NOTES

A Toxicity Risk Index, An Index for Warning Idiosyncratic Drug Toxicity

MIYOSHI MORIMOTO, KAZUO SAMIZO, SHIN OHTA, TAKASHI MIZUMA

School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 1 March 2013; revised 15 April 2013; accepted 18 April 2013

Published online 10 May 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23596

ABSTRACT: Drug toxicity impedes drug development and its clinical use. In the present study, a toxicity risk index (TRI), which is an index for warning idiosyncratic drug toxicity (IDT), was proposed. The TRI of drugs was defined as a function of dose, pharmacokinetic parameters, and toxicokinetic data from covalent binding experiment. Twenty drugs, which were classified into three categories by a report (Nakayama S, Atsumi R, Takakusa H, Kobayashi Y, Kurihara A, Nagai Y, Nakai D, Okazaki O. 2009. Drug Metab Dispos 37:1970–1977), were studied with TRI. The three categories were BBW (drugs with a block box warning for IDT), WNG (drugs without a black box warning but with a warning for IDT), and SAFE (drugs without any warning). The TRIs of drugs classified as SAFE were distinctly different from those classified as BBW. The TRI of the SAFE drugs were lower than 0.456 (nmol/mg protein). In contrast, the TRI of the BBW drugs were higher than 1.10 (nmol/mg protein). These results warned us that a drug candidate, where the TRI is higher than 1.0 nmol/mg protein, should be categorized as a BBW drug. Further study with more data of TRI will give a cutoff value with a statistical meaning. Thus, TRI may be useful for decision making in drug development and its clinical use. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3447–3450, 2013

Keywords: metabolism; pharmacokinetics; preclinical pharmacokinetics; protein binding; toxicokinetics; black box warning; drug toxicity; covalent binding; idiosyncratic drug toxicity

INTRODUCTION

Serious adverse drug reactions (ADRs) can often emerge after approval of the United States Food and Drug Administration, and the safety of new agents cannot be established with complete certainty until the drug has been used extensively and has been on the market for several[1] or many years.[2] ADRs are described in so-called "black box" warnings contained on labeling/packaging information.[1] Such drug toxicity impedes drug development and its clinical use. Idiosyncratic drug toxicity (IDT), which is one of them, is too difficult to be predicted before a clinical study is conducted. Since Benet et al.[3] studied the drug toxicity and reported a quantitative study of covalent binding, several other research groups have studied this issue. Nevertheless, the issue still remains to be resolved. Drug toxicity can occur without any awareness, and is hard to be detected in advance. Thus, at the present time, any kind of indices for warning of drug toxicity risks is needed to avoid or lessen its occurrence.

Recently, Nakayama et al.[4] classified drugs into three categories and characterized those with their maximum daily dose and covalent binding to proteins in human hepatocytes (HHC) and human liver microsomes (HLM). The three categories were BBW (drugs with a block box warning for IDT in the Physician's Desk Reference (PDR)), WNG (drugs without a black box warning but with a warning for IDT in either the PDR or Japanese labeling), and SAFE (drugs without any warning in either the PDR or Japanese labeling). Those drugs were quantitatively analyzed with only two kinds of data (maximum daily dose and covalent binding). However, the daily dose analyzed was only a maximum dose, and a minimum daily dose was excluded, although a therapeutic dose range should be considered. Moreover, no pharmacokinetic parameters were considered in the analysis. In addition, the unit of dose in the report was gram mass (mg), but

Correspondence to: Takashi Mizuma (Telephone: +81-426-76-5224; Fax: +81-426-76-5292; E-mail: mizuma@toyaku.ac.jp)

Journal of Pharmaceutical Sciences, Vol. 102, 3447–3450 (2013)

not mol. This indicates a lack of stoichiometric aspect in the analysis.

In the present paper, therefore, the drugs categorized based on the warning information in package inserts were analyzed with not only a maximum daily dose but also a minimum daily dose in mol unit, covalent binding and pharmacokinetic parameters for a stoichiometric analysis. In the analysis, a toxicity risk index (TRI), which is an index for warning of drug toxicity risks, was defined by a function of molar dose, covalent binding, and pharmacokinetic parameters.

