Composite Pharmacokinetic Profiling

Keyphrases □ Pharmacokinetics—composite profiling, ceftriaxone, diazepam □ Composite profiling—pharmacokinetics, ceftriaxone, diazepam

To the Editor:

In certain patient populations, most notably neonates, it has been difficult to obtain an adequate number of blood samples to develop complete pharmacokinetic profiles of drugs due to sample-volume limitations. For this, as well as other ethical and medical reasons, the neonate has been termed a "therapeutic orphan" in that little pharmacokinetic information has been generated in this patient group. However, since the neonate represents the most physiologically dynamic patient population, it is important to understand the pharmacokinetics of drugs that are used to treat these patients. In an effort to minimize blood sampling and still develop meaningful pharmacokinetic profiles, a composite pharmacokinetic profiling approach (*e.g.*, combining blood concentrations from patients or subjects to produce a functional profile that is not possible to derive from the concentration–time data of one individual) has been investigated and will be developed in this report using simulation and curve-fitting techniques.

Crow and Gibaldi (1) have discussed the rationale for developing a composite pharmacokinetic profile by obtaining plasma concentration–time data at different times in the same patient during several dosing intervals at steady state. These authors stated that the accuracy of this composite method depends on assay variability, intrapatient pharmacokinetic variability, dosing interval reproducibility, and patient compliance. If one assumes that plasma concentration–time data among patients are normally distributed, one can apply this same rationale to developing a pharmacokinetic profile using plasma concentration–time data from several patients following single-dose administrations. This approach eliminates intrapatient pharmacokinetic variability, constancy of dosing interval, and patient compliance as variables, but adds interpatient pharmacokinetic variation. In addition, it may offer the only reasonable and perhaps the only ethical means of developing a single-dose pharmacokinetic profile of certain drugs in premature (≤2.0 kg) neonates in whom the total blood volume is ~75–80 mL/kg.

The composite profiling technique was tested by simulating blood concentration–time profiles for short and long half-life drugs that reflect both mono- and biexponential elimination characteristics following first-order absorption using complete sampling schedules. To reflect variability in real concentration–time profiles, data for 18 patients were simulated when three sampling groups were used, 20 patients were simulated when four sampling groups were used. Normally distributed error with a coefficient of variation (*CV*) of 10% was introduced into the pharmacokinetic parameters, and normally distributed error with a *CV* of 10% was introduced into the resulting concentration data. For the biexponential long half-life case, normally distributed error with a *CV* of 25% was introduced into the pharmacokinetic parameters followed by the same 10% error introduced into the resulting concentration data. These concentration–time data were then used to establish the impact of sampling times and the number of observations per time point on parameter estimations by employing the following three sampling schedules:

1. For the monoexponential short half-life drug, patients were divided into three groups of six patients each: group I was sampled at 0, 1, 4, and 12 h; group II was sampled at 0, 2, 6, and 18 h; group III was sampled at 0, 3, 8, and 24 h.
2. For the biexponential, short half-life drug, patients were divided into three groups of six patients each: group I was sampled at 0, 0.5, 3, 8, and 24 h; group II was sampled at 0, 1, 4, 12, and 24 h; group III was sampled at 0, 2, 6, 18, and 24 h.
3. For both the mono- and biexponential, long half-life drugs, patients were divided into four groups of five patients each: group I was sampled at 0, 1, 6, and 24 h; group II was sampled at 0, 2, 8, and 36 h; group III was sampled at 0, 3, 12, and 48 h; group IV was sampled at 0, 4, 18, and 72 h.

It was assumed that sampling would be limited to five or less samples per patient. These simulated data were then used as input for curve-fitting composite profiles using six, three, and one patients per group for three group sampling schedules or five, three, and one patients per group for the four group sampling schedules. Simulations and curve-fitting procedures were conducted using the nonlinear regression program, NONLIN (2).

