PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparing Two Types of Macrolide Antibiotics for the Purpose of Assessing Population-Based Drug Interactions
AUTHORS	Garg, Amit; Fleet, Jamie; Shariff, Salimah; Bailey, David; Gandhi, Sonja; Juurlink, David; Nash, Danielle; Mamdani, Muhammad; Gomes, Tara; Patel, Amit

VERSION 1 - REVIEW

REVIEWER	John A. Tayek, M.D. Professor of Medicine-In Residence David Geffen School of Medicine at UCLA Harbor-UCLA Medical Center 1000 W. Carson Street #428 Torrance, CA, USA
REVIEW RETURNED	27-Mar-2013

THE STUDY	The choice of the control group is problematic. The 10 day duration of treatment vs the 5 day treatment is also problematic. The authors should us the control group of amoxicillin or keflix with a 10 day duration of treatment. They can keep the azithro group as a second control.
RESULTS & CONCLUSIONS	Both azithro and clarithro have sudden death and higher mortality rates then other anitibobics. The authos must use a more neutral group say those with amoxicillin or other antibiotic as the control group and not the azithro group.
GENERAL COMMENTS	You will likely find that the mortality rate is doubled with clarithro compared to a non-macrolide antiboitic. Good first attempt at data mining.

REVIEWER	Fabio Monzani M.D. Geriatrica Unit, Departemnt of Clinical and Experimental Medicine, University of Pisa, Italy I have no competing interest
REVIEW RETURNED	28-Mar-2013

RESULTS & CONCLUSIONS	The Authors did not consider in the discussion the possibility that these two agents may differ in terms of outcome (e.s. MIC, efficacy in eradication of the pathogens) in specific infectious disease. Moreover, in the analysis of the specific cause of mortality the Authors did not consider the hospitalization and death for sepsis. The authors should comment this aspect with specific references in AB pharmacodynamic differences. Moreover, the abstract conclusion is not completely consistent with the study results. The authors state that “Clarithromycin con be use to assess drug interaction…” (pag. 2, lines 39-40) but they did not

	report the differences in survival observed for the two AB. This point should be addressed. In the discussion, we suggest to better explain the sentence at pag. 12, lines 54. Why do the study results support the utility of macrolide AB to assess population-based drug interactions, if the authors documented a significant difference between the two ABs in term of overall mortality?
GENERAL COMMENTS	The authors explore a vast cohort of patients taking claritrhromycin and azithromycin that result well matched in terms of general clinical and pathological features, drug use and causes of infection. They found an increase of all cause of mortality in the group treated with clarithromycin with respect to those taking azithromycin and conclude that the difference may be probably related to the use or the nature of these two antibiotics (ABs). The study with the purpose to compare the incidence of serious adverse events for two macrolide antibiotics administered alone in a large population based study of older patients, could represent an important source of information in the field of macrolide drug interaction and clinical outcome. However, the Authors did not consider in the discussion the possibility that these two agents may differ in terms of outcome (e.s. MIC, efficacy in eradication of the pathogens) in specific infectious disease. Moreover, in the analysis of the specific cause of mortality the Authors did not consider the hospitalization and death for sepsis. The authors should comment this aspect with specific references in AB pharmacodynamic differences. Moreover, the abstract conclusion is not completely consistent with the study results. The authors state that “Clarithromycin con be use to assess drug interaction…” (pag. 2, lines 39-40) but they did not report the differences in survival observed for the two AB. This point should be addressed. In the discussion, we suggest to better explain the sentence at pag. 12, lines 54. Why do the study results support the utility of macrolide AB to assess population-based drug interactions, if the authors documented a significant difference between the two ABs in term of overall mortality?

REVIEWER	Dr Thomas M. Polasek Flinders University School of Medicine Adelaide, Australia I declare that I have no competing interests in the review of this manuscript.
REVIEW RETURNED	29-Apr-2013

