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Short communication

How to combine non-compartmental analysis with the population pharmacokinetics? A study of tobacco smoke's influence on the bioavailability of racemic citalopram in rats

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Abstract:
Background: Citalopram (CIT) is an antidepressant drug from the group of selective serotonin reuptake inhibitors in which it is the most potent selective inhibitor of serotonin uptake currently available. Patients treated with CIT are often heavy cigarette smokers. Individual pharmacokinetic parameters cannot be directly estimated if full pharmacokinetic profiles are not available for each subject. Sparse sampling is common to experiments using small animals, such as the case that our study is concerned with.
Methods: The aim of the study was to demonstrate how the two (non-compartmental analysis (NCA) and nonlinear mixed-effect (NLME)) approaches, used simultaneously, can help overcome specific limitations of these separate methods whilst at the same time preserve their respective benefits.
Results: Despite the ultra-sparse design, the NLME approach enabled us to develop a pharmacostatistic model with the required covariate – exposition to the tobacco smoke.
Conclusions: A tobacco smoke slows down the absorption of the CIT and at the same time makes it more effective. The consistency of results obtained both with NCA and NLME decreased the risk of model misspecification and increased confidence in the final conclusions. Combining NLME with NCA may therefore be recommended for investigating pharmacokinetic properties of the drug in the sparse designs.

Key words:
citalopram, tobacco smoke, population pharmacokinetics, model independent pharmacokinetics

Introduction

Depression is a common mental disorder nowadays. By the year 2020, depression is expected to reach the 2nd place of the DALYs (Disability Adjusted Life Years) ranking, which is calculated for all ages and both sexes. The pharmacological treatment of this illness is based mainly on second generation antidepressant drugs.

Citalopram (CIT) is an antidepressant drug of the group of selective serotonin reuptake inhibitors (SSRI) where it is the most potent selective inhibitor of serotonin uptake currently available [4, 10, 16]. CIT is marketed as a racemate, but it is also the only S-enantiomer that possesses SSRI activity.

CIT is biotransformed by the cytochrome P 450 enzyme to desmethylcitalopram (DCIT), which is the main metabolite, and didesmethylcitalopram (DDCIT). Baumann and Larsen reported that metabolites of CIT inhibit the reuptake of serotonin at a level of four (DCIT) and thirteen (DDCIT) times less than the parent compound [2].

The bioavailability of the drug after oral administration is 80%. The plasma levels of CIT and DCIT range from 9 to 200 ng/ml and 10 to 105 ng/ml, respectively.

CIT is widely distributed among peripheral tissues and the volume of distribution is estimated between 12 and 16 l/kg [4]. Intrinsic clearance of CIT is low and its kinetic was found linear in the dose range of 10–60 mg [4, 11].

Patients treated with CIT are often heavy cigarette smokers. It is therefore interesting to investigate whether tobacco smoke has the potential to modify pharmacokinetic properties; especially the bioavailability of this drug. However, in the present paper, the above question is not the central one (as opposed to our previous work on CIT [15]). The main goal of this study is rather more of a methodological nature. We were trying to choose an approach that is best suited to the pharmacokinetic analysis of the available data.

Individual pharmacokinetic parameters cannot be directly estimated if full pharmacokinetic profiles are not available for each subject. Sparse sampling, as used in our study, is typical of experiments with small animals.

Fortunately, a number of possible solutions to the problems concerning sparse sampling exist. The naive averaged data (NAD) approach [7] is probably the simplest one. In this method, at each time point, several concentrations, each one coming from a different subject, are determined. These measurements are then averaged, giving a single pharmacokinetic profile. In the original NAD method, a pharmacokinetic model is fitted to this averaged profile and the obtained pharmacokinetic parameters are then considered as a population mean.

In the method of Bailer [1], further developed by Jawień [12], no specific pharmacokinetic model is assumed and the pharmacokinetic parameters are estimated in the framework of the model-independent pharmacokinetics; known more often (though less correctly) as NCA [17]. These model-independent parameters, with the most frequently used area-under-the curve (AUC) among them, can be estimated along with their standard deviations. This enables a statistical comparison between groups that underwent different treatment.

While the simplicity and model-independence are benefits of this approach, the numerous drawbacks of NAD have already been indicated in earlier literature [7].

At another extreme, one can find the NLME approach. It was introduced into the field of pharmacokinetics by Sheiner and Beal and was initially implemented in their famous NONMEM system [3]. The name – population pharmacokinetics (PPK) is often used for NLME modelling of pharmacokinetic parameters. This approach requires both a strict model specification and highly sophisticated software, but offers greater flexibility regarding the choice of statistical model components and creates an opportunity to extract almost all the information contained in the experimental data. This is especially important in the case of sparse data.

With the NLME, it is possible to include covariates (such as exposure to tobacco smoke) in the pharmacostatistical model. By doing this, one can formulate and verify statistical hypotheses on the factors influencing the pharmacokinetic parameters. A recent work on the pharmacokinetic profile of propofol [19] may serve as an example of NLME being applied for the pharmacokinetic-pharmacodynamic modelling.

In the present paper, we wanted to demonstrate how these two approaches, when used simultaneously, can help overcome specific limitations of the individual methods while at the same time preserve the benefits of each approach.