**Author’s response to reviews**

**Title:** Does the placebo effect modulate drug bioavailability? Randomized cross-over studies of three drugs

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**Author’s response to reviews:**

Dear Editor,

We would like to thank you and thank the reviewers for efficient review of our manuscript. The following is our point-by-point response. All changes in the revised manuscript are highlighted.

Reviewer #1: In this manuscript the authors conducted an interesting clinical trial evaluating the drug*placebo interaction effect on drug bio-availability . For this purpose, the pharmacokinetics of oral cephalexin, ibuprofen and paracetamol was evaluated in three randomized cross-over studies. The authors found no evidence for the hypothesis that awareness of drug ingestion modulates its bioavailability. Their results also suggested that blinding subjects may not be a critical component in bio-equivalence studies and raised the awareness that considerable intra-subject bio-variability exists even comparing a drug product to itself. The studies were well conducted. Limitations of the study and interpretation of the negative findings were well discussed.

Authors reply: Thank you.
Minor issues:

1. In line 236, sentence "...paracetamol was not were..." needs clarification.

Authors reply: Thank you. The sentence is now changed to read: “However, it is also possible that a placebo effect for ibuprofen and paracetamol was not successfully elicited in the current study; other outcomes (for example pain reduction) unfortunately were not examined.”

2. Most of the citations numbers in this manuscript were inserted after comma or period. They need to be corrected.

Authors reply: Thank you. All citation numbers are now inserted after punctuations, in accordance with the Journal style.

Reviewer #2: The clinical study by Muhammad et al. entitled "Does the placebo effect modulate drug bioavailability? Randomized cross-over studies of three drugs" evaluates the bioavailability of three safety drugs in plasma. In general, the idea is not quietly fascinating and the methods are fairly straightforward. The paper needs major improvements before acceptance.

1. In the background, the author mentioned the "drug*placebo interaction effect". It should be better to design an additional experiment to determine the possible changes in the bioavailability at different combinations of the drugs.

Authors reply: It is not clear to the authors why the reviewer is recommending "experiments to determine the possible changes in bioavailability at different combinations of the drugs." The study was not set to study drug-drug interaction.

Previous studies (references 7, 8, 14) have shown that awareness of drug administration (placebo effect) may modulate the drug effect. The potential mechanism(s) underlying such interaction between the drug effect and the placebo effect (drug*placebo interaction effect) have not been well explored. This study was set to find out whether the placebo effect interacts with the drug effect by modulating drug bioavailability. Whether or not drug-drug interaction may involve modulating drug bioavailability is an interesting question but is not related to the aim of the current study (please see Abstract (first paragraph), Background (last paragraph), and Discussion (first sentence)).

2. Please address the potential mechanisms underlying the "drug*placebo interaction effect" and give reasonable explanations involving the pharmacokinetics.
Authors reply: The interaction effect may involve altering gastric emptying, intestinal transit time, or drug elimination. This is stated under Background (lines 86-88). In addition, the second sentence under Conclusions is now modified to incorporate these potential mechanisms. It now reads, “Although this may be due to inability to elicit adequate placebo effect, the results cast doubt on the concept that the drug-placebo interaction effect may involve modulating drug pharmacokinetics through mechanisms such as altering gastric emptying, intestinal transit time, or drug elimination.”

3. In addition, the authors should also pay attention to the language mistakes.

Authors reply: The manuscript was carefully reviewed for typos; corrections are highlighted.

Best regards,
Muhammad M Hammami, MD, PhD