challenge, especially in patients who have a partial response to antisecretory treatments.[8] The clinical effectiveness of the PPIs is related to the degree and duration of acid suppression[9,10] but the threshold of pH 4 only explains the effectiveness of antisecretory drugs in healing esophagitis and does not provide us with information about symptom resolution or whether a holding time above pH 6, for example, would produce superior results for healing.[11] However, our experience with a model, based on extensive antisecretory and healing data over more than 25 years and now re-analyzed with recent dexlansoprazole results, supports that this will be the case.[12]

Patients with heartburn and reflux disease present the greatest burden of clinical problems resulting from the pharmacological limitations of current delayed-release PPIs (DR-PPIs). In about two thirds of symptomatic GERD patients, reflux symptoms are not adequately controlled after the first dose of a PPI, and nearly 50% of patients still suffer symptoms 3 days later.[13] Indeed, persistence of symptoms, only partial relief from prescribed treatment, late evening symptoms or nighttime symptoms with sleep disturbance are an increasing problem.[14] More than 50% of patients taking a PPI are dissatisfied with treatment[15] and $>20\%$ are taking their PPI twice daily or purchasing OTC heartburn treatments in addition to their prescription medicine.[14]

Most of these clinical limitations of DR-PPI treatment are due to pharmacological shortcomings that are common to them all. The pharmacology has been detailed,[11,16–20] including the short plasma residence time and consequent short duration of antisecretory effect, due to the synthesis of new proton pumps; and, importantly, the need to take these drugs 30–60 min before a meal to activate the acid pumps and to achieve optimal acid antisecretory effect. Taking PPIs before breakfast, rather than without food is important advice, which should be reiterated to any GERD patient, whose symptoms are apparently refractory to PPI therapy. Continuous daily, oral administration of the DR-PPIs is required to gradually increase the inhibition of proton pumps, with optimal, steady-state acid inhibition usually reached after 3–5 days of daily dosing. This phenomenon is clinically relevant and explains the slow onset of action of PPIs in GERD in general, and heartburn relief in particular, making DR-PPIs

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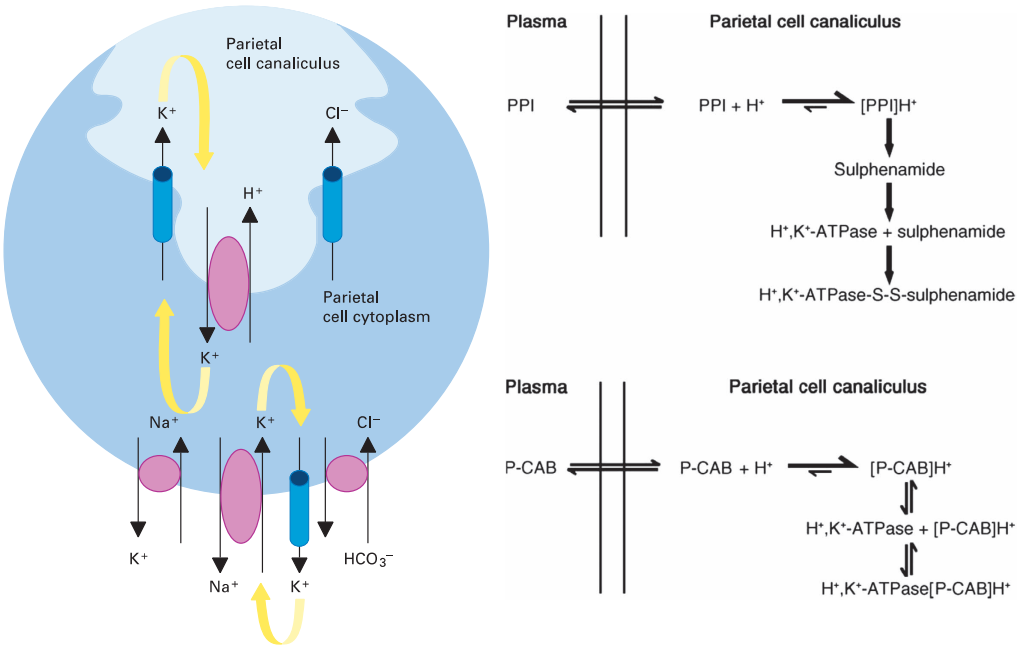