The results of the composite curve-fits of these simulations are presented in Tables I (monoexponential elimination) and II (bioexponential elimination). If one compares the parameter values from the composite profiles to the ideal parameter values, it is clear that reasonable approximation of the "true" parameter values can be obtained by fitting the composite profile even if only one patient is included in each sampling group. The least-variable parameter is clearance (*e.g.*, the parameter of greatest interest), and good estimates of the elimination rate constants are obtained (Tables I and II). These observations are in good agreement with those of Crow and Gibaldi (1). The results of fitting the composite profiles containing normally distributed error with a *CV* of 25% in the parameter values as well as a *CV* of 10% in the resulting concentration data are presented in Table III. Good approximations of the "true" parameter values were obtained even with the introduction of normally distributed error with a *CV* of 25%, *i.e.*, two *SD* encompass 50–150% (threefold) of the mean. This observation indicates that the method is robust and can accommodate even large differences associated with interindividual variation.

Experimental data from two clinical pharmacokinetic studies were used as a final test of the proposed composite profiling technique. In the first study, 2 g of ceftriaxone was administered by intravenous infusion to 12 healthy male subjects over a 30-min interval. Blood samples were obtained during and following the infusion of drug. The subjects were divided into four groups of three subjects each: group I was sampled at 0, 10, and 40 min, 2 and 10 h; group II was sampled at 0, 20, and 50 min, 4 and 12 h; group III was sampled at 0 and 30 min, 1, 6, and 16 h; group IV was sampled at 0 and 35 min, 1.5, 8, and 24 h after starting the 30-min infusion. The *CV* for the analytical data in this study was 4.4%. In the second study 10 mg of diazepam was administered orally to 20 healthy

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Table I—Pharmacokinetic Parameters Obtained by Composite Profiling Monoexponential Elimination Data [a] Which Contained 10% *CV* Random Error in Parameters and 10% *CV* Error in the Resulting Concentrations

Study Conditions			r	C_0, μg/mL	K, h^{-1}	k_a, h^{-1}	AUC, μg·h/L	CL, L/h	Vd, L
No. of Groups	Patients Per Group	No. of Replicates							
					Short (6-h) Half-Life				
			(Ideal)	100	0.116	0.693	718	13.9	120
3	6	1	0.991	96.9	0.110	0.656	733	13.6	124
3	3	1	0.992	90.9	0.104	0.623	728	13.7	132
3	3	1	0.992	100	0.113	0.730	748	13.4	118
3	1	6	0.994 ± 0.003	102 ± 25	0.111 ± 0.013	0.740 ± 0.251	741 ± 22	13.5 ± 0.4	124 ± 15
					Long (18-h) Half-Life				
			(Ideal)	100	0.039	0.347	2276	4.39	113
4	5	1	0.993	112	0.042	0.297	2290	4.37	104
4	3	1	0.992	110	0.043	0.305	2197	4.55	106
4	1	5	0.993 ± 0.002	114 ± 10	0.043 ± 0.002	0.249 ± 0.034	2287 ± 148	4.39 ± 0.27	103 ± 7

[a] Dose = 10 mg.

Table II—Pharmacokinetic Parameters Obtained by Composite Profiling Biexponential Elimination Data [a] Which Contained 10% *CV* Error in Parameters and 10% *CV* Error in the Resulting Concentrations

Study Conditions			r	A μg/mL	α, h^{-1}	B, μg/mL	β, h^{-1}	k_a, h^{-1}	AUC, mg·h/L	CL, L/h	Vd, L
No. of Groups	Patients Per Group	No. of Replicates									
						Short (6-h) Half-Life					
			Ideal	70	0.693	30	0.116	3.00	327	30.6	264
3	6	1	0.996	52.4	0.659	31.0	0.120	3.72	315	31.7	265
3	3	1	0.997	0.914	1.34	33.7	0.126	1.48	309	32.4	257
3	3	1	0.996	43.1	0.592	30.5	0.117	10.0	326	30.7	262
3	1	6	0.998	78.5	0.798	32.0	0.119	3.53	323	31.1	261
		(*SD*)	± 0.002	± 39.9	± 0.193	± 3.7	± 0.006	± 1.41	± 22	± 2.0	± 14
						Long (18-h) Half-Life					
			Ideal	70	0.231	30	0.039	1.39	1000	10.0	256
4	5	1	0.997	58.7	0.173	28.0	0.040	1.46	980	10.2	255
4	3	1	0.998	64.9	0.172	25.9	0.039	1.40	976	10.2	262
4	1	5	0.997	65.4	0.190	27.0	0.038	1.67	999	10.0	265
		(SD)	± 0.002	± 13.9	± 0.083	± 7.7	± 0.005	± 0.69	± 61	± .6	± 31

[a] Dose = 10 mg.