RESULTS & CONCLUSIONS	The title of the manuscript is currently poor since it does not represent the study.
GENERAL COMMENTS	This manuscript by Fleet et al. reports results from a retrospective cohort study examining outcomes in patients prescribed clarithromycin and azithromycin in the absence of interacting drugs. The studies conducted are methodologically sound and rigorous, and the conclusions justified based on the data. The English grammar is excellent. I have the following minor comments for the authors. Comments 1. 2/23 line 6 and 4/24: azithromycin is actually a very weak inhibitor

	of CYP3A4 (Polasek et al. 2006, European Journal of Clinical Pharmacology), it's just that this is not considered clinically relevant. 2. 2/23 line 39: consider adding the following to the first sentence of the conclusion for further clarity, " Since there is no difference between clarithromycin and azithromycin in patients outcomes in the absence of interacting drugs, clarithromycin can be used…." 3. 3/23 line 18: referent → reference. 4. 4/23 lines 40 onwards: I think the rationale for this particular study needs to be further explained in the introduction i.e., put in context with your other work awaiting publication (ref 9). Although this is discussed on page 13/23, it would be valuable to further describe the rationale early in the manuscript. 5. The title of the manuscript does not give an adequate description of the study. Indeed, macrolide antibiotics have not been used to assess population-based drug interactions in this particular work. Potential differences in endpoints between the two macrolides in the absence of interacting drugs are the focus, and this should be reflected in the title. 6. 13/23 line 46: commence new paragraph for sentence starting, "Our study has.." 7. 14/23 line 7: I disagree that drug interactions are understudied. I would offer the opinion that DDIs are one of the most widely studied areas in clinical pharmacology.

REVIEWER	Hisakazu OHTANI Ph. D., Professor, Keio University Faculty of Pharmacy. -- I have no conflicts of interests with regard to this manuscript.
REVIEW RETURNED	02-May-2013

GENERAL COMMENTS	I didn't find any crucial defect in this manuscript. However, I consider this manuscript should be joined (or included) to the authors' other article under review in Ann Intern Med (Ref #9). The article (ref #9) seems to be closely related to the present manuscript and the conclusion of this manuscript may be essential to the interpretation of the manuscript ref #9 (and vice versa). I couldn't find any reason to publish them separately.

VERSION 1 – AUTHOR RESPONSE

Reviewer: John A. Tayek, M.D.
Professor of Medicine-In Residence
David Geffen School of Medicine at UCLA
Harbor-UCLA Medical Center
1000 W. Carson Street #428
Torrance, CA, USA

The choice of the control group is problematic. The 10 day duration of treatment vs the 5 day treatment is also problematic. The authors should us the control group of amoxicillin or keflix with a 10 day duration of treatment. They can keep the azithro group as a second control.

Both azithro and clarithro have sudden death and higher mortality rates then other anitibobics. The authos must use a more neutral group say those with amoxicillin or other antibiotic as the control group and not the azithro group.

You will likely find that the mortality rate is doubled with clarithro compared to a non-macrolide antiboitic. Good first attempt at data mining.

Response: Thank you for taking the time to closely review our manuscript. While we agree that there is an inherent difference in length of treatment between the two study drugs, our objective was to assess the outcomes of two groups of macrolide antibiotics (a CYP3A4 inhibitor vs. a non-CYP3A4 inhibitor) in the absence of potentially interacting drugs. Results from this analysis inform their use in future drug-drug interaction studies at the population level. The reviewer suggests an interesting comparison of clarithromycin vs. a non-macrolide antibiotic to assess the effectiveness of clarithromycin as an antibiotic. While this does not fit with the current scope of the study, we have expanded on this point in the discussion section and now state the following: “Additionally, in the future, studies with other non-macrolide antibiotics, compared to clarithromycin, may be warranted, as macrolide antibiotics have a higher rate of mortality as they are potentially arrhythmogenic.[35-37]).” We have also updated a point in the key messages section (strengths and limitations): “Further studies examining differences in all-cause mortality between the two antibiotics as well as non-macrolide antibiotics are warranted”

Reviewer: Fabio Monzani M.D.
Geriatrica Unit, Departemnt of Clinical and Experimental Medicine, University of Pisa, Italy
I have no competing interest

The Authors did not consider in the discussion the possibility that these two agents may differ in terms of outcome (e.s. MIC, efficacy in eradication of the pathogens) in specific infectious disease. Moreover, in the analysis of the specific cause of mortality the Authors did not consider the hospitalization and death for sepsis. The authors should comment this aspect with specific references in AB pharmacodynamic differences.

Response: We thank the reviewer for his important comments about this study. It is true that we did not discuss the minimum inhibitory concentration or efficacy in eradication of the pathogens. However, we have found in further literature searches that the efficacy in eradication of pathogens is not different between the two study drugs for some illnesses and have indicated so in the discussion section with the following: “The efficacy of pathogen eradication is similar between the two macrolides for some illnesses, but was not formally assessed here.[35,36]”

Additionally, in adherence to Privacy requirements (through the Personal Health Information

Protection Act), in order to minimize the potential for re-identification of patients we can only report group sizes with greater than five patients when using our administrative datasets; however, our results for cause of death in many categories, including infectious disease, had five or less patients. We have added the following sentence to the last paragraph of the discussion: “For reasons of privacy we are not permitted to report information for small cell sizes which also precluded meaningful analysis of some types of cause of death, such as infectious disease.”

