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Wan Chai, Hong Kong, China

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 2837

Title: Effect of DA-9701 on gastric emptying in a mouse model; Assessment by 13C-octanoic acid breath test

Reviewer code: 00009415

Science editor: Gou, Su-Xin

Date sent for review: 2013-03-20 09:12

Date reviewed: 2013-03-23 17:22

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

In this study the authors investigated the effect of DA-9701 on gastric emptying in a mouse model and showed that it is similar to erythromycin



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 2837

Title: Effect of DA-9701 on gastric emptying in a mouse model; Assessment by ¹³C-octanoic acid breath test

Reviewer code: 00035938

Science editor: Gou, Su-Xin

Date sent for review: 2013-03-20 09:12

Date reviewed: 2013-03-26 07:16

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

General comments: Lim et coworkers present their results of a new prokinetic on gastric emptying. They tested an herbal extract used in traditional Oriental medicine in a mouse model using the ¹³C-octanoic breath test to assess the effect on the motility. The study is carefully designed as a randomized cross-over study assessing the effect of DA-9701, erythromycin and saline as control on gastric emptying. The data is well presented. The findings of a prokinetic effect of this herbal extract on gastric emptying is very promising in view of potential therapeutic options in functional dyspepsia. However, it remains unclear how helpful the animal model is in reflecting human conditions and correcting pathologies. Minor comments: The m-value which gives the percentage of the cumulative tracer recovery in indefinite time appears high in the mice, around 75% which is about double of what we would expect in human studies. Can you comment on this? What was the atom percent excess of the labeled ¹³C-octanoic acid? Are there any human studies underway or planned?



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 2837

Title: Effect of DA-9701 on gastric emptying in a mouse model; Assessment by 13C-octanoic acid breath test

Reviewer code: 02445683

Science editor: Gou, Su-Xin

Date sent for review: 2013-03-20 09:12

Date reviewed: 2013-03-29 01:10

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This study examines the effects of a novel, potentially useful phyto-derived prokinetic agent (i.e. DA-9701) on gastric emptying of normal C57BL/6 mice. The authors used 13C-octanoic acid breath test to investigate gastric emptying of three treatments (DA-9701, erythromycin vs saline, the latter used as placebo) with a randomized crossover design. Compared to saline, DA-9701 evoked a more rapid emptying similarly to erythromycin. The authors concluded that DA-9701 might be suggested as a novel remedy for the treatment of disorders characterized by delayed gastric emptying such as functional dyspepsia. Comments: 1. One conceptual remark is about the lack of a pathological group of animals with a delay in gastric emptying. For example the authors are encouraged to test DA-9701 in mice prone to or with diabetes mellitus, a condition known to affect gastric emptying in humans as well as in animals. Indeed, going back to the good old times when erythromycin was for the first time used in the clinical setting, that drug was tested in diabetic patients with gastroparesis. 2. Another issue pertains to the methodology and the normalization of the data vs saline in such a way to minimize the biological variability evident in Figure 4A and 4B. 3. Furthermore, from the emptying curves it is unclear what corresponds to a "lag-phase" typical of emptying of solids. 4. The paper needs a thorough editing for the English grammar. There are also typos throughout the text.



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Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 2837

Title: Effect of DA-9701 on gastric emptying in a mouse model; Assessment by ¹³C-octanoic acid breath test

Reviewer code: 00009420

Science editor: Gou, Su-Xin

Date sent for review: 2013-03-20 09:12

Date reviewed: 2013-04-03 04:06

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

The authors describe the prokinetic effect of DA-9701 on gastric emptying in mice using a breath test in comparison to the effect of erythromycin. Globally, the authors precisely describe their experiments using the breath test technique, including a power calculation. However as the effect of DA-9701 on gastric emptying is already described in rats, the paper lacks novelty. It would be interesting to investigate the dose-dependency in mice and to try to unravel the mechanism of action looking at dopamine D2 and 5-HT properties or to investigate the potential of DA-9701 in pathologically delayed gastric emptying (postoperative ileus, ...). How does the potential of DA-9701 relates to the potency of 5-HT4 receptor agonists? Could the authors please specify why they used a non-parametric analysis instead of a repeated measurements ANOVA? Please specify whether the statistical analysis indeed analysed the data of the three measurements points in the first time followed by posthoc testing. Minor remark: All data are presented in the results section and in the tables and figures repeating the same information.

