DEVELOPMENT OF PHYSIOLOGICAL BASED PHARMACOKINETIC MODELING AND SIMULATION SOFTWARE: SIMPBPK
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It is well recognized that simulation of plasma concentration profile with proper mathematical model is useful throughout the drug discovery and development process. However, there may be many barriers to conduct such simulations. The major barriers to conduct proper simulation are unfamiliarity in programming and inadequate knowledge in pharmacokinetics, especially in physiologically based pharmacokinetics (PBPK). We have developed a Microsoft Windows based software named SimPBPK that was designed to allow easy construction of PBPK models without any programming skill and with a regular knowledge in pharmacokinetics through a graphical user interface. SimPBPK can deal with seven types of compartments in which well-stirred organ, homogeneous organ, blood, solid and solution compartments are included as material compartment, and enzyme and dynamics compartments are included as functional compartment. Three types of material transfer functions such as linear transfer, non-linear transfer, and blood transfer are available. By selecting and setting proper compartments and transfer functions, a variety of models can be constructed with SimPBPK at will, such as a simple PBPK model, a complicated PBPK model incorporated with mechanism based inhibition, a classical compartment model, a dissolution-absorption model, a pharmacokinetics-pharmacodynamics model, and so on. Calculated result can be seen graphically on SimPBPK and also obtained with CSV format for further modification by users. SimPBPK has also equipped the function of sensitivity analysis and Monte Carlo simulation. With above features, SimPBPK is expected to contribute to the facilitation of a variety of drug discovery and development process.

INHIBITORY EFFECT OF ERYTHROMYCIN FOR CLOSTRIDIUM DIFFICILE ASSOCIATED DIARRHEA
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Clostridium difficile (C. difficile) is a spore-forming gram-positive anaerobic bacillus and produces Toxin A/Toxin B. It can be caused from many high-risk hospitalized patients receiving the broad-spectrum antibiotic therapy. Recently, C. difficile associated diarrhea (CDAD) becomes an important infectious disease in the hospital. Meanwhile, erythromycin (EM) is well known for their efficacy in treating acute airway infections, but just as importantly, they are also effective anti-inflammatory agents, for example inhibition of cytokine production, neutrophils and lymphocytes accumulation in the diffuse panbronchiolitis patient. Therefore, we evaluate the therapeutic effect of EM for CDAD via the immuno-modulatory effects of EM. As results, in this paper, we found that the ratio of patients with CDAD was significantly improved by the addition of low-dose and long-term EM therapy in our hospital. In addition, we examined inhibitory mechanism of EM for CDAD from the bacterial study and host response. In the bacteria side, we investigated the growth of C. difficile and production of Toxin A with or without EM. Nevertheless the bacteria counts of C. difficile was increased, the production of Toxin A was significant decreased by the addition of 1 μg/ml EM. More in a host, we investigated expression of interleukin (IL) - 8 from T84 cell varying concentrations of C. difficile Toxin A. the production of IL-8 was reduced in pre-exposure to 3 μM EM and 100 ng/ml Toxin A. In conclusion, it is suggested that erythromycin has the important roles in the inhibition of CDAD via the decrease of IL-8 production from a colonic epithelial cell and reduction of Toxin A production from C. difficile.