Responses to the editor’s and reviewer’s comments.

We thank the editor and reviewers for the review of our manuscript, along with the insightful comments. We have responded to each of the suggestions and incorporated all modifications noted by the reviewers in the revised manuscript.

Reviewer A:
This is an interesting study comparing the effect on the intragastric pH of
healthy adults of administering PPI alone versus PPI combined with a
gastric motility agent, mosapride, etiher simultaneously or with the
prokinetic preceding the PPI by an hour. The results of the study, while
small (n=12), clearly favour the combination of mosapride and PPI an hour
later, with an effect sustained for the observation period i.e. 6 hours
post-administration.

Major:The clinical relevance of this study needs clarification. What is
this study hoping to address? The introductory paragraph states that
modifying gastric acid is of interest in gastric acid-related diseases that
involve non-variceal upper GI bleeding, and that maintaining a higher pH
helps with homeostasis. There is no further mention of this indication
elsewhere in the paper; instead in the discussion section, the emphasis
shifts abruptly to symptom modification in GERD. There is a theoretical
utility of the mosapride-PPI combination in GI bleeding, where a higher
intragastric pH promotes homeostasis. In practice the study recommendations
are not easily translatable to clinical practice, when most major
guidelines (ASGE, ESGE, SIGN) include recommendations for IV (and not
oral) PPI when non-variceal GI bleeding is suspected, but not uniformly for
prokinetics (the only mention comes from ESGE, for IV erythromycin for
severe bleeding).If the discussion section i.e. emphasis on symptoms is a
better reflection of the overall aim of the study, then I would recommend
leaving out mention of GI bleeding entirely and rewrite the introduction.
Patient studies will then be critical in determining if this finding (of
achieving a higher pH faster) translates into quicker and more durable
symptom improvement, and this needs to be mentioned in the paper.

Thank you for your suggestion. We described in Introduction section as follow:

Recently the number of Japanese patients with gastroesophageal reflex disease (GERD) is increasing, because of the change in eating habits and the decrease in infection of Helicobacter pylori (H. pylori). Heartburn is a common problem in Japan and it interferes with daily life. Proton pump inhibitors (PPIs) are widely used globally for the treatment of acid related diseases such as GERD, gastric and duodenal ulcers and as a component of eradication therapy for H. pylori [1-4]. Although most GERD patients can be controlled with standard PPIs regimen, approximately 10-40% of patients have refractory symptoms yet (5). The ideal medication for treatment of acid related diseases should have a rapid onset of action to promote the symptoms.

On-demand therapy for patients with GERD is considered to be safe and cost-effective after they receive initial treatment with proton pump inhibitors [6,7]. Medication for on-demand treatment should have a rapid onset of action to ensure that the symptoms are controlled. Multiple agents, including antacids, histamine H2 receptor antagonists (H2RAs) and PPIs, are currently available [8].

Minor:The paper is intelligent and concise - almost too concise.The authors
assume a fair amount of knowledge on the readers' behalf, particularly in
terms of the significance of CYP2C19 genotyping. My guess is that this was
done to identify poor CYP2C19 metabolisers which may impact upon PPI
absorption. However this is not explained, and this may not be a well-known
fact outside of medical circles regularly seeing Asian or Japanese patient
populations in whom this phenomenon is more common. The reach of this paper
may be improved with more explanation of important technical points like
this.It would also be useful to have it spelled out clearly why mosapride
before PPI helps elevate the intragastric pH better - is this because the
increased rate of gastric emptying means that the (presumably acid-labile)
rabeprazole gets to work quicker if it leaves the stomach faster?I found the
figures confusing and I wondered if I was reading the labels and captions
correctly - I would very much appreciate the authors' clarification.
Otherwise the data is nicely presented.

Thank you for your suggestion. We described in Results section as follow:

CYP2C19 has the following alleles: wild-type, CYP2C19\*1, CYP2C19\*2 (G681A in exon 5), and CYP2C19\*3 (G636A in exon 4). CYP2C19 genotyping was determined by polymerase chain reaction and restriction fragment length polymorphism methods. This study subjects were classified into one of three genotype groups as follows: extensive metabolizer (EM: CYP2C19\*1/\*1), intermediate metabolizer (IM: CYP2C19\*1/\*2 and \*1/\*3), and poor metabolizer (PM: CYP2C19\*2/\*2, \*2/\*3, \*3/\*3).

Four subjects were genotyped as EM, five subjects were IM and the other three subjects were PM. No significant differences were observed between EM, IM and PM.

The prevalence of CYP2C19 genotype status differs among different races: prevalence of CYP2C19 EM is 56-69% in Caucasians, 81% in African-Americans, 27-35% in Japanese, 38% in Chinese and 13% in Koreans [11].

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Reviewer B:

The aim of this study is to compare the effect on gastric acid secretion
between rabeprazole given one hour after mosapride with rabeprazole alone.

This same group has already demonstrated that omeprazole administered one
hour after mosapride increases the intragastric pH more rapidly than
omeprazole alone. Is unknown whether administration of a PPI concomitantly
with mosapride  also increases the gastric pH more rapidly than PPI alone.

This study demonstrated that the average pH  during the 6 hours period
after the administration of the drugs is higher in the rabeprazole after
mosapride group compared to the concomitant rabeprazole +mosapride group.
 Nevertheless, the difference is only seen after 4 hours.

