Communications to the Editor

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INTERCONVERSION MODEL ANALYSIS AND ESTIMATION OF AVAILABLE FRACTIONS FOR 4-ACETAMINOBENZALDEHYDE AND ITS REVERSIBLE METABOLITE, 4-ACETAMINOBENZYLALCOHOL, IN THE RAT USING THE MULTI-LINES FITTING TECHNIQUE

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An interconversion model which incorporated a first-pass metabolism was applied to the disposition kinetics of 4-acetaminobenzaldehyde (AB) and its reversible metabolite, 4-acetaminobenzylalcohol (ABA) in the rat. The rates of available fraction of AB, F_{H1}, and of the sequential available fraction of ABA, F_{H2}, were estimated by application of the computer multi-lines fitting technique.

KEYWORDS— 4-acetaminobenzaldehyde; 4-acetaminobenzylalcohol; interconversion model; first-pass metabolism; multi-line fitting

When 4-acetaminobenzaldehyde (AB) is given to rats, metabolite 4-acetaminobenzoic acid (ABZ) and reversible metabolite 4-acetaminobenzylalcohol (ABA) of AB appear in the plasma. The purpose of the present paper is to develop comprehensive equations which characterize the pharmacokinetics of the reversible drug/metabolite system in the conventional mamillary analysis. A modified interconversion model[1] (Chart 1) which incorporated a first-pass metabolism[2,3] was applied to the disposition kinetics of AB and its metabolites.

X_j (j = 1 to 4) is the amounts of the drug in compartments. k, k_{10}, k_{1j} and k_{j1} (j = 2 to 3) are the first-order rate constants describing the drug transfer, and k_{20} and $k_{ss,40}$ are the first-order rate constants describing the drug loss from a compartment. AB may be administered intravenously (D_{iv}) into compartment #1 of distribution volume V_1 to give a concentration C_1. Alternatively, AB may be administered through the hepatic portal vein (D_{pv}), where A is the amount of AB at the administered site. AB may be eliminated by the clearances CL_{12} (= $k_{12}V_1$) and CL_{10} (= $k_{10}V_1$). The metabolite, ABA occupies a distribution volume V_2 at compartment #2 to give a concentration C_2, and may be eliminated by the clearances CL_{21} (= $k_{21}V_2$) to generate the AB and CL_{20} (= $k_{20}V_2$). Another metabolite, ABZ may also be eliminated by CL_{40} (= $k_{ss,40}V_{ss,4}$). Compartment #4 is shown tentatively in the moment method.

Following pv administration of AB, a certain fraction of A enters into compartment #1 intact (F_{H1}) escaping hepatic metabolism. A part of the remaining

fraction $(1-F_{H1})$ of A undergoes first-pass metabolism entering into the systemic circulation (compartment #2) as the metabolite, ABA. The F_{H2} indicates a fraction of the generated metabolite ABA which enters into compartment #2 escaping sequential hepatic biotransformation.

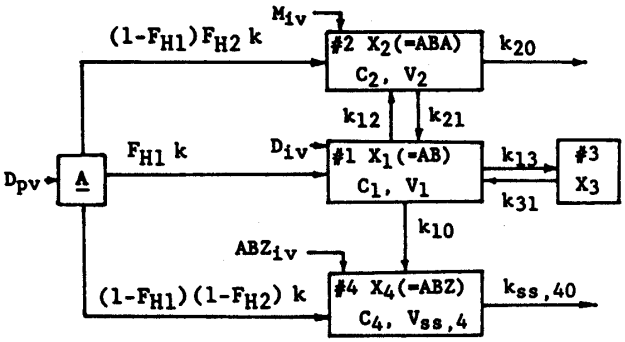

Chart 1

A system of first-order linear differential equations with constant coefficients can be written:

$$d\underline{A}/dt = -[F_{H1} + (1-F_{H1})F_{H2} + (1-F_{H1})(1-F_{H2})]k\underline{A} = -k\underline{A} \quad (1)$$

$$dX_1/dt = F_{H1}k\underline{A} - E_1X_1 + k_{21}X_2 + k_{31}X_3 \quad (2)$$

$$dX_2/dt = (1-F_{H1})F_{H2}k\underline{A} + k_{12}X_1 - E_2X_2 \quad (3)$$

$$dX_3/dt = k_{13}X_1 - k_{31}X_3 \quad (4)$$

$$dX_4/dt = (1-F_{H1})(1-F_{H2})k\underline{A} + k_{10}X_1 - k_{ss,40}X_4 \quad (5)$$

where E_i (i = 1 to 2) is the sum of first-order exit rate constants from compartment : $E_1 = k_{10} + k_{12} + k_{13}$ and $E_2 = k_{20} + k_{21}$.

