Bioavailability and Pharmacokinetic Analysis of Chlorpromazine-Induced Rectal Temperature Depression in Rabbits

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Abstract □ Chlorpromazine-induced depression of rectal temperatures in rabbits kept at 20° was used to determine relative biophasic drug levels corresponding to observed hypothermic response intensities, which then served to establish a triexponential linear mathematical model describing drug transference and drug action in this system. Comparisons of various experimentally known, slow intravenous infusion drug inputs of chlorpromazine with drug inputs computed by deconvolution, using the derived model and observed temperature depressions, served to verify the accuracy of the model for the 0.50–4.0-mg/kg dosage range.

Keyphrases □ Chlorpromazine—bioavailability and pharmacokinetics, evaluated by measurement of rectal temperature depression, rabbits □ Bioavailability—chlorpromazine, evaluated by measurement of rectal temperature depression, rabbits □ Pharmacokinetics—chlorpromazine, evaluated by measurement of rectal temperature depression, rabbits □ Tranquilizers—chlorpromazine, bioavailability and pharmacokinetics, evaluated by measurement of rectal temperature depression, rabbits

The use of pharmacological response *versus* time data can often represent an advantageous alternative to the use of data derived from the direct assay of drugs in the plasma or other body fluids. A routinized procedure for the use of pharmacological data to perform pharmacokinetic and bioavailability analyses by observing drug effects in a given system was described previously (1–3). The present report further illustrates the application of pharmacological response data to pharmacokinetic modeling for the drug chlorpromazine. Chlorpromazine-induced changes in the rectal temperature recorded in rabbits were transformed to relative biophasic drug levels, using a dose–effect curve, and subsequently utilized to establish a biomathematical model relating the drug transference and drug response behavior of the system to drug bioavailability inputs as defined by the dynamics of how the drug enters the systemic circulation.

Chlorpromazine produces a fall in body temperature in most species exposed to neutral environmental temperatures (4, 5). However, the mechanism by which the drug produces its effect on temperature is unclear. Chlorpromazine has a strong antiadrenergic effect but little or no anticholinergic activity (6), and it also exhibits a peripheral ganglionic action (7). The drug is a remarkably potent antagonist of epinephrine and norepinephrine (8). The drug could act within the central nervous system by reducing the sensitivity of the thermoregulatory process at the level of the hypothalamus or peripherally by interfering with thermoregulatory vasomotor control due to vasodilation (9, 10). Total body heat loss could be explained on the basis of an increased heat loss through vasodilation and a decrease in heat production through muscle relaxation or prevention of shivering (10–13).

Some investigations speculated that chlorpromazine might have an effect on lowering body metabolism (10), while others discount this possibility (11). In any event, the effect of chlorpromazine on body temperature is said to be poikilothermic (14) in that the body temperature tends to assume the ambient temperature of the surrounding environment. Previous animal studies also showed that the drug's effect on body temperature is dose dependent (15), with the maximum intensity of effect occurring between 1 and 3 hr after administration, depending on the species studied (11, 16). The time for maximum intensity of response to occur is relatively long, because the mechanism of drug action involves both heat production and heat loss processes which are relatively slow and continuous phenomena.

Despite the complications and the lack of definitive knowledge concerning the precise mechanism by which chlorpromazine induces its hypothermic activity, pharmacokinetic relationships between drug input and the resulting time variation of its effects can still be established provided the temporal pharmacological data are observed to behave in conformity with the assumption that the transference behavior of the drug in the body can be described by linear dynamics. Whether this is the case or not can be judged from the observed behavior of pharmacological data alone without utilizing any direct assay methods to detect the presence of the drug in the body.

When certain criteria justifying the assumption of linear system behavior are even approximately met, the relationship between the rates and extents to which a drug enters the body, *i.e.*, the drug bioavailability input, and the pharmacological effects it induces can be reliably established, even for natural product drugs whose exact chemical composition is not known or for drugs such as chlorpromazine whose rapid and complex metabolism and distribution into tissues renders it extremely difficult to detect in body fluids. As illustrated by the results of the present study, such drug input → output response relationships can be established without any specific knowledge of the site(s) and mechanism of the drug's action(s) and observed effect.