Figure 1 Role of K^+ in the H^+, K^+, ATPase functioning, and potassium-competitive interaction of P-CABs with the proton pump. For details see Scarpignato *et al.*[23] Left Panel: although it can also be activated by $NH4^+$ *in vitro*, the proton pump is highly selective for K^+. In common with many other cells, the level of K^+ in the parietal cell is higher than that in the plasma. The higher intracellular K^+ level is dependent on H^+, K^+-ATPase. This enzyme, located on the basolateral membrane of the cell, exchanges intracellular H^+ for extracellular K^+. The level of K^+ within the cell is also regulated by K^+ channels, which allow ion movement across the basolateral membrane. These channels have a particularly important role in generating negative cell membrane potential. Given the importance of the cation for enzyme function, agents that compete with the binding of K^+ are able to block acid secretion. P-CABs inhibit H^+, K^+ -ATPase by binding ionically to the enzyme and thus prevent its activation by the K^+ cation. As these molecules are larger than K^+, it is likely that they compete by preventing the access of the cation to its binding site rather than occupying the ion-binding site directly. Conversely from PPIs, P-CABs block gastric H^+, K^+-ATPase by reversible and K^+-competitive ionic binding. Right Panel: PPIs are pro-drugs, which are weak bases that concentrate in the parietal cell canaliculus, where they undergo a proton-catalyzed, three-step process to generate the active sulfenamide. This moiety interacts covalently with sulfhydryl groups on cysteine residues in the transmembrane domains of the gastric H^+, K^+-ATPase and thereby inhibits the enzyme. Since a P-CAB concentrates in the parietal cell canaliculi, it is instantaneously protonated. It then binds ionically to the gastric H^+, K^+-ATPase and inhibits acid secretion. P-CAB, Potassium-Competitive Acid Blocker; PPIs, proton pump inhibitors.

inappropriate for the treatment of breakthrough symptoms and less suitable for on-demand maintenance therapy.

Over the past decade many new drugs or alternative formulations of existing drugs have been investigated but only two new drugs, instant release omeprazole (i.e., IR-omeprazole) and modified release dexlansoprazole (MR-dexlansoprazole) have been introduced in some countries. These new drugs represent a measurable but small incremental advance in the pharmacological control of acid secretion over the DR-PPIs[21,22] but fall short of achieving the pharmacologic profile, which has been considered desirable to control acidity in those with the more complex clinical problems.[11,23]

A more innovative approach has been the development of a new class of H^+, K^+, ATPase blockers, called Potassium-Competitive Acid Blockers (P-CABs). Contrary to the classic PPIs, P-CABs result in a very fast, competitive, reversible inhibition of proton pumps. Experimental and clinical pharmacological investigations have confirmed the fast, very-effective (and reversible) blockade of acid secretion induced by this class of drugs[17,22] (Figure 1). It is evident that a P-CAB offers a more rapid elevation of intragastric pH than a PPI, while maintaining the same degree of antisecretory effect, the duration of which is dependent on half-life and can easily be prolonged by extended release formulations. Whether these favorable pharmacodynamic properties will translate into clinical benefits has yet to be confirmed. Indeed, the first marketed P-CAB (YH1885 or revaprazan), currently available only in South Korea and India, was reported to give healing rates in both duodenal[24] and gastric[25] ulcer, which were not significantly different from those seen with omeprazole. Similarly, large, randomized, controlled clinical trials did not show superiority of another P-CAB (namely AZD0865 or linaprazan) over a standard dose of esomeprazole, in terms of healing[26] or symptom relief.[27] However, the P-CAB dose used and the design of these studies were not appropriate considering that the short half-life of linaprazan called for multiple daily dosing. This contributed to the conclusion that the P-CAB class was a promise unfulfilled. Furthermore, linaprazan was associated with transaminase elevation and development was stopped, as was the case with several other P-CABs (e.g., soraprazan, CS526, and YH4808).

