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APPENDICES

APPENDIX

A   Subjects

B   Composition and Preparation of Mobile
Phase for HPLC

C   Standard Curve Determination

D   One-Compartment Pharmacokinetic Model

E   Pharmacokinetic Analysis by Using the
PCNONLIN Nonlinear Estimation Program

F   Student't-Test Using the Statistical
Package SPSS/PC

APPENDIX A

This section lists the physiological characteristics and biochemical lab results of 40 subjects in the 4 different groups of nonsmoking males, nonsmoking females, smoking males and children. The physiological characteristics and biochemical lab results of each subjects are shown in Table 7 and 8, respectively.

Table 7   Physiological Characteristics of the 40 Subjects
in 4 Different Groups

Group	Subject No.	Sex	Age (yr)	Height (cm)	Weight (kg)
A	1	M	23	168	56.0
	2	M	24	179	70.0
	3	M	36	178	87.0
	4	M	26	170	62.0
	5	M	38	160	45.0
	6	M	23	175	63.0
	7	M	24	173	53.0
	8	M	23	165	60.0
	9	M	28	168	56.0
	10	M	29	160	51.5
	range		23-38	160-179	45.0-87.0
	mean		27.4	169.6	60.4
	S.D.		5.5	6.8	11.6
B	1	F	34	161	51.5
	2	F	28	168	55.0
	3	F	23	158	64.0
	4	F	24	153	43.0
	5	F	22	160	56.0
	6	F	23	157	50.0
	7	F	27	161	50.0
	8	F	22	158	48.0
	9	F	24	157	49.0
	10	F	23	159	48.5
	range		22-34	153-168	43.0-64.0
	mean		25.0	159.2	51.5
	S.D.		3.7	3.9	5.7

A	Nonsmoking Males		M	Males
B	Nonsmoking Females		F	Females

Table 7   Physiological Characteristics of the 40 Subjects
in 4 Different Groups (cont.)

Group	Subject No.	Sex	Age (yr)	Height (cm)	Weight (kg)
C	1	M	23	165	57.0
	2	M	33	165	62.5
	3	M	31	168	60.0
	4	M	23	168	50.5
	5	M	24	164	55.0
	6	M	21	169	58.0
	7	M	25	166	46.0
	8	M	23	171	55.0
	9	M	31	165	55.0
	10	M	27	167	58.5
	range		21-33	164-171	46.0-62.5
	mean		26.1	166.8	55.8
	S.D.		4.2	2.2	4.7
D	1	M	12	145	33.0
	2	M	12	144	32.5
	3	M	12	147	37.5
	4	M	10	125	23.0
	5	M	12	141	33.0
	6	M	9	123	23.0
	7	M	9	127	25.5
	8	M	7	123	22.0
	9	M	11	124	24.0
	10	M	10	132	23.0
	range		7-12	123-147	22.0-37.5
	mean		10.4	133.1	27.6
	S.D		1.7	10.0	5.7

C   Smoking Males   M   Males
D   Children

Table 8. Biochemical Laboratory Results of the 40 Subjects in 4 Different Groups

NONSMOKING MALE GROUP

Test	Normal Values	Results 1	2	3	4	5	6	7	8	9	10
BLOOD CHEMISTRY											
BUN	5.6-16.6 mg%	12.0	9.5	17.0	15	9.0	8.0	10.0	9.5	13.0	10.0
Cr	0.8-1.4 mg%	1.0	1.1	1.0	1.2	0.7	1.0	1.0	0.8	0.9	0.8
D.Bil	0.0-0.2 mg%	0.07	0.02	0.13	0.28	0'	0.2	0.12	0	0.12	0.16
T.Bil	0.2-1.0 mg%	0.9	0.83	0.63	1.33	0.53	1.76	0.63	0.4	0.41	0.85
SGOT	up to 37 U/L	28	22	39	10	39	3	10	30	17	30
SGPT	up to 40 U/L	29	15	91	9	50	12	12	33	13	23
ALP	39-117 U/L	66	69	72	72	96	93	72	72	48	65
TP	6.7-8.3 g%	7.1	7.8	7.4	7.6	7.4	8.6	8.5	8.0	7.4	8
alb.	4.1-5.3 g%	5.0	5.0	5.2	5.2	4.6	5.2	5.5	5.0	4.9	4.8
COMPLETE BLOOD COUNT											
Hb	13-18 g/dl	16.0	15.8	13.0	14.3	13.2	14.6	16.3	15.5	13.7	13.9
Hct	40-54 %	49	48	40	44	40	44	46	47	41	41
WBC	4,500-10,000 cell/mm3	7,200	7,300	6,400	4,300	9,200	6,200	7,500	9,200	10,800	8,300
diff.											
PMN	54-75 %	35	59	45	48	60	60	58	61	60	71
eos.	1-6 %	4	2	3	1	1	-	6	4	10	6
baso.	0-0.5 %	-	-	2	1	1	2	-	2	2	1
lymphs.	20-50 %	54	32	42	46	37	34	32	30	25	20
Monos.	2-10 %	5	7	7	2	1	3	4	3	3	2
URINALYSIS		N	N	N	N	N	N	N	N	N	N

N   Within normal limits

Table 8. Biochemical Laboratory Results of the 40 Subjects in 4 Different Groups (cont.)

NONSMOKING FEMALE GROUP

Test	Normal Values		Results 1	2	3	4	5	6	7	8	9	10
BLOOD CHEMISTRY												
BUN	5.6-16.6	mg%	10.0	10.0	7.0	9.0	7.5	8.0	16.0	6.0	11.0	10.0
Cr	0.8-1.4	mg%	0.7	0.7	0.6	0.6	0.7	0.8	0.6	0.6	0.6	0.7
D.Bil	0.0-0.2	mg%	0	0.25	0.18	0.18	0.15	0.15	0.12	0.03	0.11	0.25
T.Bil	0.2-1.0	mg%	0.42	0.86	0.64	0.54	0.5	0.56	0.5	0.30	0.57	0.83
SGOT	up to 37	U/L	20	17	16	16	24	19	23	19	13	19
SGPT	up to 40	U/L	18	20	16	10	15	19	34	13	11	14
ALP	39-117	U/L	55	48	73	53	72	90	52	52	75	66
TP	6.7-8.3	g%	8	7.6	8.3	7.5	7.9	8.2	7.5	7.4	7.8	8
alb.	4.1-5.3	g%	4.9	5.0	5.3	4.8	5.1	5.1	5.2	4.9	4.9	5.1
COMPLETE BLOOD COUNT												
Hb	12-16	g/dl	13	12.2	13.9	13.2	12.3	13.9	12.2	13.5	12.5	13.8
Hct	37-47	%	40	37	42	41	37	43	38	41	39	42
WBC	4,500-10,000 cell/mm3		6,500	8,200	7,500	9,300	6,500	7,300	7,000	7,800	7,200	8,900
diff.												
PMN	54-75	%	50	66	54	74	51	50	68	62	47	70
eos.	1-6	%	-	6	2	1	1	9	1	1	5	1
baso.	0-0.5	%	-	1	-	-	-	-	2	2	1	1
lymphs.	20-50	%	46	21	38	22	39	37	27	32	39	26
Monos.	2-10	%	4	4	6	3	8	4	1	3	8	2
URINALYSIS			N	N	N	N	N	N	N	N	N	N

N   Within normal limits

Table 8. Biochemical Laboratory Results of the 40 Subjects in 4 Different Groups (cont.)