EXPERIMENTAL

Materials—Chlorpromazine hydrochloride[1] was supplied in powder form and used as received. The drug was freshly solubilized

[1] Thorazine, Smith Kline and French, Philadelphia, Pa.

Table I—Average Intensity of Rectal Temperature Depression in Rabbits Measured at 20°, Recorded as $(T_0 - T)/T_0 \times 10^4$, as a Function of Five Bolus Doses of Chlorpromazine

Minutes	Dose, mg/kg iv				
	4.0	3.0	2.0	1.0	0.5
10	49	66	42	32	26
20	96	109	87	63	49
30	149	155	132	99	81
40	197	202	174	132	112
50	242	251	213	169	140
60	285	299	250	198	162
70	327	340	282	223	180
80	365	377	309	242	191
90	396	408	339	255	204
100	426	436	369	266	213
110	452	459	392	271	221
120	474	474	406	278	219
130	493	484	412	278	217
140	513	493	416	279	209
150	525	496	422	280	212
160	533	401	421	279	212
170	537	499	414	275	209
180	543	493	418	264	203
190	544	487	412	256	204
200	540	488	403	259	196
210	531	483	396	253	189
220	527	473	385	244	180
230	519	464	375	240	173
240	514	454	364	229	171
250	505	446	354	228	169
260	491	442	343	220	163
270	480	430	331	212	158
280	475	424	326	208	—
290	464	412	319	196	—
300	452	406	312	190	—
310	441	401	298	181	—
320	434	394	291	173	—

before each experiment using normal saline for injection USP[2]. Disposable plastic syringes[3] were used, and the plastic cannulas with needles attached were 23-gauge butterfly infusion sets[3].

New Zealand white rabbits[4], 3–4-month-old males, were caged individually and received a regular diet with no restrictions on the amount of food and water consumed. All rabbits weighed between 2.5 and 3.5 kg and were used as long as they remained physically healthy.

Methods—The animals were fasted for 24 hr prior to the experiment. They were then restrained in an appropriate holder and weighed. A rectal thermistor probe[5] was inserted 8 cm into the animal's rectum and secured to the tail using several rubberbands. The rabbits were then placed into a constant-temperature incubator[6] with the ambient temperature set at 20°.

The animals were allowed 60 min to equilibrate, in which time their rectal temperatures reached a constant value of 38.5–38.8°. Rectal temperatures were observed using a temperature monitor[7] with automatic channel scanning capability and recorded on a strip-chart recorder[8] that had been previously calibrated using the rectal probes and monitor.

Once the animal's rectal temperature reached a constant value, normal saline (the control dose) or a dose of chlorpromazine was administered *via* the marginal ear vein in approximately 20 sec. The chlorpromazine dosage range was 0.5–4.0 mg/kg. The dosing schedule was randomized according to an Youden square design. Following dosing, the rectal temperature was continuously monitored for 6 hr.

The saline dose produced no change in rectal temperature. The intensity of rectal temperature depression elicited by chlorpromazine was calculated as the initial temperature at time zero minus the temperature at time t; dividing this number by the initial temperature

[2] Abbott Laboratories, Chicago, Ill.
[3] Becton-Dickinson.
[4] Nicely Farms, Greenfield, Ind.
[5] Model 402.
[6] New Brunswick Psychotherm.
[7] Model 47 Telethermonitor, Yellow Springs Instrument Co.
[8] E. H. Sargent model SR6G.

