RESPONSES TO THE REVIEWERS

February 14, 2013

Title: An herbal medicine “Rikkunshito” improved globus sensation by stimulation of gastric emptying in patients with proton pump inhibitor-refractory laryngopharyngeal reflux
-Original article-

Author: Ryoji Tokashiki, Isaku Okamoto, Nobutoshi Funato, Mamoru Suzuki

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 1972

Dear Editor,

We have enclosed our revised manuscript, **“Rikkunshito improves globus sensation in patients with proton pump inhibitor-refractory laryngopharyngeal reflux”**, in Word format (1972-revise.doc), which we resubmit for your further consideration for publication as an original article in *World Journal of Gastroenterology*.

We revised our initial manuscript (ESPS Manuscript # 1972) according to the reviewers’ suggestions. We have updated the format of the manuscript, and we provide point-by-point responses to the comments of reviewer 2 in this letter. We have changed manuscript title (12 words) according to BPG’s revision policies for original article.

Thank you for the opportunity to resubmit our manuscript, and hope you will find it worthy of publication in *World Journal of Gastroenterology*.

Sincerely yours,

Ryoji Tokashiki

Department of Otolaryngology,
Tokyo Medical University,
6-7-1 Nishishinjuku, Shinkjyukuku, Tokyo
160-0023, Japan
FAX: +81-3-3346-9275
E-mail: tokachanman@yahoo.co.jp

Reviewer 02441737

In accordance with the reviewer’s suggestion, we have reconstructed Table 2 in the revised manuscript. Furthermore, we added information concerning the biochemical mechanisms of rikkunshito to the Discussion

section, as follows:

“Furthermore, rikkunshito and atractylodin enhance reactivity of the ghrelin receptor [23]. Nahata *et al*.[24] found an association between impaired ghrelin signaling and gastrointestinal motility dysfunction and demonstrated that rikkunshito restored gastrointestinal motility by improving the ghrelin response in rat GERD models.”

Reviewer 00051367

(1) The authors MUST describe what is this kind of medicine. A partial description is provided in the discussion, nevertheless at least in the method section a description of more relevant chemical ingredients and clinical effects should be provided.

Thank you for your comment. According to your suggestion, we added the following paragraph to the *Study procedures* under the Materials and Methods section.

“We used a powdered extract of rikkunshito (Tsumura & Co., Tokyo, Japan) obtained by spray drying a hot water extract mixture of the following eight crude herbs: *Atractylodis lanceae Rhizoma* (4.0 g), *Ginseng radix* (4.0 g), *Pinelliae tuber* (4.0 g), *Hoelen* (4.0 g), *Zizyphi fructus* (2.0 g), *Aurantii nobilis pericarpium* (2.0 g), *Glycyrrhizae radix* (1.0 g), and *Zingiberis rhizoma* (0.5 g).”

(2) Refractory is defined as symptoms persisting despite therapy with a standard dose of PPI for 2 weeks or more. Most definitions of refractory GERD symptoms refer to higher dosage for more times. This inclusion could generate bias.

Thank you for your comment. We agree that the duration and dose of PPI administration are important. All patients were administered a standard dose PPI for 2 or more weeks before written informed consent to participate in the study was obtained. Following treatment with the PPI, lansoprazole (30 mg/day, QD), for at least 2 weeks, patients with PPI-refractory LPR who met the inclusion and none of the exclusion criteria were enrolled in the study. Thus, all patients received PPI monotherapy for at least 4 weeks. We provide this information in *Study procedures* in the Materials and Methods section.

(3) The number of subjects of the study is very small. In particular the section about VAS scores refers to very

few subjects and should be omitted.

We have changed the Fig. 2 into Table 2.

(4) Patients are exclude if on therapy with antipsycothic drugs, but none is written about the inclusion/exclusion of neurological patients (i.e. Parkinson's Disease)

We agree. However, the study protocol cannot be changed at this point. Neurological patients were excluded from the present study, and although not specifically mentioned, the exclusion criterion "patients who were considered unsuitable by the chief investigator" included neurological patients.

(5) Gastric emptying technique (page 7). The drugs is taken 3 times/day: which was the temporal relationship between drug intake and gastric emptying study?

Thank you for your comment. We do not fully understand your suggestion; however, radio-opaque markers were used to evaluate gastric emptying, according to the method proposed by Cremonini *et al*. (Aliment. Pharmacol. Ther. 2002;16:1781–1790) and Metcalf *et al*. (Gastroenterology 1987;92:40–47). Because gastric emptying was examined after a meal, it was not thought to be affected by drug dose.

References and typesetting have been corrected.

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see:

http://www.textcheck.com/certificate/ATR4iG