SMOKING MALE GROUP

Test	Normal Values		Results 1	2	3	4	5	6	7	8	9	10
BLOOD CHEMISTRY													
BUN	5.6-16.6	mg%	10.0	12.0	14.0	15.0	11.0	13.0	10.0	11.0	11.0	15.0
Cr	0.8-1.4	mg%	0.8	0.9	1.1	1.0	0.9	0.9	1.0	1.0	1.0	0.8
D.Bil	0.0-0.2	mg%	0	0.18	0.05	0.29	0	0.22	0.18	0.25	0.2	0
T.Bil	0.2-1.0	mg%	0.18	0.68	1.24	0.93	0.34	0.98	0.95	1.04	0.63	0.45
SGOT	up to 37	U/L	21	25	36	40	26	20	17	15	15	25
SGPT	up to 40	U/L	16	15	54	56	12	16	10	10	12	16
ALP	39-117	U/L	108	80	95	149	126	67	83	58	52	58
TP	6.7-8.3	g%	7.6	8	7.5	7.0	7.3	6.8	7.1	7.6	7.9	7.7
alb.	4.1-5.3	g%	4.8	4.9	4.7	4.0	4.7	4.7	4.7	5.2	5.0	5
COMPLETE BLOOD COUNT													
Hb	13-18	g/dl	15.2	16.1	16.1	15.2	14.3	14.6	13.7	13.9	15.1	15.1
Hct	40-54	%	4.5	49	49	45	44	44	43	44	47	45
WBC	4,500-10,000 cell/mm3		10,000	10,200	9,400	7,000	5,400	5,400	7,100	5,000	7,400	9,600
diff.												
PMN	54-75	%	39	40	39	43	49	45	53	48	45	35
eos.	1-6	%	17	15	8	6	2	11	1	6	13	5
baso.	0-0.5	%	-	1	-	1	-	1	-	-	2	-
lymphs.	20-50	%	32	37	48	46	46	39	35	42	35	56
Monos.	2-10	%	12	6	5	3	3	4	10	3	5	4
URINALYSIS			N	N	N	N	N	N	N	N	N	N

N   Within normal limits

Table 8. Biochemical Laboratory Results of the 40 Subjects in 4 Different Groups (cont.)

CHILDREN GROUP

Test	Normal Values		Results 1	2	3	4	5	6	7	8	9	10
BLOOD CHEMISTRY												
BUN	5.6-16.6	mg%	8.0	8.0	10.0	9.0	11.0	8	7.0	11.0	10.0	13.0
Cr	0.8-1.4	mg%	0.5	0.4	0.8	0.5	0.6	0.5	0.5	0.6	0.5	0.4
D.Bil	0.0-0.2	mg%	0.17	0.08	0.16	0.04	0.16	0.06	0.15	0.12	0	0.05
T.Bil	0.2-1.0	mg%	0.28	0.24	0.6	0.31	0.45	0.2	0.42	0.32	0.25	0.30
SGOT	up to 37	U/L	32	27	24	40	32	31	24	24	30	25
SGPT	up to 40	U/L	14	13	15	25	19	19	14	12	19	15
ALP	203-596	U/L	233	203	348	368	325	204	191	201	239	146
TP	6.7-8.3	g%	7.7	8.0	7.8	7.9	7.9	8.3	7.6	7.4	7.7	7.3
alb.	4.1-5.3	g%	4.7	4.6	5.0	4.8	4.7	4.8	4.5	4.7	4.6	4.5
COMPLETE BLOOD COUNT												
Hb	12.5-13	g/dl	12.7	12.7	13.8	12.7	13	12.0	12.9	12.7	13.4	13.7
Hct	36-40	%	38	38	41	38	39	36	38	37	40	41
WBC	4,500-10,000 cell/mm3		9,300	11,100	9,000	7,100	11,100	7,900	11,100	7,200	13,800	9,400
diff.												
PMN	54-75	%	50	42	61	33	48	53	56	48	45	47
eos.	1-6	%	6	6	2	3	8	9	3	6	7	5
baso.	0-0.5	%	-	-	-	-	-	-	-	1	1	-
lymphs.	20-50	%	39	45	31	44	40	36	38	38	42	47
Monos.	2-10	%	5	6	4	4	4	2	2	5	5	1
URINALYSIS			N	N	N	N	N	N	N	N	N	N

N   Within normal limits

APPENDIX B

Composition and Preparation of Mobile Phase for HPLC

Mobile phase composes of 11% acetonitrile in 0.01 M sodium acetate buffer pH 4.0. It must be freshly prepared.

The preparation procedure is as follows.

1. Acetonitrile HPLC grade

    Filter through FH 0.5 μm membrane filter using suction filtration.

2. Sodium Acetate 0.01 M pH 4.0

    Dissolve 1.3608 g of sodium acetate in distilled water. Adjust pH to 4.0 with glacial acetic acid. Add sufficient distilled water to make 1,000 ml. Filter through HA 0.45 μm membrane filter with suction filtration.

3. Pour 110 ml of the filtered Acetonitrile and 890 ml of Sodium Acetate buffer into a 1 liter bottle.

4. Mix well

5. Degas the mobile phase using a sonifier for 20-30 minutes.

APPENDIX C

Standard Curve Determination

The typical standard curve data and the curve for theophylline concentration in human plasma are presented in Table 9 and Figure 16, respectively.

Table 9 Typical Standard Curve Data of Theophylline
Concentrations in Human Plasma Estimated Using
Linear Regresstion[1]

Standard No.	Concentration (mcg/ml)	Peak area ratio $(T^*/8\text{-}CT^{**})$	Inversely estimated[2] concentration (mcg/ml)	%Theory[3]
1	0.0	0	0	
2	1.25	0.0682	1.26	100.00
3	2.5	0.1226	2.26	90.40
4	5.0	0.2703	4.98	99.60
5	7.5	0.3980	7.34	97.87
6	10.0	0.5405	9.97	99.70
7	15.0	0.8128	14.99	99.93
8	20.0	1.0904	20.11	100.55
			Mean	98.29
			S.D	3.57
			C.V[4]	3.64%

1. r^2 =0.999,

2. Inversly estimated concentration = Peak area ratio/5.421×10^{-2}

3. % Theory = $\dfrac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. Coefficient of variation(C.V.) = $\dfrac{\text{S.D.}}{\text{Mean}} \times 100$