Special assumptions were made: Null biliary and urinary eliminations of AB are assumed. The clearance of ABZ being comparatively small, the elimination rate constant $k_{ss,40}$ is negligible in this model. Therefore, Eq.(5) is excluded.

The Laplace transform[4] of the plasma concentration-time curve of the metabolite in compartment #2 after pv administration of AB, for instance, is given by

$$\tilde{C}_2^{D_{pv}}(s) = \frac{D_{pv}k[F_{H1}k_{12}(s+k_{31})+(1-F_{H1})F_{H2}(s+Y)(s+Z)]}{V_2(s+\alpha)(s+\beta)(s+\gamma)(s+k)} \quad (6)$$

where α, β, γ, Y and Z are in terms of the individual rate constants, and s is the Laplace parameter. The following relationships hold:

$$(s+Y)(s+Z) = (s+E_1)(s+k_{31})-k_{13}k_{31} \quad (7), \quad YZ = k_{31}(k_{10}+k_{12}) \quad (8), \quad E_2=\gamma \quad (9)$$

$$\alpha+\beta = Y+Z = E_1+k_{31} \quad (10), \quad \alpha\beta = k_{31}[(k_{10}+k_{12})k_{20}+k_{10}k_{21}]/(k_{20}+k_{21}) \quad (11)$$

and Y or $Z = [(\alpha+\beta)\pm\sqrt{(\alpha+\beta)^2-4k_{31}(k_{10}+k_{12})}]/2, \qquad (\alpha>Y>Z>\beta) \quad (12)$

The plasma concentration-time equations of AB and ABA are:

$$C_1^{D_{iv}} = \frac{D_{iv}}{V_1}\left[\frac{(k_{31}-\alpha)}{(\beta-\alpha)}e^{-\alpha t} + \frac{(k_{31}-\beta)}{(\alpha-\beta)}e^{-\beta t}\right] = P_1e^{-\alpha t} + P_2e^{-\beta t} \quad (13)$$

$$C_2^{D_{iv}} = \frac{D_{iv}k_{12}}{V_2}\left[\frac{(k_{31}-\alpha)}{(\beta-\alpha)(\gamma-\alpha)}e^{-\alpha(t-t_0)} + \frac{(k_{31}-\beta)}{(\alpha-\beta)(\gamma-\beta)}e^{-\beta(t-t_0)} + \frac{(k_{31}-\gamma)}{(\alpha-\gamma)(\beta-\gamma)}e^{-\gamma(t-t_0)}\right] \quad (14)$$

$$C_2^{M_{iv}} = \frac{M_{iv}}{V_2}\left[\frac{(E_1-\alpha)(k_{31}-\alpha)-k_{13}k_{31}}{(\beta-\alpha)(\gamma-\alpha)}e^{-\alpha t} + \frac{(E_1-\beta)(k_{31}-\beta)-k_{13}k_{31}}{(\alpha-\beta)(\gamma-\beta)}e^{-\beta t} + \frac{(E_1-\gamma)(k_{31}-\gamma)-k_{13}k_{31}}{(\alpha-\gamma)(\beta-\gamma)}e^{-\gamma t}\right]$$
$$= Q_1e^{-\alpha t} + Q_2e^{-\beta t} + Q_3e^{-\gamma t} \quad (15)$$