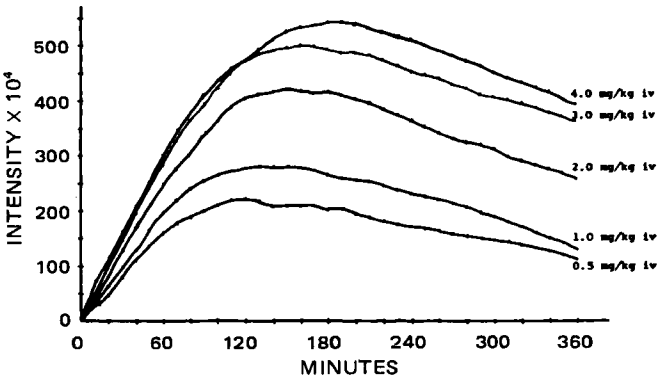

Figure 1—*Intensity of rectal temperature depression in rabbits kept at 20°, reported as* $(T_0 - T)/T \times 10^9$, *as a function of five bolus intravenous doses of chlorpromazine. Each curve represents averaged data from seven to nine rabbits.*

gave the hypothermic response intensity. These experiments were used to construct the dose–effect curve.

The validity of the models developed was checked by using the response to slow intravenous infusion of chlorpromazine. The infusion rates employed were 0.50 and 0.75 mg/kg/hr.

RESULTS AND DISCUSSION

Time Course of Drug Response—The observed time variations of the intensity of chlorpromazine-induced rectal temperature depression in rabbits kept at 20° as a function of five bolus intravenous doses of the drug are shown in Fig. 1; the average values are listed in Table I. Each curve in Fig. 1 represents averaged data from seven to nine rabbits. The observed maximum response intensities for each dose and the times of their occurrence are summarized in Table II.

It is apparent that the drug-induced rectal temperature depression is a graded response, but the times of absolute maximum response are not exactly identical. Despite this apparent nonlinear characteristic of the data, it was felt that a linear model might still adequately describe this system because virtually 90% of the response intensity maximums fell within a rather narrow time band.

Figure 1 shows that the times of maximum response occur far beyond zero time. This behavior can be taken to indicate that the biophase is removed and can be described as a "deep" compartment separate from the systemic circulation or plasma space into which the drug was administered. However, the sites of action may not necessarily be as far removed as the intensity maximums indicate since the temperature regulation mechanisms involve both direct and indirect effects on the hypothalamus and vasoconstriction. Moreover, there is the influence of the body's large heat capacity acting in a manner analogous to a low pass filter in an electrical system with regard to transmitting the results of the drug's action at receptor sites to

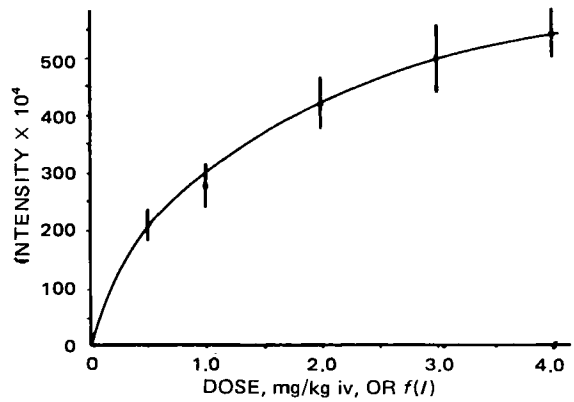

Figure 2—*Intravenous dose–effect curve for chlorpromazine-induced rectal temperature depression in rabbits constructed from the maximum intensities of temperature depression in Fig. 1, with the standard error of the mean indicated for each value. The abscissa is relabeled* f(I), *which corresponds to a relative biophasic drug level.*

Table II—Range of Maximum Intensities of Rectal Temperature Depression and Times of Maximum Response in Individual Rabbits as a Function of Five Bolus Intravenous Doses of Chlorpromazine

