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Esomeprazole Pharmacokinetics and Gastrin Rise in Healthy Males and Females after Single and Repeated Oral Doses

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Abstract

Olsalazine is a typical 5-aminosalicylic acid (5-ASA) drug that depends on gut microbiota to liberate its anti-inflammatory moiety 5-ASA in the treatment of ulcerative colitis (UC). In recent decades, 5-ASA drugs combined with probiotics have achieved a better effective treatment for UC. Mechanisms of combination therapy have been widely discussed from a pharmacodynamics perspective. However, it is still unclear whether the better therapeutic efficacy of combination therapy was made by changing the metabolism of 5-ASA drugs in the colon under the regulation of probiotics. In the present study, combined with pharmacokinetic and gut microbiota analyses, we systematically evaluated the potential effect of Lactobacillus acidophilus (L. acidophilus) on the metabolism of Olsalazine at three levels (pharmacokinetic characteristics, metabolic microbiota, and metabolic enzymes) to offer some insights into this issue. As pharmacokinetic results showed, L. acidophilus barely had an influence on the pharmacokinetic parameters of Olsalazine, 5-ASA, and N-Ac-5-ASA. Notably, the colonic exposure of 5-ASA was not affected by L. acidophilus. Gut microbiota results also illustrated that L. acidophilus did not change the total abundance of azoreductase (azoR) and N-acetyltransferase (NAT) associated gut microbiota and enzymes, which are involved in the metabolism of Olsalazine. Both pharmacokinetic and gut microbiota results revealed that L. acidophilus did not increase the colonic exposure of 5-ASA to improve the efficacy of combination therapy. L. acidophilus played its role in UC treatment by regulating gut microbiota composition and amino acid, phenolic acid, oligosaccharide, and peptidoglycan metabolic pathways. There was no potential medication risk of combination therapy of Olsalazine and L. acidophilus. In summary, this research provided strong evidence of medication safety and a comprehensive understanding of therapeutic advantages for combination therapy of probiotics and 5-ASA drugs from the pharmacokinetic and gut microbiota perspectives.

Introduction

Esomeprazole, a powerful proton pump inhibitor (PPI), is commonly used in intensive care unit (ICU) patients to prevent stress ulcers. The pharmacokinetics (PK) of esomeprazole in critically ill individuals is investigated in this study [1]. Adult ICU patients who received endotracheal intubation assisted mechanical breathing for more than 48 hours and had at least one additional risk factor for stress ulcers were included in the study. All of the patients were given 40 mg of esomeprazole intravenously (IV) once a day. Serial blood samples were taken at 3, 5, 15, 30 minutes, 1, 2, 4, 6, 8, and 10 hours after the first dosage of esomeprazole was given. UPLC-MS/MS was used to determine the total esomeprazole concentrations in the samples. Non compartmental analysis was used to examine the PK parameters of esomeprazole [2-4].

There were a total of 30 patients who could be evaluated. The average age and BMI were 61.97 years and 23.14 respectively. The following median (IQR) parameters were obtained from PK sampling on the first dose: MRT0 4.70 (3.89–5.51) h; t1/2 3.29 (2.7–3.87) h; V 24.89 (22.09–27.69) L; CL 6.13 (5.01–7.26) L/h; and C_{max} 2.56 (2.30–2.82) mg/L Our research found that ICU patients had different esomeprazole PK values than healthy volunteers, according to the drug's label. In critically ill patients, esomeprazole has unusual pharmacokinetic properties [5].

Review

The medications of choice for treating gastroesophageal reflux disease are proton-pump inhibitors (PPIs) (GERD). Esomeprazole is the most recent PPI, and it was created as the S-isomer of omeprazole to improve its pharmacokinetic features. Esomeprazole has been shown to have somewhat higher acid inhibition potency than other PPIs. Despite some debate, results from clinical studies and meta-analyses show that esomeprazole 40 mg od for up to 8 weeks resulted in higher rates of erosive GERD healing and a higher proportion of patients with prolonged heartburn relief than omeprazole 20 mg, lansoprazole 30 mg, or pantoprazole 40 mg od. In comparison to lansoprazole 15 mg od or pantoprazole 20 mg od, esomeprazole 20 mg od has been proven to be more successful in maintaining healing of erosive GERD [6-7]. It is unclear, however, whether these statistically significant changes are of important therapeutic significance. For the treatment of non-erosive reflux disease (NERD), esomeprazole 20 mg od is superior to placebo, however clinical trials have found no significant differences in efficacy between esomeprazole 20 mg and omeprazole 20 mg or pantoprazole 20 mg od. Finally, while esomeprazole treatment for GERD has been shown to improve health-related quality of life (QoL) indices, no clinical trials have looked into the prospective differences in QoL between different PPIs in GERD.

