K204 Prediction of oral bioavailability of druglike chemical compounds

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1. Introduction

Development of drugs intended for oral use often fails to succeed due to their unfavorable pharmacokinetics. Hence, evaluation of ADME profiles in the early stage of drug discovery is required. Bioavailability (BA) is one of ADME parameters and indicates how much drug reaches general circulation. Low BA is one of major reasons to discontinue drug development. If we can build more accurate BA model, it enables us to estimate BA of virtually designed compounds and to select only high BA drug candidates to synthesize.

It has been thought that absorption and metabolism have a great influence on BA. Especially, absorption is more important process than metabolism because many drugs are metabolized only to some extent after being taken into body. We need to pay very attention to the process of absorption to build a good BA model.

Unfortunately, it is difficult to apply quantitative structure-activity relationship (QSAR) analysis to BA %activity data because drugs differ very widely in chemical structure. BA values, therefore, were converted into rank-rating data and then QSAR analysis was carried out. In our precedent study, we suggested that classification of drugs into acidity, neutrality and basicity is significant to make an appropriate estimate of BA. In this study, we tried to improve BA model taking into consideration the fractions of ionized and unionized molecules[4)] of each drug in body.

Ordinal logistic regression method was applied to BA data set in this study.

2. Methods

In this study, a drug BA data set was taken from Yoshida.[1)]. Though the data set was originally classified BA into four grades, in this study BA was reclassified into three grades because there were a littile number of lower BA compounds.

Chemical structures of drugs were collected from Drug Bank[2)] and NikkajiWeb[3)].

Since experimental BA values were not obtained, the following calculated physicochemical parameters were substituted for experimental data. log*P* was calculated by using ClogP v.4.82 (Daylight Chemical Information Systems Inc.), p*K*a by using Marvin Calculator pKa plugin v.4.1.10 (ChemAxon Kft.), and other 2D structural descriptors by using MOE 2006.08 (CCG Inc.). Ordinal logistic regression analysis was performed using JMP v.7.0.1 (SAS Institute Inc.).

3. Results and Discussion

To consider ionization of molecules in the intestinal tract at pH 6.5 and blood vessel at pH 7.4, the fractions of cations (fiB), anions (fiA) and unionized (fu) were calculated by using Henderson–Hasselbalch equation. For example, the expressions of fractions for acid compound which dissociates by single-step are described in Table 1.

Table 2 shows the comparison between type (acidity/neutrality/basicity) and fractions of ionized (fiA/fiB). Both parameters were added into other explanatory variables. The explanatory variables used in both analyses except type and fractions were topological polar surface area (TPSA), the number of rotatable bond (RB), molecular weight (MW), H-bond donor count (N_{HBD}), $(ClogP)^2$, fiA and fiB ,which were selected based on the correlations between explanatory variables.

As shown in Table 2, Spearman's rank correlation coefficient including fiA and fiB is higher than that of including type in test set though they are equal in training set. Thus, it is suggested that fiA and fiB are more appropriate variables than type to express the dissociation state.

Table 1. Expressions of fractions for acid compound that dissociates by single-step.

unionized fraction(fu)	$1 / (1 + 10^{pH-pKa})$
ionized fraction(fi)	fiA+fiB
cation fraction(fiB)	1/(1+antilog(7.4-pKa))
anion fraction(fiA)	1/(1+antilog(pKa-7.4))

Table 2. Comparison with results by parameters in relation to dissociation state.

		Fractions	Type
Spearman's rank correlation coefficient	training set	0.438	0.438
	test set	0.276	0.170
accuracy	training set	49.1%	49.1%
	test set	40.0%	40.0%

References

1) F. Yoshida, J. G. Topliss, *J. Med. Chem.* 2000, *43*, 2575-2585.

2) http://redpoll.pharmacy.ualberta.ca/drugbank/index.html

3) http://nikkajiweb.jst.go.jp/nikkaji_web/pages/top.html

4) T. Ghafourian *et al*., *Int. J. Pharm.* 2006, *319*, 82-97.