In this issue of *Clinical and Translational Gastroenterology*, Sakurai *et al.*[28] from the Takeda Pharmaceutical Company present their initial experience with vonoprazan (also known as TAK-438), a novel and potent orally active P-CAB. In two independent dose-escalation studies, one in Japan in healthy male volunteers and the other in the UK in Caucasian healthy male volunteers, vonoprazan demonstrated almost linear pharmacokinetics and dose-dependent acid inhibition, which appeared similar in each of the studies with $pH > 4$ for 92% of the 24 h in the Japanese subjects and 87% in the UK subjects. Nighttime acid suppression also increased in

a dose-dependent manner. Holding time above pH > 4 and pH > 5 after the vonoprazan 40 mg dose were 100% and 99%, respectively, 12–24 h post dose in the Japanese study and 90% and 79%, respectively, from 20:00 to 08:00 in the UK study. The increase in pH was reflected by a simultaneous increase in serum gastrin and pepsinogen I concentrations. The drug was well tolerated at all doses tested, with no changes in serum transaminase levels. According to a recently published study,[29] these pharmacological effects persist with repeated administration and, after 7 days of treatment, the mean 24-h intragastric pH > 4 holding time with vonozapran 40 mg was 100% in Japanese subjects and 93.2% in UK volunteers, and mean nocturnal times spent at pH > 4 were 100% and 90.4%, respectively. Sakurai *et al.* detail the pharmacology of vonoprazan and demonstrate effective acid suppression, but it is unfortunate that their manuscript did not translate these benefits to the drug's important clinical potential.

In acid-related disorders, mucosal healing is directly related to the degree and duration of acid suppression and the length of treatment.[9,10] Considering the difficulties encountered in attaining effective symptomatic control, particularly at night, using currently available DR-PPIs once daily, newer agents that can achieve rapid, potent, and prolonged acid suppression may be able to address the unmet clinical needs.[23]

These initial results pose the question, *Will the more powerful and extended acid suppression, achieved by vonoprazan, translate into a meaningful clinical benefit?* Available data, albeit so far, only in Japanese patients, suggest that this is the case. The healing rate after 2 week treatment with vonoprazan (20 mg once daily, 90.7%) was significantly higher than with lansoprazole (30 mg once daily, 81.9%). Moreover, in patients with more severe esophageal lesions (Los Angeles Grade C/D disease), the healing rates were 98.7% vs. 87.5%, for vonoprazan and lansoprazole, respectively.[30] In a maintenance trial, esophagitis recurrence rates at week 24 were 5.1, 2.0, and 16.8%, with vonoprozan 10 mg, 20 mg, or lansoprazole 30 mg, respectively. In patients with baseline grade C/D disease, the recurrence rates were 13.2, 4.7, and. 39.0%, respectively.[31]

The benefits of this prolonged acid suppression also extend to *H. pylori* eradication, where the control of intragastric pH, especially during the night, is crucial.[32,33] Confirmation of the importance of profound and long-lasting acid suppression for *H. pylori* eradication is illustrated by two studies showing a significantly higher intragastric pH and lower percentage time spent at pH < 4 in patients successfully cured of infection vs. those in whom infection persisted.[34,35] Furthermore, the eradication rate was higher in nocturnal acid breakthrough-negative than in nocturnal acid breakthrough-positive patients.[34] Vonoprazan-based triple therapy (with amoxicillin and clarithromycin) was superior to the same lansoprazole-based treatment (92.6% vs. 75.9%, $P < 0.0001$), a difference that increased (82.0% vs. 40.0%, $P < 0.0001$) in patients with clarithromycin resistance.[36] In those patients, in whom the first line eradication therapy failed, a triple therapy with vonozopran, amoxicillin, and metronidazole achieved a 98% cure rate.[36]

