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In Silico Modeling of Drugs Milk/Plasma Ratio in Human Breast Milk Using Structures Descriptors

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Abstract : Introduction: Feeding infants with safe milk from the beginning of their life is an important issue. Drugs which are used by mothers can affect the composition of milk in a way that is not only unsuitable, but also toxic for infants. Consuming permeable drugs during that sensitive period by mother could lead to serious side effects to the infant. Due to the ethical restrictions of drug testing on humans, especially women, during their lactation period, computational approaches based on structural parameters could be useful. The aim of this study is to develop mechanistic models to predict the M/P ratio of drugs during breastfeeding period based on their structural descriptors. Methods: Two hundred and nine different chemicals with their M/P ratio were used in this study. All drugs were categorized into two groups based on their M/P value as Malone classification: 1: Drugs with M/P>1, which are considered as high risk 2: Drugs with M/P>1, which are considered as low risk Thirty eight chemical descriptors were calculated by ACD/labs 6.00 and Data warrior software in order to assess the penetration during breastfeeding period. Later on, four specific models based on the number of hydrogen bond acceptors, polar surface area, total surface area, and number of acidic oxygen were established for the prediction. The mentioned descriptors can predict the penetration with an acceptable accuracy. For the remaining compounds (N= 147, 158, 160, and 174 for models 1 to 4, respectively) of each model binary regression with SPSS 21 was done in order to give us a model to predict the penetration ratio of compounds. Only structural descriptors with p-value<0.1 remained in the final model. Results and discussion: Four different models based on the number of hydrogen bond acceptors, polar surface area, and total surface area were obtained in order to predict the penetration of drugs into human milk during breastfeeding period About 3-4% of milk consists of lipids, and the amount of lipid after parturition increases. Lipid soluble drugs diffuse alongside with fats from plasma to mammary glands. lipophilicity plays a vital role in predicting the penetration class of drugs during lactation period. It was shown in the logistic regression models that compounds with number of hydrogen bond acceptors, PSA and TSA above 5, 90 and 25 respectively, are less permeable to milk because they are less soluble in the amount of fats in milk. The pH of milk is acidic and due to that, basic compounds tend to be concentrated in milk than plasma while acidic compounds may consist lower concentrations in milk than plasma. Conclusion: In this study, we developed four regression-based models to predict the penetration class of drugs during the lactation period. The obtained models can lead to a higher speed in drug development process, saving energy, and costs. Milk/plasma ratio assessment of drugs requires multiple steps of animal testing, which has its own ethical issues. QSAR modeling could help scientist to reduce the amount of animal testing, and our models are also eligible to do that.

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