As per the reviewer comment, we have now conducted an analysis using sepsis as an outcome. As in the other results, there is no significant difference between the two macrolide groups (adjusted RR 1.38 (95% CI 0.76 to 2.49). We have added this to the manuscript as a row in table 2, as well as added the relevant codes to the appendix.

Moreover, the abstract conclusion is not completely consistent with the study results. The authors state that “Clarithromycin con be use to assess drug interaction…” (pag. 2, lines 39-40) but they did not report the differences in survival observed for the two AB. This point should be addressed.

Response: We have stated the differences in mortality in the results section of the abstract. We have also stated that due diligence should be used when assessing mortality as an outcome when comparing these macrolide antibiotics. We do feel, however, that the reviewer’s comment has merit and have now changed the conclusion of the abstract to read the following: “However, any differences in mortality observed between the two antibiotic groups in the setting of other drug use may be partially attributable to factors beyond the inhibition of drug metabolizing enzymes and transporters, as the difference for this outcome was significant.”

In the discussion, we suggest to better explain the sentence at pag. 12, lines 54. Why do the study results support the utility of macrolide AB to assess population-based drug interactions, if the authors documented a significant difference between the two ABs in term of overall mortality?

Response: Though there was a difference in overall mortality between the two antibiotics, we found no difference in several significant adverse outcomes. The outcomes we found no significant difference in would be the outcomes of interest in drug interaction studies. We could not find any clear reason for it, but in the spirit of transparency we also discussed the all-cause mortality result. In the future, as we mention in the discussion, the magnitude of the odd’s ratio between this study, and future drug-drug interaction studies can be compared using the technique of Bland and Altman (a z-test comparison). For example in this study in the absence of interacting drugs, the odds ratio was 1.27 (95% confidence interval 1.04 to 1.55). If we observe in a future study, for example, in the presence of interacting drugs an odds ratio for mortality of 1.75 (95% confidence interval of 1.36 to 1.98), then the Bland Altman statistical technique would suggest the estimates are quantitatively different (with mortality being much higher with clarithromycin vs. azithromycin in the presence of an interacting drug than in the absence of the interacting drug).

The authors explore a vast cohort of patients taking claritrhromycin and azithromycin that result well matched in terms of general clinical and pathological features, drug use and causes of infection. They found an increase of all cause of mortality in the group treated with clarithromycin with respect to those taking azithromycin and conclude that the difference may be probably related to the use or the nature of these two antibiotics (ABs).

The study with the purpose to compare the incidence of serious adverse events for two macrolide antibiotics administered alone in a large population based study of older patients, could represent an important source of information in the field of macrolide drug interaction and clinical outcome.

Reviewer: Dr Thomas M. Polasek
Flinders University School of Medicine
Adelaide, Australia

I declare that I have no competing interests in the review of this manuscript.

The title of the manuscript is currently poor since it does not represent the study.

Response: This is addressed below.

This manuscript by Fleet et al. reports results from a retrospective cohort study examining outcomes in patients prescribed clarithromycin and azithromycin in the absence of interacting drugs. The studies conducted are methodologically sound and rigorous, and the conclusions justified based on the data. The English grammar is excellent. I have the following minor comments for the authors.

Comments

1. 2/23 line 6 and 4/24: azithromycin is actually a very weak inhibitor of CYP3A4 (Polasek et al. 2006, European Journal of Clinical Pharmacology), it's just that this is not considered clinically relevant.

Response: We thank the reviewer for his assistance in improving our manuscript. We have updated the objective section of the abstract to now state the following: "Clarithromycin strongly inhibits enzyme cytochrome P450 3A4, preventing the metabolism of some other drugs, while azithromycin is a weak inhibitor."

Additionally, we have updated the first paragraph of the introduction to now read: "Interestingly, another macrolide antibiotic, azithromycin, is prescribed for similar indications and in comparable patients as clarithromycin, but unlike clarithromycin, is only a very weak inhibitor of this enzyme and transporters.[7-9]"

2. 2/23 line 39: consider adding the following to the first sentence of the conclusion for further clarity, " Since there is no difference between clarithromycin and azithromycin in patients outcomes in the absence of interacting drugs, clarithromycin can be used…."

