PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Optimisation of treatments for oral Neisseria gonorrhoeae infection: Pharmacokinetics Study (STI-PK project) – Study protocol for non-randomised clinical trial
AUTHORS	Kong, Fabian; Unemo, Magnus; Lim, Shueh; Latch, Ngaire; Williamson, DA; Roberts, Jason; Wallis, Steven C; Parker, Suzanne; Landersdorfer, Cornelia; Yap, Tami; Fairley, Christopher; Chow, Eric; Lewis, David; Hammoud, Mohamed; Hocking, Jane

VERSION 1 – REVIEW

REVIEWER	Thomas Dilworth Advocate Aurora Health Inc
REVIEW RETURNED	22-Jun-2022

GENERAL COMMENTS	The manuscript by Kong et al. presents the rationale and study protocol for an interesting PK analysis of multiple antibiotics for the treatment of NG, with sampling from multiple oral sites. This study should generate actionable data and develop a foundation for future clinical and PK/PD research in this area. As the authors correctly point out, treatment options for gonococcal infections remain, and likely will remain, limited, oropharyngeal gonococcal infection cure rates are unacceptably low and we lack solid PK data for the treatment of these infections for the antibiotics currently recommended for treatment. Reading through the protocol I found the background sufficient and well referenced, the methodology comprehensive and reproducible, and the limitations of the study design were acknowledged. The authors included a SPIRIT check list which is appreciated. They also provided a nice summary of PK sampling times in table 1 and their fully study protocol. The one suggestion I have is to revise the final bullet point on page 5 (study strengths and limitations). In this sentence the authors state they're unable to generate PD data. However, their secondary outcome is a PD analysis: PK/PD target attainment analyses using various NG MIC values. The sentence could be revised to say no real-world PD data will be generate or that PK modeling software will be used to estimate PTA for various NG MICs. These types of bullet point summaries must be accurate as they are often the first thing a reader will look at once they download the full manuscript text. Other than that one suggestion I have no additional constructive feedback. I wish the authors well in their research and look forward to the results of their study; and what research follows their study once shared with the scientific community.

REVIEWER	Jolinda de Korne-Elenbaas GGD Amsterdam, Public Health Laboratory - Department of Infectious Diseases
REVIEW RETURNED	01-Sep-2022

GENERAL COMMENTS	This protocol clearly describes the clinical trial to obtain PK data from the oral cavity and the oropharynx. This trial will yield important results that can be used for optimising antibiotic dose regimens for pharyngeal gonorrhoea. Please find below some comments or suggestions for improvement. p.8 Please add a section in the Methods with information about the baseline visit. How long does the visit take? Are the samples from 1-2h, 4h and 6h after antibiotic administration taken during that visit? Is the second 1g azithromycin dose also administered during that visit? p.8 l.43 Oral swabs/curettes specimen collection for PK and PD analysis: (a) tonsils (tonsil and posterior tonsillar pillar) by swiping both areas three times with a FloqSwab (552c; Copan, France), (b) from the posterior pharyngeal wall by swiping the site six times with FloqSwab. I wonder whether this is realistic to do this and to repeat this again after regular intervals since gag reflexes are to be expected. Therefore, the amount of actual sample will vary widely between individuals. Is there any possibility to measure a component in these samples which can be used to compare effectivity between swabbing different participants? p.12 l..48-50 We will investigate differences in the baseline oropharyngeal microbiota composition between individuals with and without specific characteristics/factors. It is unclear what is meant by specific characteristics/factors since it is nowhere stated that any characteristics of participants, and if so, which characteristics, are being collected. p.14, l.27-30: Additionally, because of trial logistics, we had to exclude those with oropharyngeal gonorrhoea and because of this, we are unable to generate PD data as there are no bacterial outcomes in the volunteers. However, using microbiome analysis, it will be possible to measure eradication of other commensal Neisseria spp., and this could be used as a proxy for Ng. Acknowledgement I would like to thank dr. Alje P van Dam for his help to complete this review.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Thomas Dilworth , Advocate Aurora Health Inc Comments to the Author:
The manuscript by Kong et al. presents the rationale and study protocol for an interesting PK analysis of multiple antibiotics for the treatment of NG, with sampling from multiple oral sites. This study should generate actionable data and develop a foundation for future clinical and PK/PD research in this area. As the authors correctly point out, treatment options for gonococcal infections remain, and likely will remain, limited, oropharyngeal gonococcal infection cure rates are unacceptably low and we lack solid PK data for the treatment of these infections for the antibiotics currently recommended for treatment.