* Theophylline

** 8-Chlorotheophylline
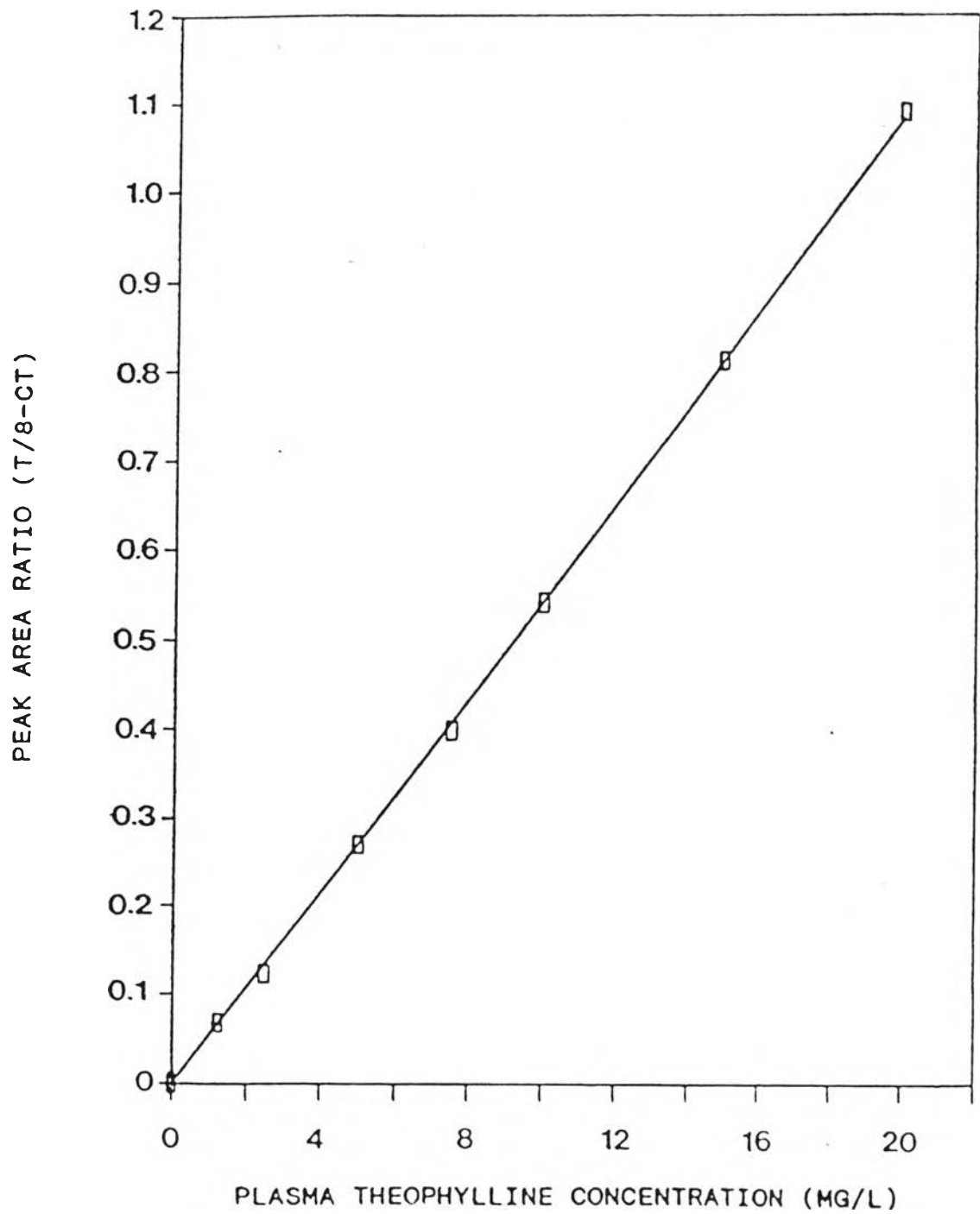
Figure 15. Typical standard curve of theophylline concentration in human plasma

APPENDIX D

One-Compartment Pharmacokinetic Model

The one-compartment model is a pharmacokinetic
model which depicts the body as a single homogeneous unit.
The mathematic functions derived from this model is
particularly useful for describing the kinetic behavior of
the drugs, which rapidly distribute between plasma and
other body fluids and tissues, and the elimination is a
first-order process (53).

Intravenous Administration

According to this model, if a drug enters the body
by intravenous injection, the rate of loss of drug from
the body is given by Eq.(A-1), (53,56)

$$\frac{dX}{dt} = -K X \qquad (A-1)$$

where X is the amount of drug in the body at time t after
injection. K is the apparent first-order elimination rate
constant for the drug. The negative sign indicates that
the drug is being lost from the body.

To describe the time course of the amount of drug

in the body after injection, Eq.(A-1) must be integrated
to give the following equation.

$$\log X = \log X_O - \frac{Kt}{2.303} \qquad (A-2)$$

Eq.(A-2). also can be expressed as

$$X = X_O e^{-Kt} \qquad (A-3)$$

where X_O is the amount injected (i.e., the dose) and e
represents the exponential term (base of the natural
logarithm).

However, the amount of drug in the body cannot be
determined directly, instead, a blood sample is removed at
periodic intervals and analyzed for drug concentration.
Thus, the volume of drug distribution, V, is used to
relate the concentration of the drug in plasma, C, and the
amount of drug in the body, X, as in the following
equation.

$$X = V C \qquad (A-4)$$

The proportionality constant V in this equation
has the unit of volume. Since this constant does not have
a true physiologic meaning in the terms of an anatomic
space, the term apparent volume of distribution is used.

By substituting Eq.(A-4) into Eq.(A-2), a similar expression based on drug concentration in plasma is obtained,

$$\log C = \log C_o - \frac{Kt}{2.303} \qquad (A-5)$$

where C and C_o is the concentrations of drug at time t and t = 0, respectively.

Eq.(A-5) indicates that a plot of log C versus t is linear under the conditions stated (Figure 16). C_o can be obtained by extrapolation of the log C versus t plot to time zero and the slope of the line resulting from this plot is equal to -K/2.303, K may be estimated directly from this slope.

However, K can be easier estimated from the relationship

$$K = \frac{0.693}{t_{1/2}} \qquad (A-6)$$

where $t_{1/2}$ is the biologic or elimination half-life of the drug. This parameter is determined from a plot of log C versus t as illustrated in Figure 16. The time required for the drug concentration at any point on the straight line to decrease by one-half is the biologic half-life. Thus, Eq.(A-6) is derived by setting C equal to $C_o/2$ and t to $t_{1/2}$ in Eq.(A-5).
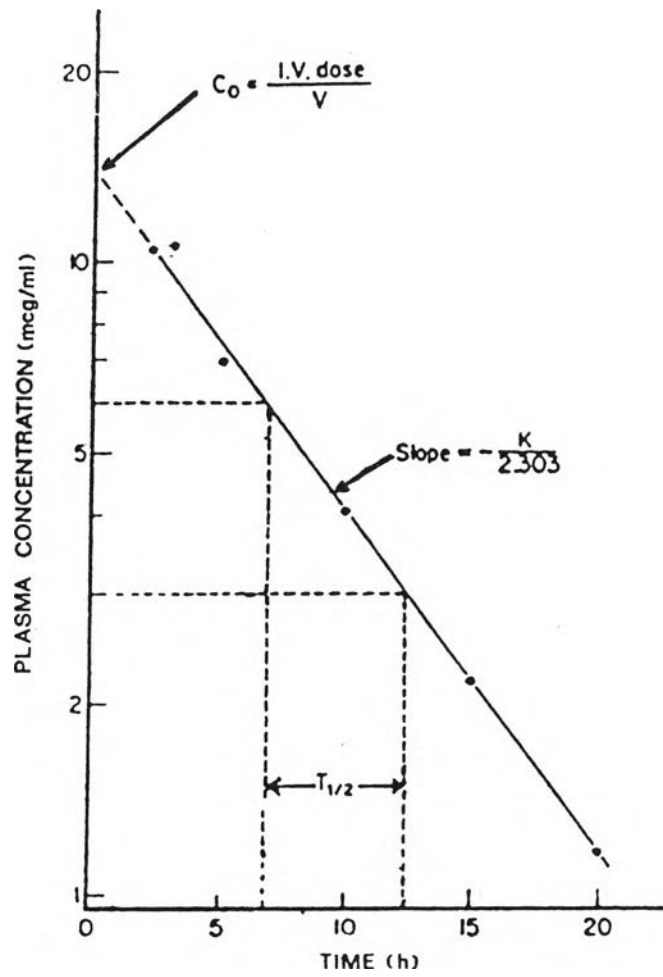
Figure 16. Graphical method for calculating pharmacokinetic parameters in one-compartment model, after intravenous injection of a drug eliminated by first-order process.