	Dose, mg/kg iv									
	4.0		3.0		2.0		1.0		0.5	
Rabbit	I_{max}	t_{max}	I_{max}	t_{max}	I_{max}	t_{max}	I_{max}	t_{max}	I_{max}	t_{max}
1	493	170	—	—	353	130	219	130	235	170
4	512 473	180 180	389	170	539	190	—	—	255	190
5	637	160	609	140	404	130	252	100	—	—
A	594	200	582	200	578	160	331	140	397	170
B	447	150	370	120	332	120	315	120	81	140
C	519	190	697	190	409	170	382	150	—	—
D	443	140	434	120	335	150	185	170	225	110
E	656	210	578	160	434	160	397	170	—	—
F	564	180	582	160	425	140	252	130	170	180
H	671	190	506	120	568	170	337	150	322	110
$\bar{X}$	546	177	527	153	438	152	297	140	241	153
SEM	25.06	6.34	33.20	9.17	28.06	6.64	22.10	6.91	30.65	9.96

manifest as an observed hypothermic effect. Conceivably, the slow loss and gain of heat by the system itself could be responsible for the peak response intensities being observed at times later than zero following the administration of the bolus intravenous doses, even though the actual drug levels at the site(s) of action are at all times in equilibrium with drug levels in the blood. In any case, the actual biophysical mechanisms involved are irrelevant to the purely phenomenological description of the developed system.

Construction of Dose–Effect Curve—Table II indicates the intensities of maximum rectal temperature depression and their times of occurrence for each dose of chlorpromazine administered to each rabbit. The average values are also indicated along with their standard deviations of the means. These average values were plotted as a function of the dose, and the resulting intravenous dose–effect curve is shown in Fig. 2. The shape of the curve appears as expected based upon the fact that chlorpromazine is known to have a high therapeutic index and the curve plateaus over a wide dose range.

When the dose–effect curve is represented by a single-valued functional relationship between dose and response intensity, as exemplified by Fig. 2, it can be used as a calibration curve to convert intensities of drug effect, observed at any time following dosing by any route, into actual or relative biophasic drug levels. The basis and purpose of the conversion were discussed previously (1–3, 17).

Transduction of I Values to $f(I)$— The observed rectal temperature response intensities were transduced to $f(I)$ values (relative biophasic drug levels) using the dose–effect curve as a calibration curve, as described in detail elsewhere (2, 17, 18). The individual dose-normalized $f(I)$ values are listed in Table III, which also contains the average $f(I)$/dose values and the standard deviations of the means. These average values, plotted as a function of time, are shown in Fig.

Table III—Rectal Temperature Response Intensities from Table I Transduced to $f(I)$ Values (Relative Biophasic Drug Levels) Using the Dose–Effect Curve as a Calibration Curve and Normalized by Dividing by the Corresponding Dose

	$f(I)$ Dose						
	Dose, mg/kg iv						
Minutes	4.0	3.0	2.0	1.0	0.5	Average	*SEM*
10	0.019	0.037	0.032	0.050	0.0	0.028	0.009
20	0.040	0.062	0.072	0.100	0.150	0.085	0.023
30	0.069	0.100	0.123	0.170	0.260	0.144	0.031
40	0.109	0.153	0.78	0.245	0.400	0.337	0.120
50	0.162	0.233	0.252	0.335	0.520	0.301	0.063
60	0.256	0.345	0.345	0.440	0.650	0.407	0.067
70	0.306	0.442	0.505	0.550	0.750	0.511	0.072
80	0.375	0.533	0.555	0.650	0.820	0.587	0.072
90	0.438	0.617	0.655	0.725	0.940	0.675	0.081
100	0.500	0.700	0.762	0.810	1.010	0.756	0.081
110	0.569	0.787	0.855	0.860	1.060	0.826	0.072
120	0.637	0.850	0.920	0.975	1.050	0.886	0.058
130	0.706	0.903	0.945	0.975	1.040	0.914	0.036
140	0.800	0.942	0.962	0.990	0.980	0.935	0.027
150	0.869	0.963	0.992	1.000	1.000	0.965	0.013
160	0.940	1.000	0.988	0.990	1.000	0.983	0.013
170	0.944	0.983	0.950	0.900	0.980	0.951	0.036
180	0.994	0.942	0.970	0.785	0.930	0.924	0.036
190	1.000	0.917	0.945	0.730	0.940	0.906	0.040
200	0.969	0.920	0.902	0.750	0.860	0.880	0.036
210	0.900	0.895	0.875	0.710	0.840	0.844	0.040
220	0.881	0.850	0.830	0.655	0.750	0.793	0.036
230	0.831	0.775	0.788	0.635	0.710	0.748	0.036
240	0.806	0.767	0.750	0.575	0.700	0.720	0.031
250	0.762	0.737	0.712	0.570	0.670	0.690	0.036
260	0.700	0.723	0.672	0.530	0.650	0.655	0.036
270	0.659	0.683	0.630	0.500	0.620	0.618	0.045
280	0.644	0.662	0.613	0.480	0.550	0.590	0.045
290	0.581	0.630	0.593	0.430	0.500	0.547	0.054
300	0.571	0.613	0.580	0.410	0.420	0.519	0.035
310	0.540	0.595	0.530	0.385	0.370	0.484	0.037
320	0.521	0.575	0.517	0.355	0.310	0.456	0.042
330	0.506	0.563	0.500	0.315	0.260	0.429	0.058

