Pharmacokinetics of Ivermectin Administered Intravenously to Cattle

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Abstract □ Ivermectin, a macrocyclic lactone disaccharide antiparasitic agent, was administered intravenously to six young calves (one bull, five steers) as a bolus dose of 200 μg/kg. The disposition kinetics of ivermectin in cattle can be described by a three-compartment open model with elimination from the central compartment. Compartmental analysis yielded mean parameters as follows: terminal elimination rate constant (β) = 0.258 d^{-1}, biological half-life ($t_{1/2\beta}$) = 2.7 d; apparent volume of distribution of the central compartment (Vd_1) = 0.45 L/kg; apparent volume of distribution at steady state (Vd_{ss}) = 2.4 L/kg. The area under the plasma concentration–time curve (AUC) was 254 ng · d/mL. Noncompartmental parameters, obtained by utilizing statistical moment theory, mean residence time (MRT), clearance *(CL)*, and Vd_{ss} were calculated to be 2.8 d, 0.79 L/kg · d, and 2.2 L/kg, respectively.

Ivermectin,[1,2] a macrocyclic lactone disaccharide, is a potent antiparasitic agent capable of controlling a broad range of external and internal parasites in livestock by oral or parenteral dosing.[3] The present study was undertaken to establish an appropriate pharmacokinetic model to describe the plasma concentration profiles of ivermectin in cattle after rapid intravenous (bolus) injection.

Experimental Section

Protocol—Six Hereford and Hereford-cross calves were used. The one bull and five steers were in good physical condition, aged less than 1 year, and weighed between 224 and 292 kg at the beginning of the trial (Table I). The animals were collectively housed in covered pens with access to open yards. Their diet consisted of alfalfa hay cubes and water ad libitum. Ivermectin was administered as a 20-mg/mL micelle solution that can be infinitely diluted with water. A single intravenous dose of 0.2 mg of ivermectin per kg of body weight was rapidly injected into a jugular vein. Blood was collected from the contralateral jugular vein in evacuated heparinized tubes. Plasma was separated by centrifugation and frozen until assayed for ivermectin.

Analytical Method—Ivermectin was determined in plasma after suitable sample preparation by reversed-phase HPLC with UV photometric detection. An accuracy of 2 ng/mL (mean deviation) and a precision in the range of 1–3 ng/mL (mean deviation) are typically observed with this method.[4]

Computer Analysis of Experimental Data—Concentrations of ivermectin in plasma of individual calves were evaluated by both compartmental and noncompartmental analysis. The data were fitted by compartmental analysis to the three-compartment open model with bolus intravenous input. In this model the concentration of ivermectin in plasma (C_1) at any time (t) is described by a triexponential equation:

$$C_1 = A_1e^{-\alpha t} + A_2e^{-\beta t} + A_3e^{-\gamma t} \quad (1)$$

where α, β, and γ are the slopes ($\gamma > \alpha > \beta$) and A_1, A_2, and A_3 are the zero time intercepts of the three exponential segments, respectively, into which the concentration–time curve was resolved. The data [weighted ($1/obs^2$)] were fitted by using the nonlinear regression analysis program NONLIN.[5] Initial parameter estimates were obtained by using the CSTRIP program.[6]

Noncompartmental analysis of the ivermectin plasma concentration–time data was made by applying the statistical moment theory as described by Gibaldi and Perrier.[7] The area under the concentration–time curve (AUC) (${}_0\int^\infty C\,dt$ – the zero moment) and the area under the first moment of the concentration–time curve (AUMC) (${}_0\int^\infty tC\,dt$ – the first moment) were calculated according to the trapezoidal rule from $t = 0$ to $t =$ time of the first measured zero concentration. The $C(0)$ plasma levels were taken to be the C_0 estimations from the compartmental analysis of the concentration–time data. The mean residence time (MRT) was calculated by the ratio of AUMC to AUC; clearance *(CL)* was calculated as the reciprocal of the zero moment of the plasma concentration–time curve normalized for the intravenous dose, and the apparent steady-state volume of distribution (Vd_{ss}) was calculated from the product of CL and MRT.

Table I—Vital Statistics of Cattle

Animal Number	Sex[a]	Weight, kg
3181	MC	241
3182	MC	292
3183	M	227
3184	MC	224
3189	MC	247
3190	MC	245

[a] Abbreviations used: M, male; MC, male castrate.

