

Title

Therapeutic drug monitoring of betalactams by using population pharmacokinetics and machine learning

Keywords

Therapeutic Drug Monitoring, beta-lactam antibiotics, pharmacokinetics, modelling, machine learning, ICU.

Start of thesis

October 2024

Abstract

It is possible to adapt the dosage of antibiotics for ICU patients by carrying out Therapeutic Drug Monitoring (TDM), using an approach based on mathematical models called Model Informed Precision Dosing (MIPD). However, its use in routine hospital practice is not widespread due to a lack of available tools.

In this project, we propose to develop new MIPD approaches for 4 antibiotics used in the ICU.

The project is divided into 4 work packages (WP):

1. Development of MIPD approaches based either on the selection of a single model or on the simultaneous consideration of all available models (model-averaging).
2. Development of MIPD approaches using machine learning.
3. Validation of the developed approaches using drug concentration data from ICU patients from 3 university hospitals.
4. Implementation of the best models in the free TDMx software.

Background

The treatment of infections in ICU patients requires individualisation of dosage regimens because of the many pathophysiological changes in these patients.

It is possible to adapt the dosage by measuring the patient's plasma concentration at specific times and then adapting the dosage by comparing the measurements with a predefined standard. However, this approach does not allow individual patient characteristics to be taken into account, and is often inapplicable on a routine basis because concentrations are measured outside the predefined times.

Model Informed Precision Dosing (MIPD) uses mathematical models to predict patient concentrations. It becomes possible to use concentrations measured at any time during treatment, and to incorporate all the individual characteristics of the patient. However, their routine use is not widespread due to a lack of available tools.

Topic description

Through this project, we propose to develop new MIPD approaches for 4 antibiotics commonly used in the ICU (amoxicillin, piperacillin, cefotaxime, meropenem).

The candidate will have to develop TDM approaches based (i) on the selection of a single model, (ii) on the simultaneous consideration of the various models available, (iii) on the application of machine learning methods. They will then have to implement the best solutions in the TDMx open-source software.

This thesis will be co-supervised by Pr Nicolas Grégoire, from the "Pharmacology of anti-infectives and antibiotic resistance" UMR INSERM 1070 team in Poitiers, and Pr Jean-Baptiste Woillard, from the "Pharmacometry & Modelling" team in the Pharmacology and Transplantation UMR INSERM 1248 laboratory in Limoges.

Methods

The project is divided into 4 work packages (WP).

WP1 will develop MIPD approaches based either on the selection of a single model or on the simultaneous consideration of all available models (model-averaging). The population pharmacokinetic models as well as the model selection and model-averaging algorithms will be coded in R software.

Work package 2 will consist of developing machine learning (ML) models trained on data produced by Monte Carlo simulation generated from the various population pharmacokinetic models.

In WP3, data on the concentrations of 4 antibiotics in ICU patients from 3 hospitals will be used to validate the models developed. Hybrid algorithms combining individual estimation by population pharmacokinetics and ML may be developed.

In WP4, the best models validated in WP3 will be implemented in the free TDMx software.

Requirements

The candidate should have basic knowledge of the use of R software.

They should have a good level of pharmacokinetics and modelling, particularly with mixed-effects models.

They should have a good understanding of written scientific English, and may be a French and/or English speaker.

Diploma required: Master 2 or equivalent.

What we offer

The future PhD student will benefit from the expertise in pharmacometrics and machine learning of Profs Grégoire and Woillard, as well as from the scientific and organisational support provided by the U1070 and U1248 teams.

They will have the opportunity to develop collaborative project management skills, interfacing with the teams of Pr Jullien (Hôpital Jean Verdier) and Pr Wicha (Univ. Hamburg).

They will take part in international scientific conferences (e.g. PAGE, IATDMCT, etc.).

Gross salary: €2,100 per month

Contract duration: 36 months

Application procedure

Provide a cover letter and a CV including your higher education curriculum and professional experience (especially research internships)

Email addresses of at least two referrals (e.g. internship supervisors)

Send to Pr Nicolas Grégoire and Pr Jean-Baptiste Woillard : nicolas.gregoire@univ-poitiers.fr and jean-baptiste.woillard@unilim.fr (make sure you send it to both email addresses !)

Euraxess link : <https://euraxess.ec.europa.eu/jobs/203480>