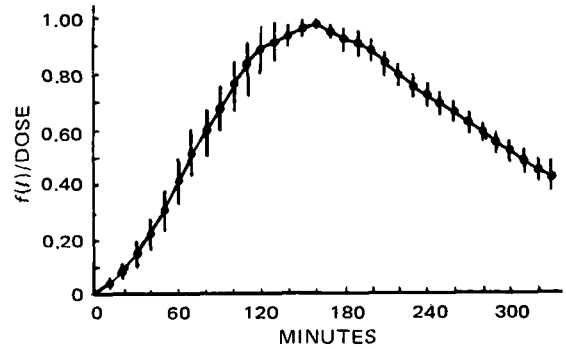

Figure 3—*Rectal temperature depression intensities from Fig. 1 transduced to* f(I) *values (relative biophasic drug levels) using the dose–effect curve as a calibration curve and normalized by dividing by the corresponding dose. The average* f(I)*/dose values are indicated along with the standard error of the mean for each value.*

3. The resulting curve represents the unit impulse response output of the system (19–21).

Curve-fitting procedures such as MULTIFIT, which operates in the time domain, and PLTEST, which performs in the frequency domain (19, 22), were then used to fit this curve with a mathematical function having the form of a sum of exponential terms.

Model Determination—Figure 4 depicts the $f(I)$/dose values experimentally determined from chlorpromazine-induced rectal temperature depression plotted for comparison with values predicted from computerized MULTIFIT mathematical model parameters. Based on this comparison, the mathematical model obtained by the use of the MULTIFIT computer program appears to be a reasonable approximation of the observed data, as evidenced by the closeness of the computed points to the experimental data points.

The parameters of the mathematical model also were determined using the PLTEST procedure (19, 22), which has the advantage of requiring less computer time than the MULTIFIT program and serves as an alternative method of obtaining the desired model parameters. A Bode diagram was constructed from the output of the PLTEST program, and the model parameters were determined from the corner frequencies (23). The details of this analysis will appear in a future report. The parameters obtained from PLTEST were compared with those obtained by the MULTIFIT procedure as listed in Table IV. The two procedures yielded essentially the same result. The MULTIFIT model was used for the remainder of the calculations.

Model Verification—The time variations of intensities of rectal temperature depression observed in single rabbits kept at 20° in response to various slow intravenous infusions of chlorpromazine are depicted by the curves in Figs. 5 and 6. These curves were smoothed to facilitate deconvolution, which is sensitive to noisy data. The smoothed data for the curves are listed in Tables V and VI. The

