



Dear Editor in Chief,

Please find the enclosed manuscript which we submit to be considered for publication in British Journal of Clinical Pharmacology. The manuscript is a review article and is entitled: "Cyclophosphamide pharmacogenomics and their effect on its bioactivation and kinetics" by: Ibrahim El-Serafi and Sinclair Steele.

Cyclophosphamide (Cy) is a prodrug that is activated by several enzymes mainly CYP2B6. The role of pharmacogenomics in Cy bioactivation has been under investigations while its results were contradictory and inconclusive. In previous studies, my group has shown that CYP2B6 polymorphisms altered the Cy bioactivation in vitro. Moreover, we have shown that the electron transfer step is affected by the amount of POR enzyme which, in turn, affected the Cy bioactivation. We were the first group to report that CYP2J2 is induced in patients treated with Cy and that it is involved in Cy bioactivation.

In the current manuscript, we have tried to summarize the most important studies reporting the effect of Cy pharmacogenomics on its kinetics. We have included all enzymes involved in Cy metabolic pathway such as CYP2B6, CYP2C19, CYP2J2, POR and GSTA1 and discussed Bu/Cy conditioning as a clinical example of drug interactions that can be affected by the enzymes' polymorphisms.

Our conclusion is that CYPs polymorphisms change the Cy kinetics. However, such an effect is complex as it is clearly multifactorial. Additionally, the clinical circumstances may mask the effect of these polymorphisms and play an important role in the clinical outcome. In order to personalize Cy dose, we recommend performing Cy therapeutic drug monitoring (TDM) for dose adjustment as well as, in the future, patient's gene sequencing as a routine investigation prior to the start of Cy treatment.

This submitted manuscript is a review article that has not been previously published and has not been submitted for publication elsewhere. The authors declare that they have no conflict of interest. Associate Professor Dr Steele, besides his medical, biochemical and pathological background, is a native English speaker who revised the text.

Thank you in advance for your consideration!
Best regards,

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