Results and Discussion

The ivermectin concentrations in plasma of the six young male calves after a 0.2-mg/kg rapid intravenous dose of ivermectin are presented in Table II. Figure 1 depicts the mean ivermectin levels in plasma. A three-compartment open model described by eq. 1 can be used to characterize the disposition kinetics of ivermectin in cattle after rapid intravenous injection. Preliminary estimates of the parameters for the nonlinear least-squares fitting were obtained by using CSTRIP.[6] Based on the "goodness-of-fit" criteria of Sedman and Wagner,[8] three of the individual data sets and the mean data demonstrated a significant improvement in fit when three instead of two exponential terms were used. In the other three cases, there was an improvement, though not

Table II—Ivermectin Concentrations in Plasma at Indicated Sampling Times Following the Rapid Intravenous Administration of Ivermectin at 0.2 mg/kg in Micelle Solution to Six Young Calves

Time, d	Ivermectin Conc., ng/mL, in Animal Number:					
	3181	3182	3183	3184	3189	3190
0.01	479	442	200	364	362	460
0.04	270	287	132	223	208	323
0.08	197	218	109	181	151	217
0.16	143	158	83	121	115	173
0.25	128	131	69	95	92	140
0.50	62	80	57	71	66	102
1.00	48	52	41	53	45	66
1.25	37	43	36	41	40	57
2.00	33	36	31	31	27	40
3.00	17	24	24	25	17	29
4.00	12	16	21	20	13	20
7.00	5	5	11	11	5	8
10.00	2	1	5	6	2	3
14.00	1	3	2	3	0	0
21.00	0	0	0	0	0	0

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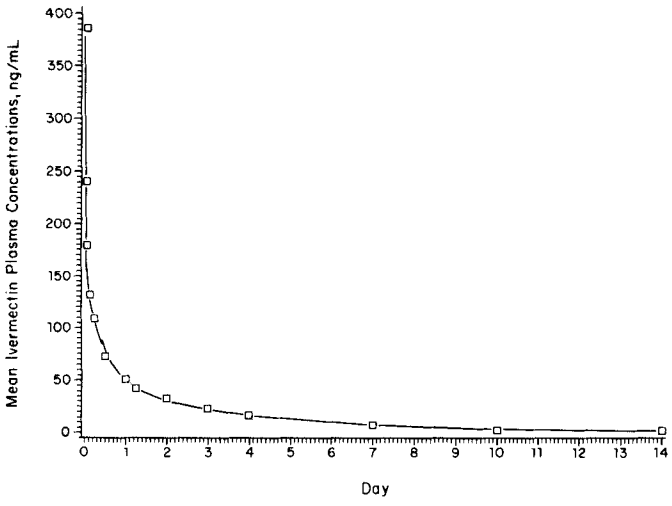

Figure 1—*Mean observed (squares) versus model predicted (continuous curve) ivermectin concentrations in plasma after the rapid intravenous administration of ivermectin to six young male calves.*

significant, in fit, with resolution of the observed data into three exponents over two exponents. All the data were consequently fitted by NONLIN according to eq. 1. Table III summarizes the parameter estimates for the nonlinear least-squares regression analysis of the ivermectin concentrations in plasma of the individual calves.

Numerous three-compartment disposition models can be envisaged with elimination from the central and/or peripheral compartments. All models are described by a triexponential equation but can be differentiated if additional information is available (e.g., drug levels in fluids other than blood or plasma and/or plasma concentrations after different routes of administration.)[9] Such data are available for ivermectin.

When ivermectin is administered to sheep intravenously and intraabomasally, the AUCs differ by only about 5%.[10] A significant hepatic first-pass effect is therefore not evident in ruminant species. On the basis of this independent observation, the first-pass three-compartment model (elimination-/metabolism via a peripheral compartment) was considered inappropriate, and the three-compartment open model with elimination from the central (rapidly equilibrating) compartment was selected as an appropriate model to describe ivermectin disposition kinetics in cattle after rapid intravenous injection.

