Commentary

Co-prescription of alginate based formulations & proton pump inhibitors (PPIs) in gastro-oesophageal reflux disease: time for rethink?

Therapeutic modalities for gastro-oesophageal reflux disease (GERD) continue to evolve despite the widespread use of proton pump inhibitors (PPIs), the most successful antireflux class of drugs. Systematic reviews for the Cochrane collaboration have confirmed that PPIs are more effective than \( \text{H}_2 \) receptor antagonists at healing oesophagitis and maintaining remission from mucosal injury and symptoms. Nevertheless, the persistence of reflux symptoms in a minority of patients receiving such therapy is a major problem in clinical practice. On demand, modalities such as antacids and alginates as well as histamine type-2-receptor antagonists continue to be popular with GERD patients who seek temporary relief of symptoms. Antacids and combined antacid-alginic acid preparations have been shown to be more effective than placebo in relieving GERD symptoms, based on measures such as lower global symptom scores, less acid regurgitation and fewer days and nights with heartburn. Alginate-based raft-forming formulations appear to act by a unique mechanism which differs from that of traditional antacids. In the presence of gastric acid, alginates precipitate, forming a gel. Alginate-based raft-forming formulations usually contain sodium or potassium bicarbonate; in the presence of gastric acid, the bicarbonate is converted to carbon dioxide which becomes entrapped within the gel precipitate, converting it into a foam which floats on the surface of the gastric contents, much like a raft on water.

Both in vitro and in vivo studies have demonstrated that alginate-based rafts can entrap carbon dioxide, as well as antacid components contained in some formulations, thus providing a relatively pH-neutral barrier. Several studies have demonstrated that the alginate raft can preferentially move into the oesophagus in place, or ahead, of acidic gastric contents during episodes of gastro-oesophageal reflux; some studies further suggest that the raft can act as a physical barrier to reduce reflux episodes. A significant number of patients take PPIs along with alginate containing antacid preparations to improve symptom control.

There is limited pharmacokinetic information regarding possible drug interaction between PPIs and alginate-based preparations. Evidence on the effect of antacids on omeprazole bioavailability is conflicting. In this issue, study done by Dettmar and colleagues to determine whether the administration of a 10 per cent w/v liquid alginate suspension affected the pharmacokinetic profile of omeprazole is reported. The study was a randomized, two-treatment, two-period, cross-over, multiple-dose pharmacokinetic study of the 20 mg omeprazole tablet (Losec® MUPS tablets) in the presence and absence of the 10 per cent liquid alginate suspension (Gaviscon Advance®). Subjects were randomly allocated to the two treatment order groups. Both treatment periods were of 3 days duration, an adequate period of time for omeprazole to reach peak
plasma concentrations. Subjects received one treatment in the first period of the study, followed by a washout period for omeprazole of 7 days before starting the other treatment in the second period. Standard pharmacokinetic parameters like $C_{\text{max}}$, $\text{AUC}_{\text{0-t}}$, and $\text{AUC}_{\text{0-\alpha}}$ were determined in both the groups. The 90 per cent confidence intervals formed the basis for assessing the equivalence of the treatments. If the point estimates of the ratios and the confidence intervals were entirely included in the range 80-125 per cent, then the treatments would be decided to be equivalent, otherwise the two treatments would be assumed to be non-equivalent.

Dettmer and coworkers found that the 90 per cent confidence intervals for $C_{\text{max}}$, $\text{AUC}_{\text{0-t}}$, and $\text{AUC}_{\text{0-\alpha}}$ are all contained within the bioequivalence interval of 80-125 per cent. These results show that the administration of Gaviscon Advance® has no effect on the plasma level curve and that it therefore does not add to the effect of the meal on omeprazole absorption from MUPS tablets.

The authors have not studied drug metabolizing enzyme polymorphisms in this pharmacokinetic study. There are several studies which now look at ethnic variations in drug metabolism in order to delineate dosing patterns and response characteristics. CYP2C19 drug metabolizing enzyme catalyzes the biotransformation of many clinically useful drugs including proton pump inhibitors. Individuals who possess CYP2C19 poor metabolizer (PM) variants may exhibit different pharmacokinetics (drug levels) than normal individuals. The prevalence of PMs was reported to be 2-5 per cent in Caucasians, 4-8 per cent in Africans, 29.7 per cent in North Indians and 14 per cent in South Indians. Systemic exposure to the proton pump inhibitors as expressed by the AUC (area under the plasma level time profiles) is 5-12-times higher in poor metabolizers than in extensive metabolizers. As the pharmacodynamic response (elevation of intragastric $pH$) to the proton pump inhibitors is related directly to their AUC, a much higher $pH$ can be maintained over 24 h in poor metabolizers than in extensive metabolizers. Further, clinical efficacy of all proton pump inhibitors depend on maintained intragastric $pH$ above certain threshold levels and significantly higher eradication rates of Helicobacter pylori have been observed in patients with poor metabolizers and heterozygous extensive metabolizers phenotype when compared to extensive metabolizers. Likewise, limited data suggest that proton pump inhibitors-induced healing rates in gastro-oesophageal reflux disease are apparently higher in poor metabolizers/heterozygous extensive metabolizers than in extensive metabolizers of CYP2C19. Therefore, initial genotyping for CYP2C19 and higher dosage in extensive metabolizers may improve the clinical efficacy of proton pump inhibitors and this needs further studies. Given the pharmacogenetic importance, the sample size would have to be larger in order to bring out these differences.

The current guidelines provided by the National Institute for Health and Clinical Excellence says that if reflux symptoms fail to respond to full dose of acid suppression by PPI given for a month, then investigations must be carried out to confirm the diagnosis of GERD. Options for treatment of non-acid reflux include increasing the dose of PPIs, adding $H_2$ receptor antagonist, alginate preparations or prokinetic drugs. The unique non-systemic mechanism of action of alginate-based preparations have ensured that they are co-prescribed along with PPIs and $H_2$ receptor antagonist in clinical practice. As raft formation occurs rapidly, often within a few seconds of dosing, alginate-containing antacids are comparable to traditional antacids for speed of onset of relief. Retention of the raft in the stomach for several hours additionally provides longer-
lasting relief with alginate-based formulations as compared to traditional antacids. The strength of the alginate raft is dependant on several factors, including the amount of carbon dioxide generated and entrapped in the raft, the molecular properties of the alginate, and the presence of aluminium or calcium in the antacid components of the formulation.

This pharmacokinetic study done in volunteers has brought out useful information regarding lack of any pharmacokinetic interaction when PPIs are co-prescribed with alginate based preparations. In the current scenario when alginate-based raft-forming formulations are also used to treat reflux symptoms in infants and children and in management of heartburn and reflux during pregnancy, safety and tolerability of concomitant administration is of great clinical importance. Hence, while alginate based preparations are effective when used alone, it is compatible with, and does not interfere with the activity of proton pump inhibitors which remains the standard management for GERD. Even with the introduction of new antisecretory and promotility agents, alginate-rafting formulations will continue to have a role in providing rapid and long-duration relief of heartburn and acid reflux symptoms.

S. Davis & N.A. Kshirsagar*
Department of Clinical Pharmacology
Seth G.S. Medical College & KEM Hospital
Parel, Mumbai 400012, India
*e-mail: dcpkem@vsnl.com

References