Gastrin increase has been widely established as a side effect of proton pump inhibitor (PPI) medication. Females on PPIs have much greater baseline gastrin levels than males, according to recent studies. The researchers wanted to look at the pharmacokinetics of esomeprazole and its short-term effect on serum gastrin levels, as well as see if there were any gender differences. For five days, healthy individuals were

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given 40 mg of esomeprazole. Blood samples for fasting gastrin and pharmacokinetic analyses were taken at scheduled time-points for eight hours after the first and fifth doses. Liquid chromatography was used to analyse esomeprazole, and radioimmunoassay was used to quantify gastrin concentrations [8].

Pharmacokinetic study and microbiota analyses

There were 30 volunteers in total. Females showed a greater baseline gastrin (pM) than males, with 12 (IQR 10–15) vs. 7 (IQR 4–11) (p = 0.03). Gastrin levels in the study cohort increased from 10 (IQR 6–14) to 15 (IQR 13–20) (p = 0.0002). From day 1 to day 5, esomeprazole serum levels increased by an average of 299.8 ng/mL (p.001)[9]. There were no significant sex-related differences in the pharmacokinetic characteristics of esomeprazole when males and females were compared. On day 5, there was no significant association between the AUC and the gastrin level (p = 0.15). After four days of PPI medication, serum gastrin levels in healthy participants increased considerably. From day 1 to day 5, serum esomeprazole levels increased significantly. There was no sex-related difference in gastrin and esomeprazole concentrations, and no significant sex-related variation in pharmacokinetic parameters [10].

In a two-part randomised crossover trial, eight healthy dogs were used to investigate the pharmacokinetic characteristics of esomeprazole following intravenous (IV) and oral (po) administration. The dogs were fasted for at least 12 hours before receiving esomeprazole intravenously (dose range 0.93–1.48 mg/kg) or orally (dose range 0.95–1.50 mg/kg). The dogs were given an alternative therapy after a one-week washout period. Plasma esomeprazole concentrations were measured using ultra-high-performance liquid chromatography–mass spectrometry after serial blood samples were taken at preset time points. Analyses of no compartmental pharmacokinetics were carried out. The area under the plasma concentration/time curve (AUC) and maximal plasma concentration (C_{max}) were then standardised to a 1.0 mg/kg esomeprazole dose, resulting in AUC/dose. For the IV and po formulations, the dose-normalized peak plasma concentration (C_{max}) values were 4.06 g/mL (2.47–4.57 g/mL) and 1.04 g/mL (0.31–1.91 g/mL), respectively. For the po formulation, the median (range) time to peak concentration (T_{max}) was 105 minutes (45–360 minutes). The IV formulation had a median (range) plasma terminal half-life (t12) of 45.56 minutes (39.43–64.20 minutes) while the enteric-coated po formulation had a median (range) plasma terminal half-life (t12) of 63.97 minutes (44.02–109.94 minutes). Po bioavailability was 63.33% (range 32.26%–79.77%) on average (range 32.26%–79.77%). Both the po and IV formulations were well tolerated in clinical trials, with few adverse effects reported.

Stability

The stabilities of Olsalazine, 5-ASA, and N-Ac-5-ASA under various conditions were presented. All stability data were within a ± 15.0% deviation range, suggesting that no significant stability-related problems occurred during routine sample analysis and sample storage.

Conclusion

In the present study, pharmacokinetic and gut microbiota analyses revealed the effect of L. acidophilus on the metabolism of Olsalazine from three levels. At the level of the pharmacokinetic characteristics, L. acidophilus barely had an influence on the pharmacokinetic parameters of Olsalazine, 5-ASA, and N-Ac-5-ASA. And most remarkably, the exposures of Olsalazine, 5-ASA, and N-Ac-5-ASA in plasma and feces were not affected by L. acidophilus. At the level of metabolic microbiota, L. acidophilus did not alter the total relative abundance of azoR and NAT-associated gut microbiota families, genera, and species. At the level of metabolic enzymes, L. acidophilus did not change the abundance of azoR and NAT-related enzymes. Our results have proved that L. acidophilus did not raise the colonic exposure of 5-ASA to achieve a better therapeutic efficacy of combination therapy for UC.

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