THEORY AND METHODS

Covalent Binding Activity

CBA is the covalent binding activity of drugs to proteins, and is defined as an amount of covalently bound to proteins per unit mass of proteins per unit concentration per unit time. CBA in the present study was calculated from the covalent binding to protein (CB) and its experimental condition (drug concentration and incubation time) in the report by Nakayama et al.[4] On the basis of the experimental condition of 10 μM drug concentration and 2 h incubation time (in the case of HHC) in the report, CBA was obtained according to the following equation.

$$\begin{aligned}\mathrm{CBA} &= \mathrm{CB\ (pmol/mg\ protein)}/10\ (\mu\mathrm{M})/2\ (\mathrm{h}) \\ &= \mathrm{CB}/20\ [\mu\mathrm{L/(mg\ protein\ h)}] \end{aligned} \quad (1)$$

Exposure Index

Exposure index (EPI) of drug is expressed by

$$\mathrm{EPI} = \frac{D \times F \times t_{1/2} \times \mathrm{fu}}{V} \quad (2)$$

D, F, $t_{1/2}$, fu, and V are daily dose, oral bioavailability, half-life, unbound fraction in plasma, and distribution volume, respectively. V is calculated as volume per 70 kg body weight. Pharmacokinetic parameters were collected from the literatures.[5–8]

Toxicity Risk Index

Toxicity risk index (TRI) is expressed by

$$\mathrm{TRI} = \mathrm{EPI} \times \mathrm{CBA} = \frac{D \times F \times t_{1/2} \times \mathrm{fu} \times \mathrm{CBA}}{V} \quad (3)$$

RESULTS AND DISCUSSION

CBA Obtained with HHC and HLM

Table 1 shows the CBA of drugs studied in the present study. The ranges of the CBA of the drugs categorized into BBW, WNG, and SAFE overlapped with each other in both samples: CBA (HHC) or CBA (HLM). This indicates that one cannot differentiate drugs in one category from another based on CBA alone.

Table 1. Covalent Binding Activities (CBA) of Drugs Classified into Three Categories

Category	Drug	CBA (HHC) [μL/(mg protein h)] mean ± SD	CBA (HLM) [μL/(mg protein h)] mean ± SD	Literature for Pharmacokinetic Parameters
BBW	Clozapine	4.135 ± 0.385	4.470 ± 0.260	G&G (12th Edition)
	Nevirapine	0.145 ± 0.095	1.910 ± 0.130	G&G (10th Edition)
	Ritonavir	2.385 ± 0.180	25.330 ± 2.480	G&G (12th Edition)
	Valproic acid	0.465 ± 0.035	0.630 ± 0.330	G&G (12th Edition)
WNG	Acetaminophen	0.420 ± 0.075	8.520 ± 0.570	G&G (12th Edition)
	Atorvastatin	10.460 ± 0.855	35.230 ± 6.040	G&G (12th Edition)
	Diclofenac	2.630 ± 0.130	1.590 ± 0.340	G&G (12th Edition)
	Fluoxetine	0.450 ± 0.120	1.500 ± 0.390	G&G (12th Edition)
	Imipramine	0.775 ± 0.015	13.380 ± 0.700	G&G (10th Edition)
	Phenytoin	0.185 ± 0.125	0.440 ± 0.040	G&G (10th Edition)
	Propranolol	0.470 ± 0.035	7.000 ± 1.230	G&G (12th Edition)
	Sulfamethoxazole	0.040 ± 0.005	0.320 ± 0.070	G&G (11th Edition)
	Tacrine	0.270 ± 0.010	13.700 ± 0.750	Daily Med
	Verapamil	0.800 ± 0.020	6.560 ± 1.000	G&G (12th Edition)
SAFE	Amlodipine	0.665 ± 0.090	0.730 ± 0.100	G&G (10th Edition)
	Olanzapine	1.925 ± 0.045	13.890 ± 4.780	G&G (10th Edition)
	Olmesartan	0.070 ± 0.045	0.340 ± 0.030	G&G (12th Edition)
	Pravastatin	0.125 ± 0.030	0.370 ± 0.110	G&G (10th Edition)
	Varsartan	0.020 ± 0.010	0.140 ± 0.060	G&G (11th Edition)
	Warfarin	0.400 ± 0.090	1.590 ± 0.260	G&G (12th Edition)

CBA (HHC), covalent binding activity with human hepatocytes; CBA (HLM), covalent binding activity with human liver microsomes; BBW, drugs with a block box warning for idiosyncratic drug toxicity (IDT); WNG, drugs without a black box warning but with a warning for IDT; SAFE, drugs without any warning. Literature: G&G (10th Edition),[5] G&G (11th Edition),[6] G&G (12th Edition),[7] and Daily Med.[8]