• Response: The abstract currently has a limit of 300 words, and we have 296 words. We do agree however that the above message is important. We have instead updated the key messages in the article summary to read as follows, in order to abide by the word count limit: "Since there is no difference between clarithromycin and azithromycin in hospitalization outcomes in the absence of interacting drugs, the use of azithromycin as a reference group is appropriate in drug-drug interaction studies."

3. 3/23 line 18: referent → reference.

Response: This has been updated.

4. 4/23 lines 40 onwards: I think the rationale for this particular study needs to be further explained in the introduction i.e., put in context with your other work awaiting publication (ref 9). Although this is discussed on page 13/23, it would be valuable to further describe the rationale early in the manuscript.

Response: Thank you for pointing this out. While we identified the need for the current study (to

assess outcomes of two macrolide groups in the absence of interacting drugs) while conducting our other study, an extensive literature review has revealed that multiple drugs have the potential to interact with clarithromycin, such as statins, calcium channel blockers, immunosuppressants, and some anticonvulsants and antipsychotics. This paper is crucially important because it not only supports the methodology we employed in our other study (which has been accepted for publication by the Annals of Internal Medicine and will be published on June 6th, 2013), but for all future population-based projects which characterize the risk of clarithromycin interactions with other CYP3A4 metabolized drugs as well.
To further convey this rationale, we have added the following to the last paragraph of the introduction: "For example, we recently published a study assessing statin and macrolide drug interactions, and noted older patients co-prescribed clarithromycin were more likely to be hospitalized with acute kidney injury in the subsequent 30 days compared to older patients co-prescribed azithromycin.[10] Observing an increase in the risk of acute kidney injury with clarithromycin vs. azithromycin in the presence of a statin, but not in the absence of statin, would provide additional evidence of statin toxicity from clarithromycin.[10]"

5. The title of the manuscript does not give an adequate description of the study. Indeed, macrolide antibiotics have not been used to assess population-based drug interactions in this particular work. Potential differences in endpoints between the two macrolides in the absence of interacting drugs are the focus, and this should be reflected in the title.

Response: We agree that the title does not accurately reflect what was done in the study. We have changed the title to "Comparing two types of macrolide antibiotics for the purpose of assessing population-based drug interactions."

6. 13/23 line 46: commence new paragraph for sentence starting, "Our study has.."

Response: This has been changed.

7. 14/23 line 7: I disagree that drug interactions are understudied. I would offer the opinion that DDIs are one of the most widely studied areas in clinical pharmacology.

Response: We agree that the sentence described in the discussion was not clear. We were referring to drug interactions at a population level, though case studies and pharmacokinetic drug interaction studies are plentiful. We have changed the sentence to the following: "Drug-drug interactions at the population level in routine care are complex and understudied."

Reviewer: Hisakazu OHTANI Ph. D., Professor, Keio University Faculty of Pharmacy.

-- I have no conflicts of interests with regard to this manuscript.

I didn't find any crucial defect in this manuscript.

However, I consider this manuscript should be joined (or included) to the authors' other article under review in Ann Intern Med (Ref #9). The article (ref #9) seems to be closely related to the present manuscript and the conclusion of this manuscript may be essential to the interpretation of the manuscript ref #9 (and vice versa). I couldn't find any reason to publish them separately.

Response: Thank you for reviewing this manuscript. The other manuscript referenced here has now officially been accepted in Annals of Internal Medicine, and will be published on June 6th 2013. Our extensive literature review has identified multiple drugs that have potential interactions with clarithromycin which include statins, but also calcium channel blockers, immunosuppressants, and

some anticonvulsants and antipsychotics. Because of this, we feel the need to establish that in the absence of interacting drugs, the two groups of macrolides are comparable on potential adverse outcomes. This was the impetus for conducting this study. This paper is crucially important because it not only supports the methodology we employed in the Annals paper, but for all our future drug drug interaction projects as well. To ensure due diligence in this fundamental analysis, we produced a full manuscript describing this issue.

VERSION 2 – REVIEW

REVIEWER	Monzani, Fabio University of Pisa, Clinical and Experimental Medicine
REVIEW RETURNED	03-Jun-2013

GENERAL COMMENTS	The Authors addressed all the questions and criticisms raised by the reviewer

REVIEWER	Dr Thomas M. Polasek Flinders University School of Medicine Adelaide, Australia
REVIEW RETURNED	02-Jun-2013

GENERAL COMMENTS	I have not further comments for the authors, they have addressed my concerns.