Table III—Pharmacokinetic Parameters Obtained by Composite Profiling Biexponential Long Half-Life Data [a] Which Contained 25% *CV* Error in Parameters and 10% *CV* Error in the Resulting Concentrations

Study Conditions			r	A, μg/mL	α, h^{-1}	B, μg/mL	β, h^{-1}	k_a, h^{-1}	AUC, mg·h/L	CL, L/h	Vd, L
No. of Groups	Patients per Group	No. of Replicates									
			Ideal	70	0.231	30	0.039	1.39	1000	10	256
4	5	1	0.997	50.0	0.210	36.2	0.048	1.35	928	10.8	225
4	3	1	0.998	59.5	0.239	39.4	0.051	1.26	943	10.6	208
4	1	5	0.997 ± 0.002	66.9 ± 28.4	0.297 ± 0.154	37.7 ± 14.3	0.047 ± 0.005	1.26 ± 0.39	962 ± 158	10.6 ± 1.5	230 ± 48

Table IV—Pharmacokinetic Parameters Obtained by Fitting Ceftriaxone and Diazepam Data

Fitting Procedure	r	A, μg/mL	α, h^{-1}	B, μg/mL	β, h^{-1}	k_a, h^{-1}	t_{lag}, h	AUC, μg·h/mL	CL, L/h	Vd, L
					Ceftriaxone Data					
Mean of Individual Fits	0.993–0.998	101	5.20	3210	0.119	NA[a]	NA	1656	1.21	10.2
Fit of Mean Data	0.999	96	4.62	3210	0.119	NA	NA	1653	1.21	10.2
Fit of All Data	0.996	93	4.66	3150	0.121	NA	NA	1617	1.24	10.3
Composite Fit of Four Groups	0.997	84	5.90	3170	0.122	NA	NA	1624	1.23	10.1
					Diazepam Data					
Mean of Individual Fits	0.904–1.000	570	1.49	124	0.026	10.8	0.16	5088	1.96	75.6
Fit of Mean Data	1.000	592	1.51	129	0.025	3.71	0.19	5358	1.87	74.7
Fit of All Data	0.910	440	1.50	116	0.025	4.07	0.32	4797	2.08	83.2
Composite Fit of Four Groups	0.898	1450	2.03	118	0.024	2.66	0.29	5041	1.98	82.7

[a] Not applicable.

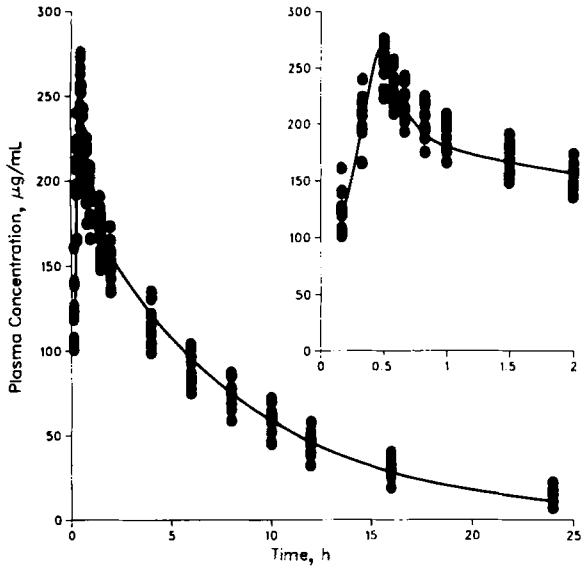

Figure 1—*All ceftriaxone plasma concentration–time data from 12 subjects together with the curve fitted using the composite pharmacokinetic profiling technique and three subjects in each of four sampling groups, as depicted in Table IV (inset).*