C_o which is obtained, as described, may be used to calculate the apparent volume of distribution. Since X_o equals the amount of drug injected (i.e., the intravenous dose), V may be estimated from the relationship

$$V = \frac{X_o}{C_o} \qquad (A-7)$$

Eq.(A-7) is theoretically correct only for a one-compartment model where the drug distribution between plasma and tissue is instantaneous. Since this is rarely true, a calculation base on Eq.(A-7) will almost always overestimate the apparent volume of distribution.

There is another method which is more accurate and more general for calculating V (56). From Eq.(A-1), the rate of drug loss from the body $\frac{dX}{dt}$ is -K X.

By substitution of Eq.(A-4), X = VC, into Eq.(A-1), the following expression is obtained.

$$\frac{dX}{dt} = -K V C \qquad (A-8)$$

Rearrangement of Eq.(A-8) gives

$$dX = -K V C \, dt \qquad (A-9)$$

Since both K and V are constants, Eq.(A-9) may be integrated from time zero to time infinity as follow

$$\text{dose} \quad = \quad K \ V \ AUC \qquad (\ A\text{-}10 \ )$$

where AUC is obtained from the integral $\quad C \int_{0}^{\infty} dt \quad$ which represents summation of the area under the concentration-time curve from $t = 0$ to $t = \infty$, and is estimated by the trapezoidal rule. Rearrangement of Eq.(A-10) yields

$$V \quad = \quad \frac{\text{Dose}}{K \ AUC} \qquad (\ A\text{-}11 \ )$$

Since the relationship in Eq.(A-11) is not dependent on instantaneous distribution of drug between plasma and tissue as in the case for Eq.(A-7), this relationship is used widely for calculating the apparent volume of distribution.

First-Order Absorption

For a drug that enters the body by an apparent first-order absorption process (i.e., extravascular drug administration), is eliminated by a first-order process, and distributes in the body according to a one-compartment model, the following differential equation is applied (53,56),

$$\frac{dX}{dt} \quad = \quad K_a \ X_{\varepsilon} \ - \ K \ X \qquad (\ A\text{-}12 \ )$$

where X and K are as defined previously, K_a is the apparent first-order absorption rate constant, and X_a is the amount of drug at the absorption site.

The rate of loss of drug from the absorption site is

$$\frac{dX_a}{dt} = -K_a X_a \qquad (A-13)$$

Eq.(A-13) is integrated

$$X_a = F X_0 e^{-K_a t} \qquad (A-14)$$

where F is the fraction of the administered dose X_0 that is absorbed following extravascular administration.

By substituting Eq.(A-14) into Eq.(A-12)

$$\frac{dX}{dt} = K_a F X_0 e^{-K_a t} - K X \qquad (A-15)$$

Eq.(A-15) can be integrated to give the general oral absorption equation for describing the relationship between the drug concentration in the body and time, as follows

$$C = \frac{K_a F X_0}{V (K_a - K)} (e^{-Kt} - e^{-K_a t}) \qquad (A-16)$$

For most drugs administered extravascularly in conventional dosage form, the absorption rate constant is significantly larger than the elimination rate constant (53). Thus, as a result of setting the term $e^{-K_a t}$ approaching zero, whereas the term e^{-Kt} is finite, Eq.(A-16) reduces to

$$C = \frac{K_a F X_0 e^{-Kt}}{V(K_a - K)} \qquad (A-17)$$

Eq.(A-17) describes the postabsorptive phase (i.e., the time when absorption is no longer occurs) of a plasma concentration-time curve. Eq.(A-17) also can be expressed as

$$\log C = \log \frac{K_a F X_0}{V(K_a - K)} - \frac{K t}{2.303} \qquad (A-18)$$

With the Eq.(A-16), a plot of logarithm of plasma theophylline concentration versus time would be biexponential curve with a terminal linear portion. By drawing a straight line through a few points of this terminal portion would obtain the terminal line, as described by Eq.(A-18)), of which slope was $-K/2.303$ (Figure 17). Extrapolation of this terminal line to time zero would yield an intercept equal to log $[K_a F X_0/V(K_a-K)]$.

The method of residuals (53) was used to obtain
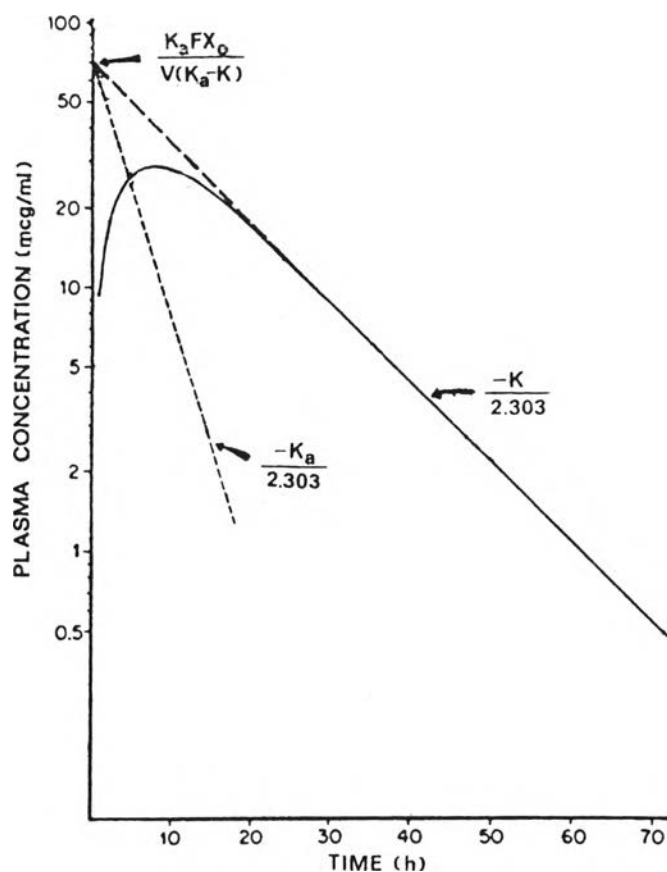
Figure 17. Graphical method with the method of residuals for estimating pharmacokinetic parameters in one-compartment model, after oral administration of a drug eliminated by first-order process. The solid line was described by Eq (A-16). The extrapolated line of terminal log-linear portion (depicted by long dashes) was described by Eq (A-18). The residual line (depicted by short dashes) was described by Eq (A-19).

the residual line described by the following equation, which was attained by substracting Eq.(A-16) from Eq.(A-17).

$$\log C_r = \log \frac{K_a F X_o}{V (K_a - K)} - \frac{K_a t}{2.303} \qquad (A-19)$$

where C_r was the residual plasma concentration.

