



CORRESPONDENCE

No evidence for cardiotoxicity of miltefosine[☆]



Dear Editor,

In a recent article, Barroso et al.¹ reported on the comparison of cardiotoxicity between N-methyl glucamine antimoniate, better known as meglumine antimoniate, and miltefosine. As the authors indicate, antimonial compounds are notorious for their extensive toxicity, particularly cardiotoxicity, leading to pronounced prolongation of corrected QT interval (QTc) and risk of developing abnormal heart rhythms that can cause sudden death.

The only significant result the authors report is a decreased relative risk in QTc > 440 msec for meglumine antimoniate (n=38) compared to miltefosine (n=15) on day 7 of treatment. Looking at it longitudinally for the miltefosine-regimen, the proportion of patients with QTc > 440 msec appeared to increase in the first week of treatment, but thereafter completely disappeared: 1/15, 5/15, 0/15, 0/15, for day 0, 7, 14, and 21, respectively, while it steadily increased in the meglumine antimoniate-treated group, culminating to 35.3% of patients with an abnormal QTc. Instead of looking at relative risk at each of the measured time points, assessing longitudinal changes within treatment groups would potentially have been a more relevant way of analyzing and interpreting these data.

The authors suggest that the cardiotoxicity of miltefosine has been described before, but to the best of my knowledge, this is not the case. The phase 3 study² to which the authors refer reports no abnormalities in electrocardiography, with a 14 msec increase in QTc from baseline during miltefosine. Such a clinically non-relevant increase in QTc is seen for many anti-infective drugs, also for those not exhibiting cardiotoxicity, probably due to recovery from infection and waning of fever, which can have a prolonging effect itself on QTc.³

From a pharmacokinetic angle, there is little rationale for a QTc prolongation only in the first treatment week. Miltefosine keeps accumulating during the 28-day treatment regimen, reaching a steady state in the last week of treatment.⁴ Maximal drug concentrations in the first week are < 50% of those expected in the fourth week of treatment. Moreover, no mechanisms of cardiotoxicity are known from

pre-clinical and clinical pharmacological research on miltefosine. Recently, a dedicated study investigating the effect of miltefosine on QTc in 42 Bolivian mucocutaneous leishmaniasis patients was concluded. While results remain to be published, the updated FDA miltefosine label mentions no evidence of QTc prolongation or increases >20 msec from baseline were observed in this study.

The conclusion should be that there is no convincing evidence nor pharmacokinetic-pharmacodynamic rationale that miltefosine causes cardiotoxicity.

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Author' contributions


Thomas P.C. Dorlo: Preparation and writing of the manuscript; study conception and planning; approval of the final version of the manuscript.

Conflicts of interest

None declared.

References

1. Barroso DH, Gomes CM, Silva AM, Sampaio RNR. Comparison of cardiotoxicity between N-methyl-glucamine and miltefosine in the treatment of American cutaneous leishmaniasis. *An Bras Dermatol.* 2021;96:502–4.
2. Sundar S, Jha TK, Thakur CP, Engel J, Sindermann H, Fischer C, et al. Oral miltefosine for Indian visceral leishmaniasis. *N Engl J Med.* 2002;347:1739–46.
3. Chan XHS, Win YN, Haeusler IL, Tan JY, Loganathan S, Saralamba S, et al. Factors affecting the electrocardiographic QT interval in malaria: A systematic review and meta-analysis of individual patient data. *PLoS Med.* 2020;17:e1003040.
4. Dorlo TPC, Balasegaram M, Beijnen JH, de Vries PJ. Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. *J Antimicrob Chemother.* 2012;67:2576–97.

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No evidence for cardiotoxicity of miltefosine – Reply*

*Dear Editor,*

The authors are pleased to read Professor Dorlos' comments on the article that we published in this journal.¹ As the professor rightly states cardiotoxicity of Meglumine Antimoniate (NMG) is well established, and there is no convincing pharmacokinetic evidence that miltefosine causes cardiotoxicity. We, however, cannot arrive at any specific conclusion on the pharmacokinetics of miltefosine based on our data as we have not investigated drug absorption, distribution, metabolism, or excretion in this study. Also, many explanations are possible, other than miltefosine-specific cardiotoxicity, to account for the increase in QTc interval observed in Sundar's et al. study.² The present study suggests that miltefosine may have some specific but transitory cardiotoxicity since the same increase in the QTc interval was not observed on the meglumine antimoniate treatment during the same period. Certainly, as we have stated in the paper, our conclusions are exploratory and deserve to be confirmed by evidence from other studies. The actual absence of pharmacokinetic evidence to support our findings, however, does not exclude their relevance. As correctly stated by the author, the strategy employed in the study has to be viewed with skepticism, especially considering the increased type 1 error rate related to multiple comparisons.³ Nevertheless, the statistical analysis must be adapted to the characteristics of the variables studied. As precisely said, the QTc interval is not a clinical outcome, and its significance is related to the possibility of cardiac arrhythmias. To account for that, we have dichotomized the variable to separate patients with increased risk of arrhythmia (QTc \geq 440 ms) and those with no increased risk (QTc <440 ms). Additionally, aggregating the different time points of the subjects may overlook a transitory and potentially fatal increased risk of cardiac death. Thus, we understand that the analysis in each time point is important to account for intrasubject variability in this case. The cardiotoxicity of miltefosine is not well established in the literature, and we continue to prefer this drug over NMG in patients with high cardiac risk. Nevertheless, any signal of miltefosine cardiotoxicity deserves to be reported, especially considering the increased interest of the scientific community in combination therapy, as evidenced by the many studies done on the subject.^{4,5} Finally, considering that safety is the primary

concern when dealing with human lives, any case of cardiotoxicity related to miltefosine should be included in the pharmacovigilance data. This is even more important now, once miltefosine has been incorporated in countries where leishmaniasis is endemic.

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Authors' contributions

Daniel Holanda Barroso: Drafting and editing of the manuscript; critical review of the manuscript.

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Conflicts of interest

None declared.

References

1. Barroso DH, Gomes CM, da Silva AM, Sampaio RNR. Comparison of cardiotoxicity between n-methyl-glucamine and miltefosine in the treatment of American cutaneous leishmaniasis. *An Bras Dermatol.* 2021;96:502–4.
2. Sundar S, Jha T, Thakur C, Engel J, Sindermann H, Fischer C, et al. Oral miltefosine for Indian visceral leishmaniasis. *N Engl J Med.* 2002;347:1739–46.
3. Motulsky H. *Intuitive biostatistics: a nonmathematical guide to statistical thinking.* 4th ed. USA: Oxford University Press; 2018.
4. Dorlo TP, Balasegaram M, Beijnen JH, de Vries PJ. Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. *J Antimicrob Chemother.* 2012;67:2576–97.
5. Martins SS, Barroso DH, Rodrigues BC, da Motta JDOC, Freire GSM, Pereira Lida, et al. A pilot randomized clinical trial: oral miltefosine and pentavalent antimonials associated with pentoxifylline for the treatment of American tegumentary leishmaniasis. *Front Cell Infect Microbiol.* 2021;11:700323.

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