Author’s response to reviews

Title: The effects of oral administration of Cola nitida on the pharmacokinetic profile of metoclopramide in rabbits

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POINT BY POINT RESPONSE TO REVIEWERS’ COMMENTS

REVIEWER 3:

1. COMMENT: My major concern is that the authors claim in the abstract and in the discussion conclusion, that the decrease of metoclopramide plasma levels following Cola nitida co-administration is attributable to mechanisms involving CYP2D6 and SULT2A1, P-gp and so on. These claims are not backed up by any data in the manuscript. The authors need to change the text accordingly, clearly indicating these statements as only possible mechanisms not investigated in the experiments.

RESPONSE: Texts have been revised accordingly. Abstract page 1, lines 18 and 19; Discussion section, page 8, lines 29 and 30; Conclusion section, page 9, lines 2-4

2. COMMENT: Introduction: metoclopramide is a prokinetic drug but that is due to its 5-HT4 receptor agonist effect, not D2 antagonist effect (anti-emetic effect). Please correct the Introduction accordingly.

RESPONSE: Texts have been revised accordingly. Introduction page 3, lines 27 and 28

3. COMMENT: Figure: is it correct to illustrate the plasma levels as immediately increasing following oral administration of the drug?

RESPONSE: Yes, the illustration showing immediate increase in plasma level after oral administration is correct.

Following oral administration, drug concentrations increase while the rate of absorption exceeds the rate of elimination and the peak (Cpeak or Cmax) is reached when the rate of elimination matches the rate of absorption.

REVIEWER 4:

COMMENT: Unfortunately, I have some concerns about the experimental protocol. The sample size
was very small (5 rabbits) and there were no controls. Metoclopramide was administered to rabbits, and then after washout was re-administered in the presence of Cola nitida. Differences between the pharmacokinetics between the first and second administration were attributed to Cola nitida. However, given the absence of controls, differences could have occurred owing to other factors (and given the small sample size, due to chance). Unfortunately, I can't see how any causative induction can be made from these data. This is a pity as you have made careful measurements and you I would suggest that you repeat the experiment with a larger sample size, and randomise the animals to receive either metoclopramide OR metoclopramide + cola, then wash-out and cross-over to the alternative treatment. 

RESPONSE: For experiments using laboratory animals such as rats, guinea pigs, rabbits, dogs etc. Sample size of five (5) and above is scientifically accepted. Based on the protocol adopted form previously published work (Nwafor et al., 2003; Sv et al., 2003 (Karademir et al., 2016; Sv, Co, Ca, & Cs, 2003)) sample size n=5 is not small and hence performing a repeat of the experiment would not be necessary at this point.

The experiment was carried out in two phases. The first phase is the control phase (paracetamol alone) while the experimental phase (paracetamol and Cola nitida) is the second phase. This protocol was adopted from previously published articles. See references below.

The experiment was carried out under controlled scientific conditions. Given that the drug was administered orally, the animals were starved prior to the experiment with samples collected and measured accurately and hence data obtained cannot be attributed to chance.

COMMENT: A minor point is that your graphs appear to have been fitted to an unusual formula which makes the lines curve in places which are not implied by your data. This is sometimes an automatic feature in MS Excel which can (and should) be adjusted, unless you have a particular reason to fit your data to a particular formula.

RESPONSE: In pharmacokinetics, plasma drug concentrations are determined using a non-compartmental model. Data points are joined and area under the curve is then either be calculated by means of the linear trapezoidal rule or by the log-linear trapezoidal rule. The total area is then measured by summing the incremental area of each trapezoid (Gabrielsson & Weiner, 2012). Samples articles with similar graphs includee:(Jin & Han, 2010; Kamath, Yao, Zhang, & Chong, 2005; Volak et al., 2013)

REFERENCES