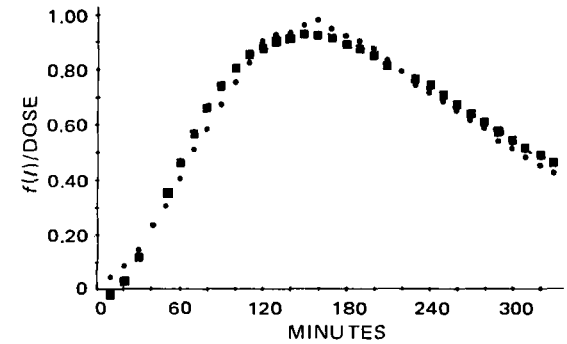

Figure 4—*The* f(I)*/dose values experimentally determined from rectal temperature depression (●) and computer-predicted values (■) based upon a triexponential model obtained by fitting the data via a least-squares procedure. The model has the general form:*

$$y = \sum_{i=1}^{n} A_i e^{-m_i t}$$

where the A_i*'s and* m_i*'s are constants* ($A_1 = 4.86563$, $A_2 = -9.26821$, $A_3 = 4.40259$, $m_1 = 0.006803$, $m_2 = 0.015532$, *and* $m_3 = 0.026769$).

Table IV—Comparison of the Mathematical Model Parameters Describing Chlorpromazine-Induced Rectal Temperature Depression in Rabbits Calculated from MULTIFIT and PLTEST Procedures

MULTIFIT	PLTEST
$A_1 = 4.86563$	$A_1 = 3.83573$
$A_2 = -9.26821$	$A_2 = -7.66823$
$A_3 = 4.40259$	$A_3 = 3.83300$
$m_1 = 0.006803$	$m_1 = 0.0063708$
$m_2 = 0.015532$	$m_2 = 0.020332$
$m_3 = 0.026769$	$m_3 = 0.020337$

Table V—Intensity of Rectal Temperature Depression in a Single Rabbit at 20°, Expressed as $(T_0 - T)/T_0 \times 10^4$, in Response to a Slow Intravenous Infusion of Chlorpromazine, the Infusion Rate Being 0.50 mg/kg/hr

Minutes	I^a	$f(I)$
10	5	0.013
20	31	0.050
30	46	0.073
40	75	0.123
50	100	0.173
60	121	0.218
70	147	0.275
80	170	0.350
90	185	0.398
100	208	0.483
110	237	0.620
120	257	0.738
130	283	0.913
140	296	1.005
150	311	1.125
160	325	1.220
170	332	1.263
180	335	1.275
190	335	1.275
200	335	1.275
210	335	1.275
220	335	1.275
230	335	1.275
240	335	1.275
250	335	1.275
260	335	1.275
270	335	1.275
280	335	1.275
290	335	1.275
300	335	1.275

[a] The intensity values were transduced to $f(I)$ values (relative biophasic drug levels) using the dose–effect curve as a calibration curve.

infusion rates employed were 0.50 and 0.75 mg/kg/hr. These slow intravenous infusions served as test inputs into the system and are obviously different from the bolus drug inputs that provided the data from which the transfer function model had been determined.

By using the response output elicited by these infusions and the transfer function model, the fidelity of the linear model may be evaluated. This is done by calculating the input function responsible for the observed pharmacological response output and comparing the experimentally known inputs with the values computed from the

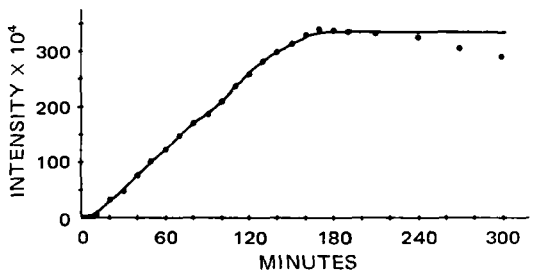

Figure 5—*Intensity of rectal temperature depression in a single rabbit at 20° in response to a slow intravenous infusion of chlorpromazine, the infusion rate being 0.50 mg/kg/hr.*

Table VI—Intensity of Rectal Temperature Depression in a Single Rabbit at 20°, Expressed as $(T_0 - T)/T_0 \times 10^4$, in Response to a Slow Intravenous Infusion of Chlorpromazine, the Infusion Rate Being 0.75 mg/kg/hr

