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W.E.A. de Witte, G. Vauquelin, P.H. van der Graaf, E.C.M. de Lange

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The influence of drug distribution and drug-target binding on target occupancy: The rate-limiting step approximation

W.E.A. de Witte[a], G. Vauquelin[b], P.H. van der Graaf[a,c], E.C.M de Lange[a*]

[a] Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, 2333 CC Leiden, The Netherlands

[b] Department of Molecular and Biochemical Pharmacology, Vrije Universiteit Brussel, Brussels, Belgium

[c] Certara Quantitative Systems Pharmacology, Canterbury Innovation Centre, Canterbury CT2 7FG, United Kingdom

* Correspondence: ecmdelange@lacdr.leidenuniv.nl (E.C.M. de Lange)

Abstract

The influence of drug-target binding kinetics on target occupancy can be influenced by drug distribution and diffusion around the target, often referred to as "rebinding" or "diffusion-limited binding". This gives rise to a decreased decline of the drug-target complex concentration as a result of a locally higher drug concentration that arises around the target, which leads to prolonged target exposure to the drug. This phenomenon has been approximated by the *steady-state approximation*, assuming a steady-state concentration around the target. Recently, a *rate-limiting step approximation* of drug distribution and drug-target binding has been published. However, a comparison between both approaches has not been made so far.

In this study, the *rate-limiting step approximation* has been rewritten into the same mathematical format as the *steady-state approximation* in order to compare the performance of both approaches for the investigation of the influence of drug-target binding kinetics on target occupancy.

While both approximations clearly indicated the importance of k_{on} and high target concentrations, it was shown that the *rate-limiting step approximation* is more accurate than the *steady-state approximation*, especially when dissociation is fast compared to association and distribution out of the binding compartment.

It is therefore concluded that the new *rate-limiting step approximation* is to be preferred for assessing the influence of binding kinetics on local target site concentrations and target occupancy.

Keywords: binding kinetics, rebinding, distribution, pharmacokinetics, rate-limiting step, diffusion