Inhibition of gastric acid secretion by different mechanisms of action in the conscious gastric fistula rat

Jill Darton, Sarah Hadingham, Julia Smith, Peter McLean, Kevin Lee

GlaxoSmithKline, Harlow, Herts, UK

The short acting H2-receptor antagonist (H2RA), Ranitidine, is commonly used in the treatment of gastrointestinal reflux disease (GERD) which affects 10-14% of the western population (Williams et al., 2007). Ranitidine has efficacy coupled with a relatively short duration of action. Potassium-competitive acid blockers (also known as acid pump antagonists, APAs) and long-acting H2RA have the potential to offer an improvement in the duration of action (Scarpignato et al., 2006). The aim of these studies was to compare the different mechanisms of action with respect to efficacy and duration of action of APAs (GSK1007066A) and H2RAs, comparing the competitive-H2RA (Ranitidine) with a long acting H2RA (Lavoltidine) in a conscious gastric fistula rat model.

Experiments were performed on male CD rats (Charles River: 300-325g) that had previously been chronically implanted with a titanium gastric cannula; with an external jugular vein cannulated for i.v. administration of pentagastrin (PTG), test compounds and/or vehicle. The surgically prepared rats were fasted overnight on grid-bottomed cages. On the morning of the experiment, rats were gently restrained in Bollman cages, the cap removed from the fistula and the stomach washed with warm water to remove residual debris. The fistula was recapped and the rats were allowed a ‘resting’ period prior to the start of the collection period. Gastric samples were collected every 30 minutes throughout the experiment (5 hours). Two basal secretions were collected prior to the start of continuous intravenous PTG infusion (8ug/kg/hr) to stimulate gastric acid secretion. Gastric secretions were collected for 150 minutes prior to iv administration of the test compound and/or vehicle. The gastric acidity of each sample (total acid output µEqH+/30min) was determined using an autotitrator. Data are presented as mean ± standard error and tested for statistical significance using repeated measures ANOVA test.

Ranitidine (1 or 5mg/kg i.v.) failed to achieve a prolonged suppression of acid secretion, with maximum suppression of 67% and 88% post-dose respectively. Lavoltidine (0.03, 0.1 and 1mg/kg i.v.) produced a suppression of acid secretion of 95%, 95% and 23% post-dose respectively. At 3.5h post-dose, there was a significant suppression of acid secretion at 0.1 and 1mg/kg i.v. Similarly, GSK1007066A (0.3 and 1mg/kg i.v.) produced a significant and sustained suppression of acid secretion of 98% and 96% post-dose respectively and this suppression was maintained at 3.5h post-dose.

This study demonstrated that each compound displayed a rapid onset of acid suppression, regardless of mechanism of action. These data suggest that development of either a long acting H2RA or an APA could have the potential to improve treatment for gastro-oesophageal reflux disease.