$$C_{2pv}^{D} = \frac{D_{pv}k}{V_2}\left[\frac{F_{H1}k_{12}(k_{31}-\alpha)+(1-F_{H1})F_{H2}((E_1-\alpha)(k_{31}-\alpha)-k_{13}k_{31})}{(\beta-\alpha)(\gamma-\alpha)(k-\alpha)}e^{-\alpha(t-t_0')}\right.$$
$$+\frac{F_{H1}k_{12}(k_{31}-\beta)+(1-F_{H1})F_{H2}((E_1-\beta)(k_{31}-\beta)-k_{13}k_{31})}{(\alpha-\beta)(\gamma-\beta)(k-\beta)}e^{-\beta(t-t_0')}$$
$$+\frac{F_{H1}k_{12}(k_{31}-\gamma)+(1-F_{H1})F_{H2}((E_1-\gamma)(k_{31}-\gamma)-k_{13}k_{31})}{(\alpha-\gamma)(\beta-\gamma)(k-\gamma)}e^{-\gamma(t-t_0')}$$
$$\left.+\frac{F_{H1}k_{12}(k_{31}-k)+(1-F_{H1})F_{H2}((E_1-k)(k_{31}-k)-k_{13}k_{31})}{(\alpha-k)(\beta-k)(\gamma-k)}e^{-k(t-t_0')}\right] \quad (16)$$

where superscripts indicate the administration routes of AB (D) and the preformed ABA (M), and t_0 and t_0' are the lag times, respectively.

AB, ABZ and other reagents are of special reagent grade, and ABA was given by reduction of AB with $NaBH_4$ in MeOH. Doses (0.4 mmol/kg) of AB, ABA and ABZ dissolved in pH 7.4 phosphate buffer solution were administered iv or pv to male Wistar rats (220-350 g). Plasma samples (0.2 ml) collected at regular intervals were assayed by HPLC (Shimadzu LC-6A, UV 254 nm and 290 nm for AB) with an internal standard of 4-acetaminoacetophenone. The mean plasma concentrations of AB and its metabolites are shown in Figs. 1 and 2. Terminal elimination slopes λ, AUC's and four fundamental clearances[1] are indicated in Table I.

Table I. Parameters Characterizing the Dispositions of AB, ABA and ABZ

Terminal slope (min^{-1})		AUC (μmol·min/ml)		Clearance (l/min·kg)		Distribution volume (l/kg)		Rate constant (min^{-1})			
λ^{D}_{iv}	0.396	AUC^{D}_{1iv}	0.46	CL_{10}	0.835[a]	V^{D}_{ss}	1.73[b]	k_{10}	1.61	α	2.70
		AUC^{D}_{2iv}	1.21	CL_{12}	0.096	V_1	0.52[c]	k_{12}	0.19	β	0.52
λ^{M}_{iv}	0.159	AUC^{M}_{2iv}	11.7	CL_{20}	0.014	V^{M}_{ss}	0.14	k_{20}	0.10	γ	0.28
		AUC^{M}_{1iv}	0.29	CL_{21}	0.023	V_2	0.13[d]	k_{21}	0.18		
		AUC^{D}_{1pv}	0.33					k_{31}	0.83[e]		
		AUC^{D}_{2pv}	2.63					k	16[f]		
λ^{ABZ}_{iv}	3.7×10^{-3}	AUC^{ABZ}_{iv}	100	CL_{40}	4.5×10^{-3}	$V_{ss,4}$	1.51	$k_{ss,40}$	5.5×10^{-3}		

a) $CL_{10}=(AUC^{M}_{2iv}D_{iv}-AUC^{D}_{2iv}M_{iv})/\Delta$, $CL_{12}=AUC^{D}_{2iv}M_{iv}/\Delta$, $CL_{20}=(AUC^{D}_{1iv}M_{iv}-AUC^{M}_{1iv}D_{iv})/\Delta$ and $CL_{21}=AUC^{M}_{1iv}D_{iv}/\Delta$, where $\Delta=(AUC^{D}_{1iv}AUC^{M}_{2iv}-AUC^{D}_{2iv}AUC^{M}_{1iv})$.
b) $V_{ss}=Dose\cdot MRT/AUC=CL/K_{ss}$, $AUC=\int_0^T Cdt+C_T/\lambda$ and $MRT=(\int_0^T t\cdot Cdt+TC_T/\lambda+C_T/\lambda^2)/AUC$.
c) $V_1=D_{iv}/(P_1+P_2)$. d) $V_2=M_{iv}/(Q_1+Q_2+Q_3)$, and V_2 is almost equal to V^{M}_{ss}. e) Calcd from Eq.(11). f) $k=1/F_{H1}(MRT^{D}_{1pv}-MRT^{D}_{1iv})$.