Methods:

Is it not mentioned the sample size calculation

Thank you for your suggestion.

Because this was an exploratory study, no formal sample-size calculation was performed.

It is not mentioned the precise location of the stomach electrode. By ph

drop? The ideal is to have it standardized with manometry localization of

the LOS.

Thank you for your suggestion. We described in Method section as follow:

The pH electrode was inserted transnasally under local anesthesia and was located to the body of the stomach.

There is not a direct comparison on the average pH between rabeprazole +

mosapride group and rabeprazole administered one hour after mosapride.

They compared both against rabeprazole but the face to face comparison is

the best indicator.

Thank you for your suggestion. We did direct comparison on the average pH between rabeprazole+mosapride group and rabeprazole administered one hour after mosapride. We described in Results section as follow:

And no significant differences were found between the average pH during the 6-hour period after the administration of rabeprazole with mosapride and rabeprazole one hour after mosapride (median: 3.81 versus 4.41, respectively; p = 0.116) (Fig. 1).

And We remade figure1, 2, and 3.

Discussion:

They assume that mosapride accelerates the absorption of rabeprazole but in

the discussion, it is pertinent to mention the ideal scenario would be to

measure the plasmatic concentration of rabeprazole in the different groups.

Thank you for your suggestion.

We didn’t measure the plasmatic concentration of rabeprazole. But, Arai K et al. measured the concentration of rabeprazole. Their study showed that the use of mosapride resulted in significant increases of mean C(max) and mean AUC of rabeprazole.

We described in Discussion section as follow:

Mosapride influence pharmacokinetics of rabeprazole. The use of mosapride resulted in significant increases of mean C(max) and mean AUC of rabeprazole [20].

They give examples on the effect of mosapride on the gastric emptying time

and on oral lavage solutions but they do not mention if mosapride or another

prokinetic accelerates the absorption of any drug.

Thank you for your suggestion. We described in Discussion section as follow:

Mosapride influence pharmacokinetics of rabeprazole. The use of mosapride resulted in significant increases of mean C(max) and mean AUC of rabeprazole [20].

We described in Discussion section as follow:

No reference is made of the CYP2C19 genotype and the implication for this

study.

Thank you for your suggestion. We described in Results section as follow:

CYP2C19 has the following alleles: wild-type, CYP2C19\*1, CYP2C19\*2 (G681A in exon 5), and CYP2C19\*3 (G636A in exon 4). CYP2C19 genotyping was determined by polymerase chain reaction and restriction fragment length polymorphism methods. This study subjects were classified into one of three genotype groups as follows: extensive metabolizer (EM: CYP2C19\*1/\*1), intermediate metabolizer (IM: CYP2C19\*1/\*2 and \*1/\*3), and poor metabolizer (PM: CYP2C19\*2/\*2, \*2/\*3, \*3/\*3).

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The prevalence of CYP2C19 genotype status differs among different races: prevalence of CYP2C19 EM is 56-69% in Caucasians, 81% in African-Americans, 27-35% in Japanese, 38% in Chinese and 13% in Koreans [11].

And we described reference.

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Editor's comments:

1. The summary box should be improved in order to be according to Journal's

guidelines (What is already known

about this subject: 3-4 bullet points What are the new findings: 3-4 bullet

points).

Thank you for your suggestion. We described in Summary box section as follow:

What is already known about this subject:

1. Oral administration of H2RA plus mosapride citrate increased the intragastric pH more rapidly than H2RA alone.

2. Omeprazole administered one hour after mosapride increased the intragastric pH more rapidly than omeprazole alone.

3. No study has yet examined whether administration of a PPI plus mosapride might also produce a more rapid increase of the intragastric pH than a PPI alone.

What are the new findings:

1. The average intragastric pH of healthy male subjects in the six hours after the administration of 20 mg rabeprazole one hour after the ingestion of 5 mg mosapride was significantly higher than that after the administration of 20 mg rabeprazole alone.

2. In contrast, no significant difference in the average pH was found when rabeprazole was administered simultaneously with mosapride and compared with rabeprazole alone.

3. Oral administration of 20 mg rabeprazole preceded by 5 mg mosapride tablets might be suitable for the on-demand treatment of patients with mild GERD.

2. The results on CYP2C19 genotype could be presented (preferably in a extra

table) and discussed in more detail.

Thank you for your suggestion. We presented table 1 of the results on CYP2C19.

And, we described in Results section as follow:

CYP2C19 has the following alleles: wild-type, CYP2C19\*1, CYP2C19\*2 (G681A in exon 5), and CYP2C19\*3 (G636A in exon 4). CYP2C19 genotyping was determined by polymerase chain reaction and restriction fragment length polymorphism methods. This study subjects were classified into one of three genotype groups as follows: extensive metabolizer (EM: CYP2C19\*1/\*1), intermediate metabolizer (IM: CYP2C19\*1/\*2 and \*1/\*3), and poor metabolizer (PM: CYP2C19\*2/\*2, \*2/\*3, \*3/\*3).

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The prevalence of CYP2C19 genotype status differs among different races: prevalence of CYP2C19 EM is 56-69% in Caucasians, 81% in African-Americans, 27-35% in Japanese, 38% in Chinese and 13% in Koreans [11].

And we described reference.