This model (Fig. 2) is described by eq. 2:

$$C_1 = \frac{D}{Vd_1}\left[\frac{(E_2-\alpha)(E_3-\alpha)}{(\beta-\alpha)(\gamma-\alpha)}e^{-\alpha t} + \frac{(E_2-\beta)(E_3-\beta)}{(\alpha-\beta)(\gamma-\beta)}e^{-\beta t} + \frac{(E_2-\gamma)(E_3-\gamma)}{(\alpha-\gamma)(\beta-\gamma)}e^{-\gamma t}\right] \quad (2)$$

Table III—Estimates of Parameters for Nonlinear Least-Squares Regression Analysis of Ivermectin Concentrations in Plasma Fitted to the Three-Compartment Open Model (Equation 1)

Parameter	Animal Number					
	3181	3182	3183	3184	3189	3190
A_1, ng/mL	136.0	203.0	62.0	129.0	85.0	133.0
α, d^{-1}	2.34	5.42	3.45	2.87	1.94	2.41
A_2, ng/mL	40.1	82.1	49.2	45.9	45.0	74.3
β, d^{-1}	0.284	0.429	0.227	0.199	0.313	0.321
A_3, ng/mL	394.0	264.0	123.0	295.0	306.0	337.0
γ, d^{-1}	28.9	45.5	31.9	37.2	29.1	25.9

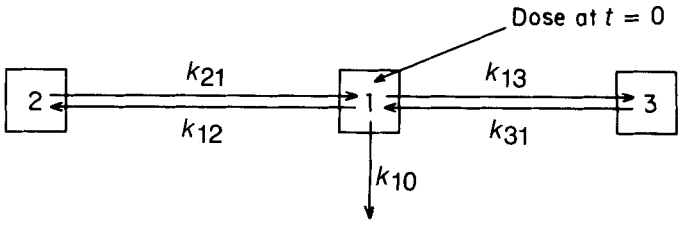

Figure 2—*Three-compartment open model with bolus intravenous injection into and elimination from the central compartment.*

where D is the administered dose, Vd_1 is the volume of distribution of the central compartment, E_2 and E_3 are the sums of the exit-rate constants out of compartments 2 and 3, respectively,[11] and α, β, and γ are the slopes of the exponential segments of the concentration–time curves noted above. The microscopic rate constants, k_{12}, k_{21}, k_{13}, k_{31}, and k_{10}, were determined by appropriate manipulation[12] of equation 2. Table IV presents the parameter estimates and measures of fit for the NONLIN analysis of the mean ivermectin concentration–time data fitted to eq. 2.

Table V presents the summary of "noncompartmental" parameter estimates based on statistical moment theory for the mean ivermectin concentration–time data. The MRT, calculated from the areas under the first and zero moment curves, corresponds well with its "compartmental" analogue, $t_{1/2\beta} = 0.693/\beta$ (Table IV). The Vd_{ss}, based on MRT and CL, is approximately the same value estimated from the compartmental microconstants:

$$Vd_{ss} = Vd_1\left[1 + \frac{k_{12}}{k_{21}} + \frac{k_{13}}{k_{31}}\right] \quad (3)$$

(Table IV). This close agreement between the pharmacokinetic parameters for drug residence and Vd highlights the

Table IV—Parameter Estimates for Nonlinear Least-Squares Regression Analysis[a] of Mean Ivermectin Concentrations in Plasma Fitted According to the Three-Compartment Open Model with Elimination from the Central Compartment (eq. 2)

Parameter	Estimate
γ, d^{-1}	24.8
α, d^{-1}	2.13
β, d^{-1}	0.258
k_{12}, d^{-1}	12.5
k_{21}, d^{-1}	9.68
k_{13}, d^{-1}	2.43
k_{31}, d^{-1}	0.789
k_{10}, d^{-1}	1.79
C_0, ng/mL	442.0
Vd_1, L/kg	0.452
Vd_{ss}, L/kg	2.43
AUC, ng · d/mL	254.0

[a] Measures of fit: R^2 = (WYS − WS)/WYS = 1.000, where WYS = $\sum_j W_{ij}(Y_{ij} - \bar{Y})^2$ and WS = $\sum_j (Y_{ij} - YCALC_{ij})^2 W_{ij}$; and COR = 0.999 = the correlation between observed and predicted concentrations.

Table V—Summary of Noncompartmental (Statistical Moment Theory) Analysis for Ivermectin Administered Intravenously in Cattle

Parameter	Equation[a]	Value
AUC	$_0\int^\infty CdT$	254 ng · d/mL
AUMC	$_0\int^\infty tCdT$	714 ng · d^2/mL
MRT[b]	AUMC/AUC	2.8 d
CL	D_{iv}/AUC	0.79 L/kg · d
Vd_{ss}	$D_{iv}[\frac{AUMC}{AUC^2}]$	2.2 L/kg

[a] Equations from ref. 7. D_{iv} = 200,000 ng/kg. [b] MRT, Mean residence time.

appropriateness of the compartmental analysis. This pharmacokinetic model will provide the basis for evaluation of the "formulation effects" in dosage-form design research and development of ivermectin products in cattle.

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