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Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 2837

Title: Effect of DA-9701 on gastric emptying in a mouse model; Assessment by ¹³C-octanoic acid breath test

Reviewer code: 02441737

Science editor: Gou, Su-Xin

Date sent for review: 2013-03-20 09:12

Date reviewed: 2013-04-03 06:55

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

Comments of the manuscript: Effect of DA-9701 on gastric emptying in a mouse model; Assessment by ¹³C-octanoic acid breath test; of the authors: Chul-Hyun Lim, et al. This study is interesting and original in its methodological part because it presents a novel method to assess gastric emptying over time rather than evaluating a single moment after sacrificing laboratory animals. However, below there are some recommendations for authors to improve their manuscript. Abstract: It is important to make a modification of the conclusions; which should say the aspects more related to the experiment made for the researchers. For example, the authors tested the hypothesis of the effects of DA-9701 on gastric emptying in a mouse model and demonstrated that gastric emptying can be measured repeatedly in the same animal. Introduction: The introduction describes, explains and predicts the study problem; however, it is advisable to present more citations from scientific papers to explain the pharmacokinetics and pharmacodynamics of DA-9701. Methodology: Further explanation why the authors choose erythromycin, as an agent to compare the effects of DA-970. In the statistical analysis of data, it is advisable the authors perform the following steps: 1. To determine differences pre-post treatment (DA-9701, erythromycin and saline) in gastric emptying times [the half time (T_{1/2}), the lag phase for 10% emptying (T_{lag10}), and the lag phase for 15% emptying (T_{lag15})]. 2. To compare the differences described above in point 1, using rank Kruskal Wallis test. It is advisable to use rank Kruskal-Wallis test; to compare the effects of the drug treatments on gastric emptying the cumulative excretion curve for ¹³C-octanoic acid breath showed accelerated gastric emptying after treatment with DA-9701 compared with that after treatment with saline and with that of erythromycin. Results: Avoid repeating the results already presented in figures and tables.



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Instead better highlight the most important results found by the authors. Explain if all animals that began the study completed it. Also explain the adverse effects or undesirable with DA-9701 or erythromycin. In Table 1, show the number of animals per group. Conclusions: It is important to make a modification of the conclusions; which should say the aspects more related to the experiment made for the researchers.



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Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 2837

Title: Effect of DA-9701 on gastric emptying in a mouse model; Assessment by ¹³C-octanoic acid breath test

Reviewer code: 00058696

Science editor: Gou, Su-Xin

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This manuscript has been carefully evaluated. The authors describe the kinetics of radiolabeled octanoic acid in the breath of a mouse model to characterize the effect of a novel prokinetic agent on gastric emptying. Comparators were saline and erythromycin. Major concerns include: What is the hypothesis of this study? While the methodology and statistics are described, it is rather difficult to envision what the actual data looks like from interquartile kinetics and half-times. It appears that 12 mice had 3 tests, and a subset, 10 mice had an additional test to offer reproducibility. Were 2 mice excluded? The authors obtained breath samples at 15 minutes intervals, but the difference in median 1/2 gastric emptying time between DA-9701 and saline controls is 12 min. Is this difference significant? The authors state that the study was powered to detect an expected difference in 1/2 gastric emptying time of 50 minutes. By comparison, there was a 12 minute difference in 1/2 gastric emptying times in 10 control mice evaluated at a 1 week interval.



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Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 2837

Title: Effect of DA-9701 on gastric emptying in a mouse model; Assessment by 13C-octanoic acid breath test

Reviewer code: 02444990

Science editor: Gou, Su-Xin

Date sent for review: 2013-03-20 09:12

Date reviewed: 2013-04-14 18:38

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The article has some clinical value so is worthy of publication