Reading through the protocol I found the background sufficient and well referenced, the methodology comprehensive and reproducible, and the limitations of the study design were acknowledged. The authors included a SPIRIT check list which is appreciated. They also provided a nice summary of PK sampling times in table 1 and their fully study protocol.

The one suggestion I have is to revise the final bullet point on page 5 (study strengths and limitations). In this sentence the authors state they're unable to generate PD data. However, their secondary outcome is a PD analysis: PK/PD target attainment analyses using various NG MIC values. The sentence could be revised to say no real-world PD data will be generate or that PK modeling software will be used to estimate PTA for various NG MICs. These types of bullet point summaries must be accurate as they are often the first thing a reader will look at once they download the full manuscript text.

Thank you for highlighting this discrepancy. We will be estimating PK/PD target achievement based on the PK data and models. This has been revised in the summary

Other than that one suggestion I have no additional constructive feedback. I wish the authors well in their research and look forward to the results of their study; and what research follows their study once shared with the scientific community.

Thank you

Reviewer: 2
Dr. Jolinda de Korne-Elenbaas, GGD Amsterdam Comments to the Author:
This protocol clearly describes the clinical trial to obtain PK data from the oral cavity and the oropharynx. This trial will yield important results that can be used for optimising antibiotic dose regimens for pharyngeal gonorrhoea. Please find below some comments or suggestions for improvement.

p.8 Please add a section in the Methods with information about the baseline visit. How long does the visit take? Are the samples from 1-2h, 4h and 6h after antibiotic administration taken during that visit? Is the second 1g azithromycin dose also administered during that visit?

Samples from time 0h (baseline) to the 6h time point will be all collected at the same visit i.e. a day stay at the clinic. We have annotated this in Table 1 and clarified in the methods section.
We have also clarified that the second 1g azithromycin dose will be administered after the 6h samples are taken if the participant is not experiencing significant adverse effects. If they are, they will be asked to take the second dose before they go to sleep (approximately 9pm or 12 hours after the dose). We have added this to the 'treatment and allocation' section.

p.8 l.43 Oral swabs/curettes specimen collection for PK and PD analysis: (a) tonsils (tonsil and posterior tonsillar pillar) by swiping both areas three times with a FloqSwab (552c; Copan, France), (b) from the posterior pharyngeal wall by swiping the site six times with FloqSwab. I wonder whether this is realistic to do this and to repeat this again after regular intervals since gag reflexes are to be expected. Therefore, the amount of actual sample will vary widely between individuals. Is there any possibility to measure a component in these samples which can be used to compare effectivity between swabbing different participants?

Thank you for this concern. We had the same concerns. We developed a method in collaboration with Dr Yap, the oral pathologist and investigator in this project. Participants are asked to open their mouth, inhale and hold their breath gently before the procedure which minimises the gag reflex. During early recruitment we have found this to be effective. We have added this to the methods

p.12 l..48-50 We will investigate differences in the baseline oropharyngeal microbiota composition between individuals with and without specific characteristics/factors.

It is unclear what is meant by specific characteristics/factors since it is nowhere stated that any characteristics of participants, and if so, which characteristics, are being collected.

The specific characteristics/factor are those collected in the baseline survey e.g. smoking status, oral hygiene etc. We have clarified this in the section.

p.14, l.27-30: Additionally, because of trial logistics, we had to exclude those with oropharyngeal gonorrhoea and because of this, we are unable to generate PD data as there are no bacterial outcomes in the volunteers.
However, using microbiome analysis, it will be possible to measure eradication of other commensal Neisseria spp., and this could be used as a proxy for Ng.

Thank you for this comment and we agree. However commensal Neisseria may have different susceptibilities to treatments compared to pathogenic NG. In this instance we would prefer not to use commensals as proxy. See below reference for interest showing high MICs of commensals vs pathogenic NG.
https://pubmed.ncbi.nlm.nih.gov/34066576/

VERSION 2 – REVIEW

REVIEWER	Jolinda de Korne-Elenbaas GGD Amsterdam, Public Health Laboratory - Department of Infectious Diseases
REVIEW RETURNED	20-Sep-2022

GENERAL COMMENTS	I would like to thank the authors for their revision and I wish them good luck with the study. I am looking forward to the results.