This residual line would yield a slope of $-K_a/2.303$ and a zero-time intercept of log $[K_a FX_o/V(K_a-K)]$.

Consequently, the initial estimates of the absorption and elimination rate constants (K_a and K) could be determined from the slope of each line using Eq.(A-20) and (A-21), respectively.

$$S_r = \frac{-K_a}{2.303} \qquad (A-20)$$

$$S_t = \frac{-K}{2.303} \qquad (A-21)$$

where S_r and S_t were the slopes of the residual and terminal lines, respectively.

Since this graphical approach for estimating K_a and K is useful only if the two rate constants are substantially different, the rate constants are best estimated by fitting the concentration time data to Eq.(A-16) with the aid of a nonlinear least-squares

regression program and a digital computer (53).

To determine the apparent volume of distribution or systemic clearance, Eq.(A-16) must be integrated from time zero to time infinity

$$AUC = \frac{F X_o}{V K} \qquad (A-22)$$

It follows that the apparent volume of distribution is given by

$$V = \frac{F X_o}{K \ AUC} \qquad (A-23)$$

and the systemic clearance by

$$Cl = V K = \frac{F X_o}{AUC} \qquad (A-24)$$

where AUC was the summation of the area under the curve from time zero to time infinity, calculated directly by using a trapezoidal rule (53). F, as defined previously, was set to 1 , assuming that the absorption was complete (36).

Furthermore, Eq.(A-16) can be developed to estimate the time at which a peak plasma concentration of drug should be observed, t_{max} , and the maximum plasma concentration at this time, C_{max} , following first-order

input into the body. By differentiating Eq.(A-16) with setting dC/dt = 0 , when the plasma concentration reaches a maximum, C_{max}, at time t_{max} yields

$$t_{max} = \frac{2.303}{K_a - K} \log \frac{K_a}{K} \qquad (\text{ A-25 })$$

The maximum plasma concentration is determined by substituting t_{max} for t in Eq.(A-16)

$$C_{max} = \frac{K_a F X_o}{V (k_a - K)} (e^{-Kt_{max}} - e^{-K_a t_{max}}) \qquad (\text{ A-26 })$$

APPENDIX E

Pharmacokinetic Analysis by Using the PCNONLIN
Nonlinear Estimation Program

An example output of fitting data into PCNONLIN nonlinear estimation program using model 3 is shown in Figure 18.

```
LISTING OF INPUT COMMANDS
mode 3,'one'
MODEL 3
REMARK  ONE COMPARTMENT MODEL - FIRST ORDER INPUT AND OUTPUT
REMA
REMA   NO.    PARAMETER      CONSTANT      SECONDARY PARM.
REMA   ---    ---------      --------      ---------------
REMA   1      VOLUME         DOSE              AUC
REMA   2      K01                          K01 HALF LIFE
REMA   3      K10                          K10 HALF LIFE
REMA   4                                      TMAX
REMA   5                                      CMAX
REMA*****************************************************************
REMA              I-------------------I
REMA              I                   I
REMA   K01  --> I   COMPARTMENT  1   I  ---> K10
REMA              I                   I
REMA              I-------------------I
REMA*****************************************************************
COMM
NPARM 3
NCON 1
NSEC 5
PNAMES 'VOLUME', 'K01', 'K10'
SNAMES 'AUC', 'K01-HL', 'K10-HL', 'TMAX', 'CMAX'
END
TEMP
D=CON(1)
V=P(1)
K01=P(2)
K10=P(3)
T=X
END
FUNC1
COEF=D*K01/(V*(K01-K10))
F=COEF*(DEXP(-K10*T)-DEXP(-K01*T))
END
SECO
S(1)=D/V/K10
S(2)=-DLOG(.5)/K01
S(3)=-DLOG(.5)/K10
TMAX=(DLOG(K01/K10)/(K01-K10))
S(4)=TMAX
S(5)=(D/V)*DEXP(-K10*TMAX)
END
EOM
cons 129.6
init 24.804 1.88 0.093
nobs 11
data
begin
```

Figure 18.   The output of fitting data to PCNONLIN nonlinear

estimation program (cont.)

PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION	WEIGHTED SS	VOLUME	K01	K10
0	.912456E-01	24.80	1.880	.9300E-01
	TAU = .4313E-04	RANK = 3	COND = 205.4	
1	.802662E-01	25.15	1.963	.9195E-01
	TAU = .4297E-04	RANK = 3	COND = 205.5	
2	.802133E-01	25.15	1.963	.9178E-01
	TAU = .4302E-04	RANK = 3	COND = 205.6	
3	.802015E-01	25.16	1.966	.9176E-01
	TAU = .4303E-04	RANK = 3	COND = 205.5	
4	.801611E-01	25.18	1.968	.9157E-01
	TAU = .4305E-04	RANK = 3	COND = 205.8	

CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN   .000100
```
    4        .801569E-01      25.18        1.970       .9159E-01
```

PCNONLIN NONLINEAR ESTIMATION PROGRAM

PARAMETER	ESTIMATE	STANDARD ERROR	95% CONFIDENCE LIMITS		
VOLUME	25.182396	.470304	24.097862	26.266931	UNIVARIATE
			23.497298	26.867495	PLANAR
K01	1.969883	.120681	1.691590	2.248177	UNIVARIATE
			1.537484	2.402282	PLANAR
K10	.091595	.004185	.081945	.101245	UNIVARIATE
			.076601	.106589	PLANAR

PCNONLIN NONLINEAR ESTIMATION PROGRAM

*** CORRELATION MATRIX OF THE ESTIMATES ***

```
 1.00000
  .71719   1.00000
 -.83122   -.60747   1.00000
```

*** EIGENVALUES OF (A TRANSPOSE A) MATRIX ***

NUMBER	EIGENVALUE
1	1853.
2	1.466
3	.4377E-01

Figure 18. The output of fitting data to PCNONLIN nonlinear

estimation program (cont.)

PCNONLIN NONLINEAR ESTIMATION PROGRAM

*** SUMMARY OF NONLINEAR ESTIMATION ***

FUNCTION   1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.0000	.0000	.0000	.0000	1.000	.0000	.0000
.5000	3.172	3.140	.3192E-01	1.000	.8218E-01	.5585
1.000	4.159	4.172	-.1321E-01	1.000	.5646E-01	-.1599
1.500	4.349	4.423	-.7440E-01	1.000	.4858E-01	-.8501
2.000	4.419	4.389	.3005E-01	1.000	.5310E-01	.3541
3.000	4.196	4.086	.1100	1.000	.5181E-01	1.285
4.000	3.569	3.740	-.1707	1.000	.4438E-01	-1.902
6.000	3.201	3.115	.8566E-01	1.000	.4034E-01	.9350
8.000	2.720	2.594	.1261	1.000	.4716E-01	1.428
10.00	2.097	2.160	-.6271E-01	1.000	.5435E-01	-.7460
12.00	1.734	1.798	-.6420E-01	1.000	.5898E-01	-.7938

CORRECTED SUM OF SQUARED OBSERVATIONS =   18.4629
 WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS =   18.4629
 SUM OF SQUARED RESIDUALS =   .801569E-01
 SUM OF WEIGHTED SQUARED RESIDUALS =   .801569E-01
 S = .100098   WITH   8 DEGREES OF FREEDOM
 CORRELATION (Y,YHAT) = .998

PCNONLIN NONLINEAR ESTIMATION PROGRAM

SUMMARY OF ESTIMATED SECONDARY PARAMETERS

PARAMETER	ESTIMATE	STANDARD ERROR
AUC	56.187193	1.790644
K01-HL	.351872	.021535
K10-HL	7.567542	.345401
TMAX	1.633591	.061941
CMAX	4.431239	.049672

Figure 18.   The output of fitting data to PCNONLIN nonlinear

estimation program (cont.)

PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

*** ARE CALCULATED POINTS, OOO ARE OBSERVED POINTS

```
  6.000    I
  5.500    I
  5.000    I
  4.500    I              OOO*O*
  4.000    I               *      *O**
  3.500    I              O*         **O*
  3.000    I              *             ***O*
  2.500    I                              **O**
  2.000    I              *                   **O
  1.500    I              *
  1.000    I
   .5000   I
   .0000   I              O
  -.5000   I
 -1.000    I
 -1.500    I
           ----+---------+---------+---------+---------+---------+---------+-----
             -6.00      -1.00      4.00      9.00      14.0      19.0
                                    X
```
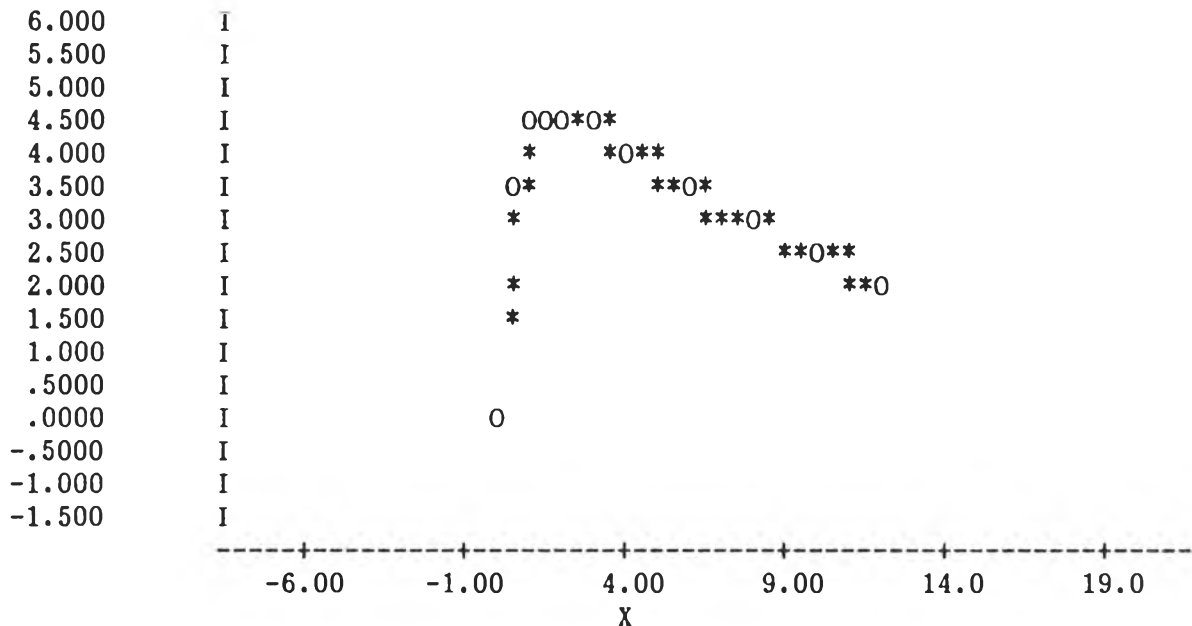
FUNCTION 1
PLOT OF OBSERVED Y VS. WEIGHTED CALCULATED Y

WEIGHTED CALCULATED Y
```
  6.000    I
  5.500    I
  5.000    I
  4.500    I                                          * **
  4.000    I                                      *
  3.500    I                                  **
  3.000    I                              *
  2.500    I                        *
  2.000    I                    *
  1.500    I
  1.000    I
   .5000   I
   .0000   I       *
  -.5000   I
 -1.000    I
 -1.500    I
           ----+---------+---------+---------+---------+---------+---------+-----
             -.200      .800      1.80      2.80      3.80      4.80
                                OBSERVED Y
```
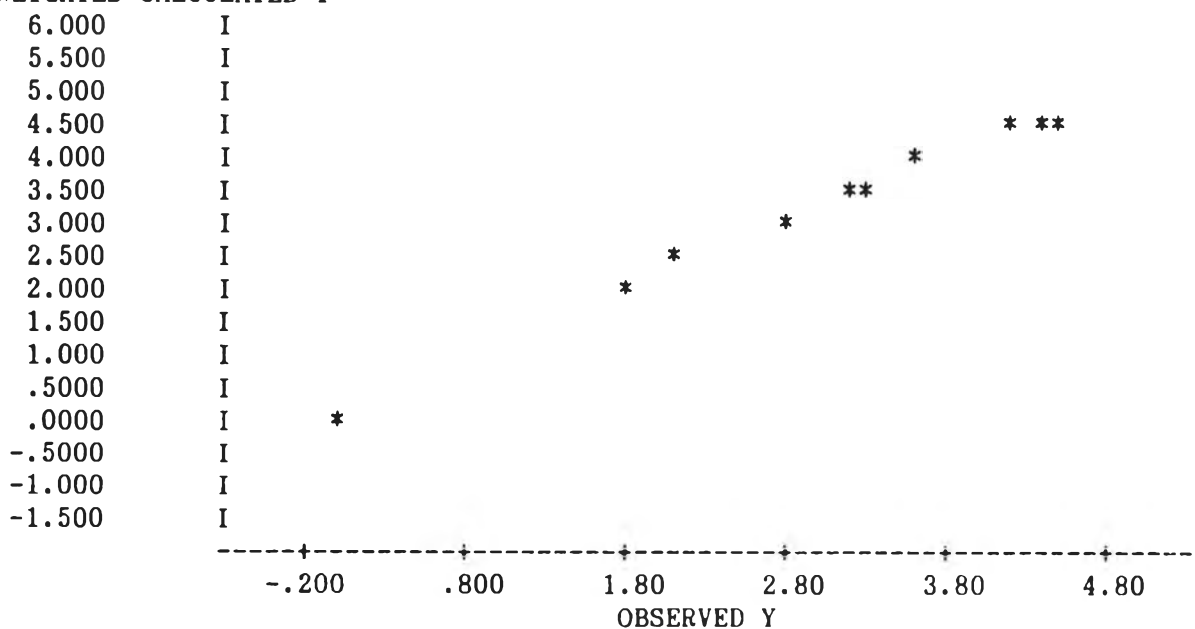
Figure 18.   The output of fitting data to PCNONLIN nonlinear

estimation program (cont.)

PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF WEIGHTED CALCULATED Y VS. WEIGHTED RESIDUAL

```
WEIGHTED RESIDUAL
    .3500      I
    .3000      I
    .2500      I
    .2000      I
    .1500      I                                  *          *
    .1000      I                                       *
    .5000E-01  I                                       *      *
    .0000      I     ------------------*------------------*--------------
   -.5000E-01  I                             *  *              *
   -.1000E+00  I
   -.1500      I                                    *
   -.2000      I
   -.2500      I
   -.3000      I
   -.3500      I
   -.4000      I
             ----+---------+---------+---------+---------+---------+-----
               -2.60     -.600     1.40      3.40      5.40      7.40
                                    WEIGHTED CALCULATED Y
```
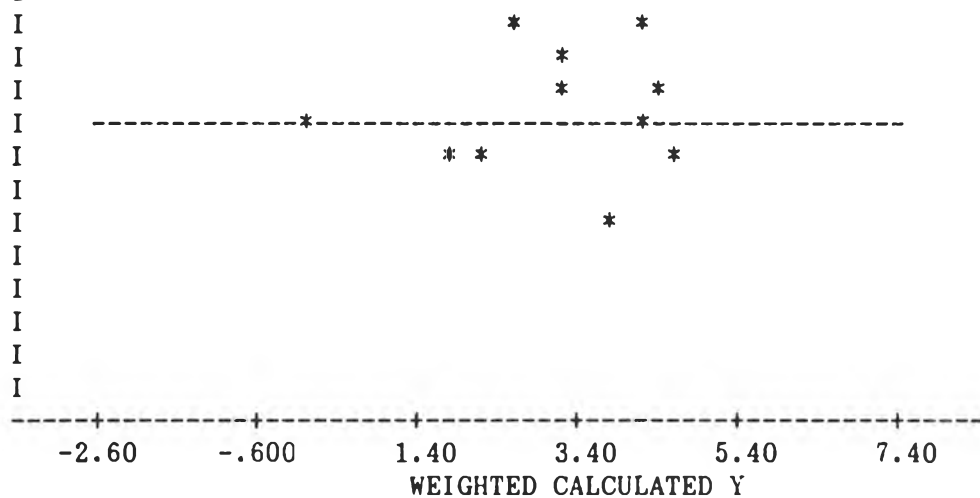
FUNCTION 1
PLOT OF X VS. WEIGHTED RESIDUAL Y

```
WEIGHTED RESIDUAL
    .8000      I
    .7000      I
    .6000      I
    .5000      I
    .4000      I
    .3000      I
    .2000      I                          *          *
    .1000      I                   *    *       *
    .0000      I     ---------------*-**-----------------*---*--------------
   -.1000      I                          *
   -.2000      I
   -.3000      I
   -.4000      I
   -.5000      I
   -.6000      I
   -.7000      I
             ----+---------+---------+---------+---------+---------+-----
               -6.00     -1.00     4.00      9.00      14.0      19.0
                                         X
```
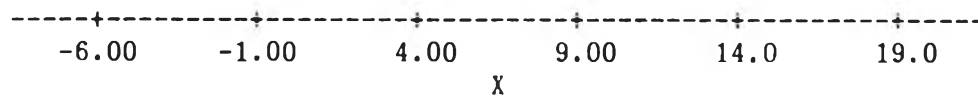
Figure 18.   The output of fitting data to PCNONLIN nonlinear

estimation program (cont.)

Student't-Test Using the Statistical Package SPSS/PC

t-test groups=groups(1,2)/variables= k_a

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: NONSMOKING FEMALES

t-test for: K_a

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	4.5496	4.902	1.550
Group 2	10	4.9689	5.881	1.860

		3	Pooled Variance Estimate			3	Separate Variance Estimate		
F Value	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob.
1.44	.596	3	-.17	18	.864	3	-.17	17.43	.865

Figure 19.   The output of student't-test using the statistical

package SPSS/PC

t-test groups=groups(1,2)/variables= T_{max}

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: NONSMOKING FEMALES

t-test for: T_{max}

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	1.2601	.534	.169
Group 2	10	1.4157	.775	.245

		3	Pooled Variance Estimate			3	Separate Variance Estimate		
F Value	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob.
2.10	.283	3	-.52	18	.608	3	-.52	15.98	.608

---

t-test groups=groups(1,2)/variables= C_{max}

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: NONSMOKING FEMALES

t-test for: C_{max}

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	4.5270	.411	.130
Group 2	10	5.6697	.663	.210

		3	Pooled Variance Estimate			3	Separate Variance Estimate		
F Value	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob.
2.60	.170	3	-4.63	18	.000	3	-4.63	15.02	.000

Figure 19. The output of student't-test using the

statistical package SPSS/PC (cont.)

t-test groups=groups(1,2)/variables= AUC

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: NONSMOKING FEMALES

t-test for: AUC

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	64.6257	9.997	3.161
Group 2	10	80.9391	9.349	2.956

			Pooled Variance Estimate				Separate Variance Estimate	
F Value	2-Tail Prob.		t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
1.14	.845		-3.77	18	.001	-3.77	17.92	.001

----

t-test groups=groups(1,2)/variables= V_d

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: NONSMOKING FEMALES

t-test for: V_d

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	.4842	.048	.015
Group 2	10	.3799	.034	.011

			Pooled Variance Estimate				Separate Variance Estimate	
F Value	2-Tail Prob.		t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
2.08	.290		5.60	18	.000	5.60	16.03	.000

Figure 19. The output of student't-test using the

statistical package SPSS/PC (cont.)

```
t-test groups=groups(1,2)/variables= K
```

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: NONSMOKING FEMALES

t-test for: K

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	.0787	.012	.004
Group 2	10	.0790	.010	.003

		3 Pooled Variance Estimate			3 Separate Variance Estimate		
F Value	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob.	3 t Value	Degrees of Freedom	2-Tail Prob.
1.63	.478	3	-.07	18	.949	3 -.07	17.02	.949

```
t-test groups=groups(1,2)/variables= Cl
```

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: NONSMOKING FEMALES

t-test for: Cl

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	.0380	.006	.002
Group 2	10	.0299	.004	.001

		3 Pooled Variance Estimate			3 Separate Variance Estimate		
F Value	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob.	3 t Value	Degrees of Freedom	2-Tail Prob.
2.51	.187	3	3.64	18	.002	3 3.64	15.19	.002

Figure 19. The output of student't-test using the

statistical package SPSS/PC (cont.)

t-test groups=groups(1,3)/variables= k_a
```
--------------------------------------------------------------------
                           SPSS/PC+
```

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: SMOKING MALES

t-test for: K_a

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	4.5496	4.902	1.550
Group 2	10	5.7323	5.550	1.755

		3	Pooled Variance Estimate		3	Separate Variance Estimate		
F Value	2-Tail Prob.	3 3 3 3	t Value	Degrees of Freedom	2-Tail Prob. 3 3 3	t Value	Degrees of Freedom	2-Tail Prob.
1.28	.718	3	-.51	18	.620	3 -.51	17.73	.620
```
--------------------------------------------------------------------
```

t-test groups=groups(1,3)/variables= T_{max}
```
--------------------------------------------------------------------
                           SPSS/PC+
```

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: SMOKING MALES

t-test for: T_{max}

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	1.2601	.534	.169
Group 2	10	1.0086	.414	.131