The relationships[3] among AUC's of AB and/or ABA following iv and pv administration of AB are:

$$F_m = \frac{AUC^{D}_{2pv}/D_{pv}}{AUC^{D}_{2iv}/D_{iv}} = \lim_{s\to0}\frac{\tilde{C}^{D}_{2pv}(s)/D_{pv}}{\tilde{C}^{D}_{2iv}(s)/D_{iv}} = F_{H1}+\frac{(1-F_{H1})F_{H2}}{k_{12}/(k_{10}+k_{12})} \quad (17)$$

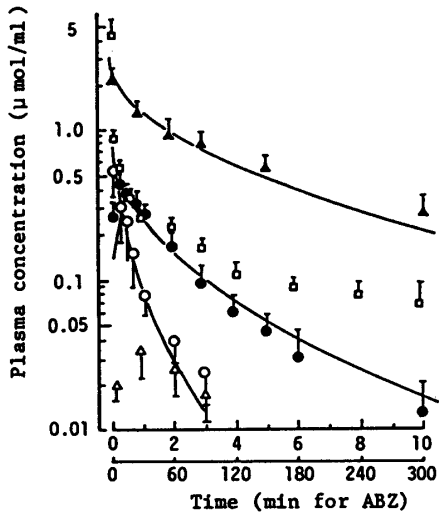

Fig. 1. Mean Plasma Concentrations for AB (○) and Its Reductive Metabolite (●), ABA (▲) and Its Oxidised Metabolite (△), and ABZ (□) after iv Administrations of Respective 0.4 mmol/kg Doses in Rats (n=3-5)

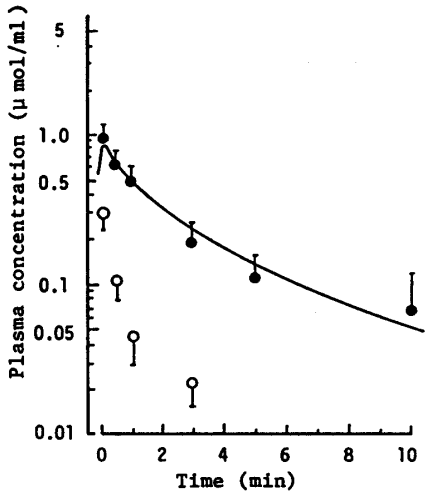

Fig. 2. Mean Plasma Concentrations for AB (○) and Its Reductive Metabolite (●) after pv Administration of 0.4 mmol/kg Dose of AB in Rats (n = 3) Lines in both figures indicate the curves obtained from computer multi-lines fitting.

$$\text{and} \quad F = \frac{(CL_{10}AUC_1^{D_{pv}} + CL_{20}AUC_2^{D_{pv}})/D_{pv}}{(CL_{10}AUC_1^{D_{iv}} + CL_{20}AUC_2^{D_{iv}})/D_{iv}} = 1 - (1 - F_{H1})(1 - F_{H2}) \qquad (18)$$

Substituting each value given in Table I into Eqs. (17) and (18), F_{H1} and F_{H2} were found to be about 0.6 and 0.4, respectively. Besides, the simultaneous computer multi-lines fitting of the plasma concentration equations of (13), (14), (15) and (16) was tested with a Simplex algorithm of the program, MULTI[5] using the parameters in Table I as the initial values. The lag times were treated in trial and error. The pharmacokinetic parameters to be estimated were P(1), P(2) ・・・ P(14) in Eqs. (9) to (16). The weight of data points adopted was 1/C. The converged values of respective parameters are listed in Table II.

Table II. Pharmacokinetic Parameters Obtained from the Multi-Lines Fitting

	Rate constant (min^{-1})					Lag time (min)		Distribution volume (l/kg)		F_{H1}	F_{H2}	SS[a]	AIC[b]
α	2.34	k_{10}	2.68	k_{20}	0.063	t_0	8.7×10^{-3}	V_1	0.49	0.25	0.38		
β	0.41	k_{12}	0.50	k_{21}	0.33	t_0'	9.8×10^{-3}	V_2	0.17				
γ	0.32			k	17.2							0.94	26.4

a) Residual sum of squares. b) An information criterion proposed by Akaike.

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