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Quantitative Structure-Pharmacokinetic Relationship (QSPkR) Analyses of Opioids

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[Introduction] The prediction of the pharmacokinetic properties of opioids for which it is difficult to gain pharmacokinetic parameters, is useful in a variety of situations. In clinical practice, evaluating the mean residence time (MRT) and terminal half-lives ($t_{1/2}$) of active metabolites from opioids is necessary to understand the exact duration of activity. Pharmacokinetic knowledge is also important in the care of poisoned patients with compounds that are modified opioids structures such as designer drugs. Therefore, the construction of prediction models for MRT as well as $t_{1/2}$ was attempted with QSPkR analyses.

[Methods] After the construction of a dataset, consisting of opioids with pharmacokinetic parameters, a number of descriptors including physico-chemical, quantum-chemical and structural parameters were calculated from each optimized structure. A small number of parameters with importance for the prediction of MRT were selected and used for the construction of the MRT-prediction model by artificial neural network analyses.

[Results and Discussion] A pharmacokinetic dataset with 26 kinds of opioids such as morphine, phentanyl, and methadone was constructed. Remifentanyl was eliminated because of becoming an obvious outlier in the construction process of the MRT prediction model. LogP and Bond Information Content index (BIC) were the important parameters related to MRT. As a result of the feature selection, artificial neural network model for MRT prediction was constructed with two structural descriptors with high generalization capability verified by cross-validation and external validation. This model is applicable for estimating terminal $t_{1/2}$ because it was able to predict from MRT with a high accuracy in opioids.