NSAID-gastropathy is a pH-dependent phenomenon: the higher the intragastric pH, the lower the extent and severity, as well as the probability, of mucosal damage.[37] Most NSAIDs are taken more than once daily, or are available as "sustained release" formulations to provide 24 h benefit. In addition, some compounds (e.g., naproxen) undergo enterohepatic circulation, further extending GI exposure. As a result, patients who take an existing DR-PPI once daily will have residual acid secretion during the 24-hour period and will continue to be at risk of GI injury from their NSAID therapy.[37] A once daily antisecretory drug with a true 24-hour acid suppression effect from once-daily therapy would be expected to display an improved mucosal protection and clinical trial data with vonoprazan in the primary prevention of NSAID ulcers are awaited with interest. Similarly, a sustained intragastric pH > 6, to promote platelet aggregation, clot formation, and stability,[38] should be of benefit in upper GI bleeding. The pharmacodynamic properties of oral vonoprazan would be expected to achieve the same (or even better) outcomes to those obtained with intravenous PPIs.

So do we need a new antisecretory drug and if so, how might it be used and what concerns should we consider? Vonoprazan is already available in Japan although not yet in Europe or North America where several identifiable unmet needs continue to present challenging and costly clinical management decisions. These are seen especially in patients with GERD where the choice of a treatment with rapid onset and sustained antisecretory effect would be particularly advantageous.[1–4,23] The profile presented here for vonoprazan, will advance the therapeutic choice for more effective management by clinicians who have been held hostage for almost a quarter of a century to the "one drug (class) fits all" treatment protocol of the DR-PPIs. Vonoprazan provides a more potent and longer acting antisecretory drug choice but not all patients with ARDs, such as those with simple heartburn, will require this drug as first line (either alone or in combination with other drugs with a different mechanism of action). However, the 20% or so of reflux patients with persistent or troublesome symptoms late in the day or at night will be among the thankful beneficiaries of a P-CAB with this profile. Furthermore, the prospects for improving *H. pylori* eradication therapy are exciting and the results reported here increase the possibility of effective and simple dual therapy.[39–41] The large number of patients who continue to be at risk of upper GI complications from aspirin and NSAIDs,[23,37] and those with non-variceal upper GI bleeding[23,38] are all likely to benefit from clinicians having a real choice for treating the most problematic acid-related complications.

The introduction of any new drug is dependent on responsible marketing in support of thoughtful prescribing and careful observation of all patients treated, which must be the standard of care. The safety profile of vonoprazan to date has been excellent but overuse and misuse may always challenge the safety profile of a new drug. Looking forward, adverse events related to a marked and long-lasting acid suppression are to be expected.[42] Our experience with the H_2-receptor antagonists and the PPIs confirm that these are related to the degree and duration of acid suppression rather than drug or dose and include some undesirable effects (e.g., occurrence of fundic polyps, infectious consequences, need to taper the dose when ending long-term treatment etc.).[42–45] Specific PPI related adverse events are unlikely, due to the

different drug (PPI and P-CAB) class and molecular structure of vonoprazan. As adverse events related to the antisecretory effect are still likely to be present and exaggerated, the indications for treatment with this drug should be in keeping with difficult to treat acid-related disorders identified as unmet needs. Then we expect the benefit to risk ratio will be most favorable.[46] It is hoped that vonoprazan will be fully evaluated in Europe and North America where our choice of antisecretory treatments remains limited. However, every time a promising new drug appears on the horizon, critical evaluation is needed to ascertain whether it is effective and safe and whether it is really superior to currently available treatments. Only then will this new medication find its place, and appropriate level of use, in our therapeutic armamentarium.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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