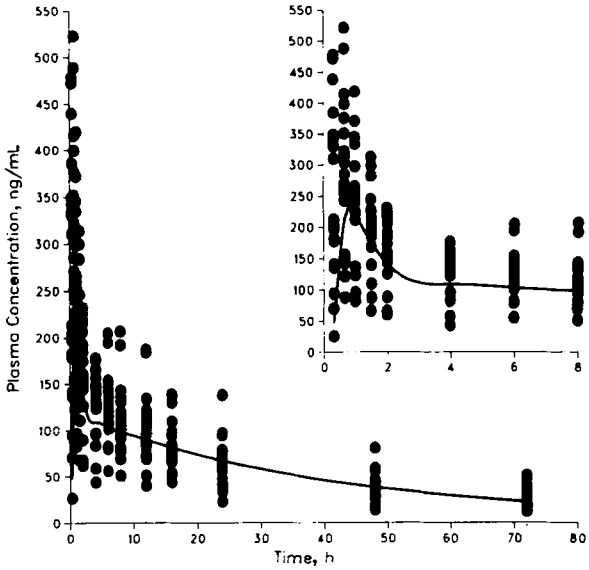

Figure 2—*All diazepam plasma concentration–time data from 20 subjects together with the curve fitted using the composite pharmacokinetic profiling technique and five subjects in each of four sampling groups, as depicted in Table IV (inset).*

subjects. Blood samples were obtained at specific times over the following 72 h. The subjects were divided into four groups of five subjects each: group I was sampled at 0, 0.33, 2, 12, and 72 h; group II was sampled at 0, 0.67, 4, 16, and 72 h; group III was sampled at 0, 1, 6, 24, and 72 h; group IV was sampled at 0, 1.5, 8, 48, and 72 h after the oral dose. The analytical *CV* for this study was 11.3%.

Four curve-fitting techniques were used to evaluate the data: (*a*) concentration–time data from the individual subjects were fitted and the mean parameters were calculated; (*b*) a single mean concentration–time profile from all subjects was fitted to determine parameter values; (*c*) all concentration–time data were fitted simultaneously to determine the parameter values; (*d*) a limited sample composite concentration–time profile was fitted to determine the parameter values. The results of these fitting procedures are presented in Table IV. In the first three of the methods, all of the concentration–time data were used in the sampling/fitting procedure, whereas in the final method, four groups of three or five patients, respectively, were used for ceftriaxone and diazepam. There was good general agreement of parameter estimates obtained by each of the four sampling/fitting techniques. The parameters A and α were variable among the four sampling/fitting procedures, and for the oral absorption of diazepam, k_a was variable as well. However, the remaining parameters for both diazepam and ceftriaxone were extremely consistent among the four methods. Again it should be noted that the clearances, volumes of distribution, and elimination rate constants show little variability. All ceftriaxone and diazepam concentration–time points, together with the composite profiling fits, are presented in Figs. 1 and 2, respectively, to show the randomness of scatter around the fitted curves.

The results of these simulations and curve-fitting procedures indicate that the composite pharmacokinetic profiling technique developed herein is a useful method that can be utilized to minimize the number of blood samples and, therefore, the total blood volume withdrawn. The application of this technique can allow for the development of pharmacokinetic profiles in patient populations, including neonates and certain disease states, in which little information has been generated due to sampling limitations. This technique has been used to develop a preliminary pharmacokinetic profile of vitamin E following an intramuscular injection to premature neonates (3).

(1) J. W. Crow and M. Gibaldi, *Drug Intell. Clin. Pharm.*, **12**, 612 (1978).

(2) C. M. Metzler, G. L. Elfring, and A. J. McEwen, *Biometrics*, **30**, 562 (1974).

(3) W. A. Colburn and R. A. Ehrenkranz, *Pediatr. Pharmacol.*, **3**, 7 (1983).

Wayne A. Colburn ˣ
Donald M. Gibson
Department of Pharmacokinetics,
Biopharmaceutics and Drug Metabolism
Hoffmann-LaRoche Inc.
Nutley, NJ 07110

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Disposition of Nitrofurantoin and Nitrofurazone in the Isolated Perfused Rat Kidney

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To the Editor:

Nitrofurantoin is frequently used clinically to treat urinary tract infections, but little is known of its renal metabolism. The side effects of nitrofurantoin therapy, pulmonary and hepatic toxicities, and polyneuropathies, are thought to be a consequence of its reductive metabolic activation (1–5). The end

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