		3	Pooled Variance Estimate		3	Separate Variance Estimate		
F Value	2-Tail Prob.	3 3 3 3	t Value	Degrees of Freedom	2-Tail Prob. 3 3 3	t Value	Degrees of Freedom	2-Tail Prob.
1.67	.459	3	1.18	18	.255	3 1.18	16.94	.256
```
--------------------------------------------------------------------
```

Figure 19. The output of student't-test using the

statistical package SPSS/PC (cont.)

t-test groups=groups(1,3)/variables= C_{max}

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: SMOKING MALES

t-test for: C_{max}

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	4.5270	.411	.130
Group 2	10	4.8705	.720	.228

			Pooled Variance Estimate			Separate Variance Estimate		
F Value	2-Tail Prob.		t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
3.07	.110		-1.31	18	.206	-1.31	14.30	.211

----

t-test groups=groups(1,3)/variables= AUC

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: SMOKING MALES

t-test for: AUC

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	64.6257	9.997	3.161
Group 2	10	55.1169	15.477	4.894

			Pooled Variance Estimate			Separate Variance Estimate		
F Value	2-Tail Prob.		t Value	Degrees of Freedom	2-Tail Prob.	t Value	Degrees of Freedom	2-Tail Prob.
2.40	.209		1.63	18	.120	1.63	15.40	.123

Figure 19.   The output of student't-test using the

statistical package SPSS/PC (cont.)

t-test groups=groups(1,3)/variables= V_d

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: SMOKING MALES

t-test for: V_d

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	.4842	.048	.015
Group 2	10	.4574	.074	.023

F Value	2-Tail Prob.	Pooled Variance Estimate t Value	Degrees of Freedom	2-Tail Prob.	Separate Variance Estimate t Value	Degrees of Freedom	2-Tail Prob.
2.33	.224	.96	18	.349	.96	15.52	.351
----

t-test groups=groups(1,3)/variables= K

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: SMOKING MALES

t-test for: K

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	.0787	.012	.004
Group 2	10	.1020	.021	.007

F Value	2-Tail Prob.	Pooled Variance Estimate t Value	Degrees of Freedom	2-Tail Prob.	Separate Variance Estimate t Value	Degrees of Freedom	2-Tail Prob.
2.91	.128	-3.06	18	.007	-3.06	14.53	.008

Figure 19. The output of student't-test using the

statistical package SPSS/PC (cont.)

```
t-test groups=groups(1,3)/variables= Cl
-----------------------------------------------------------------------
                               SPSS/PC+
```

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: SMOKING MALES

t-test for: Cl

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	.0380	.006	.002
Group 2	10	.0470	.013	.004

			Pooled Variance Estimate				Separate Variance Estimate		
F Value	2-Tail Prob.		t Value	Degrees of Freedom	2-Tail Prob.		t Value	Degrees of Freedom	2-Tail Prob.
5.22	.022		-1.93	18	.070		-1.93	12.33	.077

```
-----------------------------------------------------------------------
t-test groups=groups(1,4)/variables= k_a
-----------------------------------------------------------------------
                               SPSS/PC+
```

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: CHILDREN

t-test for: K_a

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	4.5496	4.902	1.550
Group 2	10	4.6268	5.734	1.813

			Pooled Variance Estimate				Separate Variance Estimate		
F Value	2-Tail Prob.		t Value	Degrees of Freedom	2-Tail Prob.		t Value	Degrees of Freedom	2-Tail Prob.
1.37	.648		-.03	18	.975		-.03	17.58	.975

```
-----------------------------------------------------------------------
```

Figure 19. The output of student't-test using the

statistical package SPSS/PC (cont.)

t-test groups=groups(1,4)/variables= T_{max}

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: CHILDREN

t-test for: T_{max}

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	1.2601	.534	.169
Group 2	10	1.3617	.685	.217

		3	Pooled Variance Estimate		3	Separate Variance Estimate		
F Value	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob.	3 t Value	Degrees of Freedom	2-Tail Prob.
1.64	.471	3	-.37	18	.716	3 -.37	16.99	.716

----

t-test groups=groups(1,4)/variables= C_{max}

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: CHILDREN

t-test for: C_{max}

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	4.5270	.411	.130
Group 2	10	5.0259	.896	.283

		3	Pooled Variance Estimate		3	Separate Variance Estimate		
F Value	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob.	3 t Value	Degrees of Freedom	2-Tail Prob.
4.75	.030	3	-1.60	18	.127	3 -1.60	12.63	.134

Figure 19.   The output of student't-test using the

statistical package SPSS/PC (cont.)

t-test groups=groups(1,4)/variables= AUC

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: CHILDREN

t-test for: AUC

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	64.6257	9.997	3.161
Group 2	10	47.2975	13.994	4.425

		3	Pooled Variance Estimate		3	Separate Variance Estimate		
F Value	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob. 3	t Value	Degrees of Freedom	2-Tail Prob.
1.96	.331	3	3.19	18	.005 3	3.19	16.29	.006

----
t-test groups=groups(1,4)/variables= V_d

SPSS/PC+

Independent samples of GROUPS

Group 1: NONSMOKING MALES   Group 2: CHILDREN

t-test for: V_d

	Number of Cases	Mean	Standard Deviation	Standard Error
Group 1	10	.4842	.048	.015
Group 2	10	.4171	.057	.018

		3	Pooled Variance Estimate		3	Separate Variance Estimate		
F Value	2-Tail Prob.	3	t Value	Degrees of Freedom	2-Tail Prob. 3	t Value	Degrees of Freedom	2-Tail Prob.
1.39	.630	3	2.83	18	.011 3	2.83	17.53	.011

Figure 19. The output of student't-test using the

statistical package SPSS/PC (cont.)

```
t-test groups=groups(1,4)/variables= K
-----------------------------------------------------------------------
                            SPSS/PC+

Independent samples of  GROUPS

Group 1:  NONSMOKING MALES          Group 2:  CHILDREN


t-test for:  K

                    Number              Standard    Standard
                  of Cases    Mean     Deviation     Error

        Group 1      10       .0787      .012         .004
        Group 2      10       .1327      .034         .011


               3 Pooled Variance Estimate 3 Separate Variance Estimate
               3                           3
    F    2-Tail 3   t    Degrees of 2-Tail 3   t    Degrees of 2-Tail
  Value  Prob.  3 Value   Freedom   Prob.  3 Value   Freedom   Prob.
               3                           3
  7.61   .006   3 -4.78     18      .000   3 -4.78    11.33     .001
-----------------------------------------------------------------------

t-test groups=groups(1,4)/variables= Cl
-----------------------------------------------------------------------
                            SPSS/PC+

Independent samples of  GROUPS

Group 1:  NONSMOKING MALES          Group 2:  CHILDREN


t-test for:  Cl

                    Number              Standard    Standard
                  of Cases    Mean     Deviation     Error

        Group 1      10       .0380      .006         .002
        Group 2      10       .0556      .017         .005


               3 Pooled Variance Estimate 3 Separate Variance Estimate
               3                           3
    F    2-Tail 3   t    Degrees of 2-Tail 3   t    Degrees of 2-Tail
  Value  Prob.  3 Value   Freedom   Prob.  3 Value   Freedom   Prob.
               3                           3
  8.28   .004   3 -3.09     18      .006   3 -3.09    11.14     .010
-----------------------------------------------------------------------
```

Figure 19.   The output of student't-test using the

statistical package SPSS/PC (cont.)

VITA

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