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Editorial: control of acid secretion

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In a recent edition of AP&T, Sunwoo and colleagues published the results of a phase 1 study of DWP14012, a new potassium-competitive acid blocker (P-CAB) (1). The advent of the P-CABs marks the latest development in our ability to control gastric acid secretion.

The dawn of the 20th century began with the statement “No acid, no ulcer” (2) heralding massive efforts to control acid secretion by the stomach since peptic ulcer was then a major cause of morbidity and mortality. Surgical approaches were reasonably successful, starting with vagotomy (3).

There were no well tolerated drugs available until the work of Black and colleagues who developed the first H_2-receptor antagonist (H_2RA), burimamide (4), which was modified to generate cimetidine, the first marketed medical therapy for peptic ulcer disease. Although the H_2RAs revolutionised the medical treatment of peptic ulcer disease, they all showed tolerance where their efficacy dropped by 50% after 1 week’s treatment.

Serendipitously, a compound, timoprazole was found to be a potent inhibitor of gastric acid secretion although it affected the thyroid and the thymus. A modification of this to omeprazole (4-methoxy-3,5-dimethylpyridyl, 5-methoxybenzimidazole) ablated the thyroid and thymus effects, and was the first proton pump inhibitor (PPI) (5).

All the PPIs are weak bases with a pyridine pKa between 4 and 5 and thus accumulate in the luminal compartment of the parietal cell’s secretory canaliculus. The benzimidazole N has a pKa of ~1 and is protonated only at the pH of the active gastric acid pump, converting the sulfinyl moiety to a sulfenic acid or a sulfenamide (6) allowing covalent reaction with cysteine 813 in the proton channel of the α-subunit of the gastric H, K ATPase. However, the short half-life (60–90 minutes) allows gastric pH to drop to about 3.0 at night time even at twice-daily dosing. A pH of 3.0 prevents growth of *H. pylori* and generates resistance to amoxicillin that requires growth for bactericidal efficacy (7).

In 1983, Schering-Plough synthesised SCH28080. This was a potassium-competitive antagonist of the gastric H, K ATPase with a short duration of action, but some hepatotoxicity (8). This compound was the first Figure 1). Subsequent compounds had a short duration of action and never reached market until Takeda introduced vonoprazan (1-[5-(2-fluorophenyl)-1-pyridine-3-ylsulfonyl pyrrol-3-yl] N methyl methanamine fumarate), which had a long duration of action and showed excellent efficacy at treating GERD and, in combination with antibiotics, eradication of *H. pylori* (9). Analysis of the crystal structure of

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the gastric H, K ATPase with bound vonoprazan (10) showed that the methylmethaneamine moiety (pKa 9.4) bound at glutamine 343, the potassium-binding site of the pump.

Currently, a homolog of vonoprazan, DWP14012 (1-(5-2,1-4-difluorophenyl)-1-3-((3-fluorophenyl)sulfonyl)-4-methoxy-1H-pyrrol -3-yl)-N-methylmethanamine hydrochloride) is being developed in Korea (1). This compound has remarkably similar properties to vonoprazan; it is potassium-competitive with a long duration of action (the pyridine is replaced by a fluorophenyl) and promises a successful launch.

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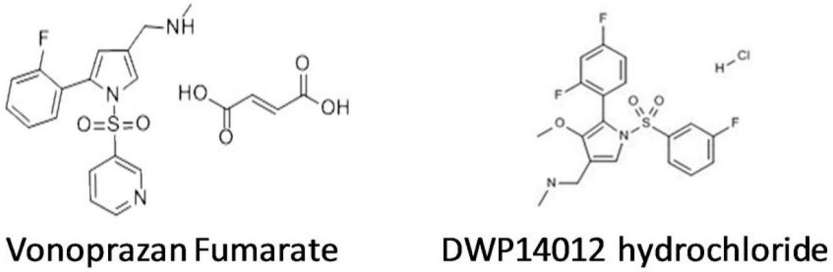

Figure 1.

Structures of vonoprazan fumarate and DWP14012 hydrochloride. The benefits of these two P-CABs are predicted to be: (1) Elevation of pH to >5.0, 24 hours from a single dose; (2) Improved treatment of acid-related diseases; (3) Eradication of *H. pylori* in combination with amoxicillin only; (4) Immediate onset of action; (5) No requirement for enteric coating; (6) Meal independence; (7) Easy solution formulation. A dose of 40 mg once a day would maintain a pH >5.0 for 24 hours per day.