Minutes	I^a	$f(I)$
10	5	0.013
20	15	0.025
30	52	0.080
40	98	0.163
50	131	0.243
60	170	0.350
70	209	0.488
80	245	0.663
90	282	0.913
100	315	1.150
110	350	1.400
120	375	1.575
130	395	1.750
140	410	1.875
150	420	1.962
160	423	1.987
170	424	1.995
180	425	2.000
190	425	2.000
200	425	2.000
210	425	2.000
220	425	2.000
230	425	2.000
240	425	2.000
250	425	2.000
260	425	2.000
270	425	2.000
280	425	2.000
290	425	2.000
300	425	2.000

[a] The intensity values were transduced to $f(I)$ values (relative biophasic drug levels) using the dose–effect curve as a calibration curve.

pharmacological response data observed following administration of the drug input used to test the fidelity of the model.

This comparison of known and computed drug inputs was performed using the response intensity values listed in Tables V and VI, which were transduced to $f(I)$ values (relative biophasic drug levels) using the dose–effect curve in the manner described in detail elsewhere (1, 2, 17, 18–22). These $f(I)$ values observed for the slow intravenous infusions then served as inputs to a deconvolution digital computer program (22), which calculated the cumulative drug input from the transfer function and the relative biophasic drug level response output of the system. These calculated inputs were compared with the known inputs to verify the transfer function model for chlorpromazine-induced rectal temperature depression in rabbits (Figs. 7 and 8).

Table VII indicates the amounts of chlorpromazine known to have been infused at 0.50 mg/kg/hr *versus* the amounts calculated wholly from observed pharmacological response intensities. Table VIII presents a similar comparison of results for a 0.75-mg/kg/hr infusion rate.

All data indicate good agreement between experimentally known chlorpromazine drug inputs and corresponding values calculated from the drug-induced rectal temperature depression. Based on these results, the mathematical model describing the dynamics of the drug's input–output response behavior for the dosage range employed may be considered as satisfactory, even though a linear model does not rigorously describe the dynamics of the system's response behavior.

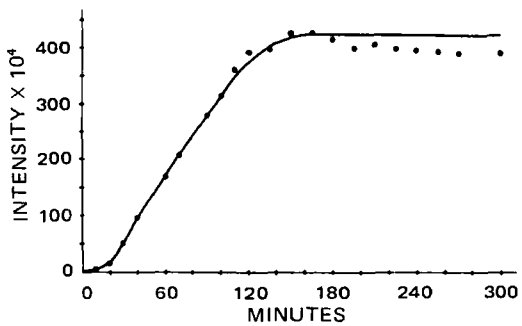

Figure 6—*Intensity of rectal temperature depression in a single rabbit at 20° in response to a slow intravenous infusion of chlorpromazine, the infusion rate being 0.75 mg/kg/hr.*

Table VII—Comparison of Experimentally Known Amounts of Chlorpromazine Infused at a Rate of 0.50 mg/kg/hr with Theoretical Amounts Computed from Rectal Temperature Depression Measured in a Single Rabbit

$A(t)_{theor}$	$A(t)_{exp}$
0.0833	0.3100
0.1667	0.2600
0.2500	0.2923
0.3333	0.5028
0.4167	0.4100
0.5000	0.4950
0.5833	0.7353
0.6667	0.6400
0.7500	0.7500
0.8333	1.3907
0.9167	1.4753
1.000	1.7200
1.0833	1.6000
1.1667	1.3705
1.2500	1.7760
1.3333	1.4000
1.4167	1.1797
1.5000	1.2458
1.5833	1.3900
1.6667	1.5078
1.7500	1.5639
1.8333	1.6100
1.9167	1.6550
2.0000	1.7000
2.0833	1.7459
2.1667	1.7900
2.2500	1.8343
2.3333	1.8806
2.4167	1.9300
2.5000	

SUMMARY AND CONCLUSIONS

A method of performing a pharmacokinetic analysis of drug-responding systems was further confirmed using the results of observed intensities of chlorpromazine-induced rectal temperature depression to establish a pharmacokinetic model to relate drug bioavailability inputs to the time variation of hypothermic response intensity induced by the drug in rabbits. A simplified explication and details of the method were described elsewhere (24, 25). The dosage range of chlorpromazine employed was 0.5–4.0 mg/kg; a third-order (triexponential) transfer function model describing the drug's dynamic response behavior in this system was determined from the results of bolus intravenous dosing in this range and confirmed the use of slow intravenous infusions of the drug as test inputs.

