Many dosing regimens applied in neonatal medicine today originate from clinical studies conducted more than 40–50 years ago. Although we have nowadays sophisticated mathematical modeling tools to enhance and personalize these dosing regimens, it is seldom done in clinical practice.

The dosing regimen of caffeine to treat apnea of prematurity is such an example. Two recently published mathematical modeling efforts showed that the traditional caffeine regimen can be improved to adapt for effects of maturation. In the following, we (i) recapitulate the story of caffeine dosing in preterm neonates, (ii) present some remarks about mathematical pharmacokinetic modeling, and (iii) demonstrate the application of mathematical modeling to improve dosing regimens.

In 1979, Aranda et al. [1] suggested a 20 mg/kg loading dose followed by 5 mg/kg maintenance doses for caffeine citrate based on data from 32 premature neonates. Interestingly, in the same year, Aranda et al. [2] already reported, in another article, effects of maturation of caffeine clearance. Le Guennec et al. [3] confirmed in 1985 the significant effects of maturation on caffeine concentrations based on a larger dataset, that is, the half-life of caffeine strongly decreased within the first postnatal weeks.

Nevertheless, the traditional dosing regimen suggested by Aranda et al. [1] in 1979 is still applied in 2020 without adapting to these known developmental changes.

Mathematical modeling of the pharmacokinetics of drugs is not new and was introduced by the pediatrician F. H. Dost in the 1950s [4, 5]. Briefly, pharmacokinetic modeling allows quantification of the dynamics of drug concentrations by parameters such as clearance and volume of distribution. However, what brought pharmacokinetic modeling to the next level was the additional application of statistical nonlinear mixed effects methods (NLME), as introduced by Sheiner et al. [6] and Beal et al. [7] in the late 1970s. With this approach, the pharmacokinetics of many individuals, a population, can be simultaneously characterized and sources of inter-individual variabilities can be revealed. Subsequently, the NLME method was extended with covariate analysis techniques to further explain variability, for example, a covariate in neonatology can be weight, postnatal age, or gestational age.

Falcao et al. [8] in 1997 (75 preterm neonates) and Charles et al. [9] in 2008 (110 preterm neonates) analyzed the pharmacokinetics of caffeine in a population of preterm neonates with the NLME approach and mathema-
cally characterized the postnatal age and weight dependence of caffeine clearance. Recently in 2017, Koch et al. [10] combined these 2 developed pharmacokinetic models to optimize the almost 40-year-old caffeine dosing regimen by suggesting a step-wise increase of the maintenance doses. This assures a stable caffeine concentration with a target trough level of 15 mg/L for a typical preterm neonate with a gestational age of 28 weeks and consequently a constant caffeine exposure for this neonate. Hence, currently applied traditional dosing regimens are not carved in stone; in contrary, they can and have to be improved or, let us say, have to “mature” as well with the help of mathematical modeling.

In this respect, Engbers et al. [11] performed a clinical study with 39 preterm neonates (median gestational age 25.6 weeks) treated with caffeine and some of these neonates also received doxapram. The authors applied NLME pharmacokinetics modeling to analyze caffeine concentration data and showed that caffeine clearance was not affected by concomitant doxapram therapy and they also confirmed a rapid maturation with respect to postnatal age. Based on these findings they concluded that the decreased exposure to caffeine upon increasing postnatal age might partially explain the need for doxapram therapy after the first week of life. The work from Engbers et al. [11] nicely shows that the application of mathematical modeling is a must to further improve and personalize dosing regimens in neonatology.

What can we learn from this caffeine example? Well, we have to revise traditional dosing regimens to further improve the benefit for the patient. Although this seems difficult at first glance, actually all pieces of the puzzle are available. We have known for decades that developmental changes occur in preterm neonates and nowadays sophisticated mathematical modeling tools are available to include these maturation effects. Moreover, as has been shown in this example, even clinical studies have already been performed and mathematically analyzed [8, 9]. What has to happen now is to create teams that will be able to put together all the necessary pieces.

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References