**Pharmacometric modelling of deuterium exposure in breastfeeding mother-infant pairs for the determination of exclusive breastfeeding practice**

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**Background:** The World Health Organization (WHO) recommends exclusive breastfeeding (EBF) for the first 6 months after birth. A stable isotope deuterium dose-to-mother (DTM) technique can be used to determine whether an infant is EBF by estimating quantitatively the intake of breastmilk and non-breastmilk water intake. This method has several advantages as it is non-invasive, simple to perform, robust, and accurate. However, a validated cut-off value of non-breastmilk water intake to distinguish EBF from non-EBF is not available. Also DTM technique is not an ideal field tool for measuring EBF in population-based surveys as it involves 7 days of post-dose saliva sample collections from mother and infant over a 14-day study period. Shortening of the sampling protocol has been proposed but whether it resembles the original protocol remains unknown.

**Aims:** The 1st aim was to determine a cut-off value of non-breastmilk water intake to distinguish EBF from non-EBF based on analysis of data arising from DTM saliva samples from mother-infant pairs. The 2nd aim was to design a streamlined DTM technique protocol which is more field friendly, i.e. less number of post-dose saliva samples.

**Methods:** Data were available from 9 countries including 790 mother-infant pairs. The data was split into, (1) model building data set (565 pairs, including 113 EBF-controlled pairs as calibration data); (2) evaluation data set (225 pairs). The model analysis applied a nonlinear hierarchical model in a fully Bayesian framework using a Markov chain Monte Carlo (MCMC) approach implemented in Stan. A four-stage method used: (i) determination of EBF criterion using the calibration data, (ii) assignment of subjects in the model building data set to EBF or non-EBF categories, (iii) optimising a field friendly study, (iv) evaluation of the optimised design involving the evaluation data set.

**Results:** Two linked 1-compartment models (mother and infant) with combined error model, and addition of mother’s body weight on mother’s volume of distribution and infant’s body weight on infant’s water clearance rate provided an adequate description of the data. One-hundred and thirteen EBF infants were included in the calibration data and using the 90th percentile of the distribution of the population non-milk water intake, we estimated a cut-off value of 86.6 g/d, with a lower limit 95% CI of approximately 56 g/d [1]. Two post-dose windows (days 7-9 and 13-14) yielded optimal categorisation (>95% sensitivity and specificity) in the model building dataset. This design was validated in the evaluation data set with similar performance.

**Discussion:** A less time and resource intensive DTM deuterium two-day post-dose sampling design together with the determined cut-off value were found to be capable of separating EBF from non-EBF infants. The design has been used in the field study in Indonesia with more flexibility. The next step is to promote the whole method developed in this study to future field studies.

**References:**

# 1. Liu Z, Diana A, SlaterC, PrestonT, GibsonRS, HoughtonL, Duffull SB.Development of a nonlinear hierarchical model to describe the disposition of deuterium in mother-infant pairs to assess exclusive breastfeeding practice. Journal of Pharmacokinetics and Pharmacodynamics. doi: 10.1007/s10928-018-9613-x