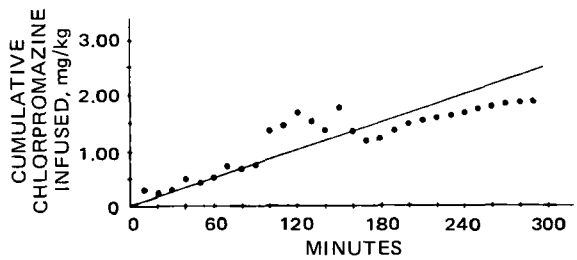

Figure 7—*Experimentally determined amounts of chlorpromazine slowly infused in a single rabbit as a function of time using intensities of rectal temperature depression from Fig. 5 and the transfer function model from Fig. 4 in a deconvolution procedure. The response intensity values were transduced to* f(I) *values (relative biophasic drug levels) using the dose–effect curve and deconvolved with the transfer function to yield cumulative amounts of chlorpromazine infused. The solid line represents the actual amount of chlorpromazine infused during the experiment, 0.50 mg/kg/hr.*

Table VIII—Comparison of Experimentally Known Amounts of Chlorpromazine Infused at a Rate of 0.75 mg/kg/hr with Theoretical Amounts Computed from Rectal Temperature Depression Measured in a Single Rabbit

$A(t)_{theor}$	$A(t)_{exp}$
0.125	0.1136
0.250	0.3500
0.375	0.7286
0.500	0.7276
0.625	0.8200
0.750	1.2030
0.875	1.5820
1.000	2.2500
1.125	2.5000
1.250	2.4698
1.375	2.3100
1.500	2.2000
1.625	2.4089
1.750	2.1834
1.875	1.9800
2.000	1.9000
2.125	2.1573
2.250	2.2950
2.375	2.3700
2.500	2.4651
2.625	2.5411
2.750	2.6100
2.875	2.6830
3.000	2.7528
3.125	2.8250
3.250	2.8940
3.375	2.9640
3.500	3.0366
3.625	3.1050
3.750	

Although the linear mathematical model described here was considered to be relatively adequate in describing the biokinetic behavior of the drug in this system, the systematic differences of computed values from the experimentally known amounts of drug infused (Figs. 7 and 8) indicate a need for further model tuning. It was considered that the application of further linear mathematical modeling techniques would be of little value in improving the fidelity of the drug's input–output response relationship describing the dynamics of chlorpromazine-induced temperature depression. Therefore, future studies will explore an approach involving a systematic variation of the transfer function parameters which is dependent at any time upon the level of response intensity observed at that time. It is anticipated that this type of linear approximation transfer function model will yield improved results as compared with those using the linear transference model presently employed.

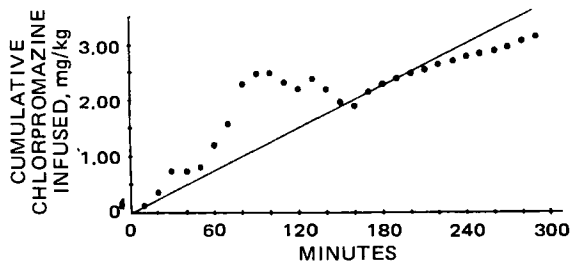

Figure 8—*Experimentally determined amounts of chlorpromazine slowly infused in a single rabbit as a function of time using intensities of rectal temperature depression from Fig. 6 and the transfer function model from Fig. 4 in a deconvolution procedure. The response intensity values were transduced to* f(I) *values (relative biophasic drug levels) using the dose–effect curve and deconvolved with the transfer function to yield cumulative amounts of chlorpromazine infused. The solid line represents the actual amount of chlorpromazine infused during the experiment, 0.75 mg/kg/hr.*

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