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APPENDICES

APPENDIX A

TEST PRODUCTS

Code	Brand name	Manufacturers	Mfg.date	Batch no.
A	Tagamet[R]	Smith Kline& French[a]	15/3/85	51713
B	Siamidine[R]	Siam Bheasach	20/3/85	220C08
C	Citidine[R]	Atlantic Lab.	20/7/85	850203
D	Cimidine[R]	Berlin Pharm.	29/5/85	850047
E	Cimulcer[R]	Biolab Co.,Ltd	1/7/83	S 507010
I	Tagamet-Injection	Smith Kline& French[a]	13/11/84	KEA02B

[a] Repacked for Smith Kline & French by Olic (Thailand).

APPENDIX B

STANDARD CURVE DETERMINATION

The typical standard curves and data for cimetidine concentrations in 0.1 N sulfuric acid, carbondioxide-free deionized water and human plasma are presented in Tables 11-13 and Figures 9-11, respectively. The correlations coefficient of the fit to the straight line were highly significant (r^2= 0.999).

Table 12 Typical Standard Curve Data for Cimetidine Concentrations in 0.1 N Sulfuric Acid Estimated Using Linear Regression[1].

Standard No.	Concentration (µg/ml)	Absorbance at λ 219	Inversely[2] estimated concentration (µg/ml)	% - Theory[3]
1	2.00	0.157	1.94	96.76
2	4.00	0.313	4.04	101.08
3	6.00	0.458	6.00	100.00
4	8.00	0.609	8.04	100.53
5	10.00	0.759	10.07	100.69
6	12.00	0.895	11.91	99.23
				Mean 99.72
				S.D. 1.58
				C.V.[4] 1.58 %

1. $r^2 = 0.999$

2. Inversely estimated concentration = $\frac{\text{Absorbance} - 0.014}{7.399 \times 10^{-2}}$

3. % Theory = $\frac{\text{Inversely estimated concentration}}{\text{Concentration}} \times 100$

4. C.V. = $\frac{\text{S.D.}}{\text{Mean}} \times 100$

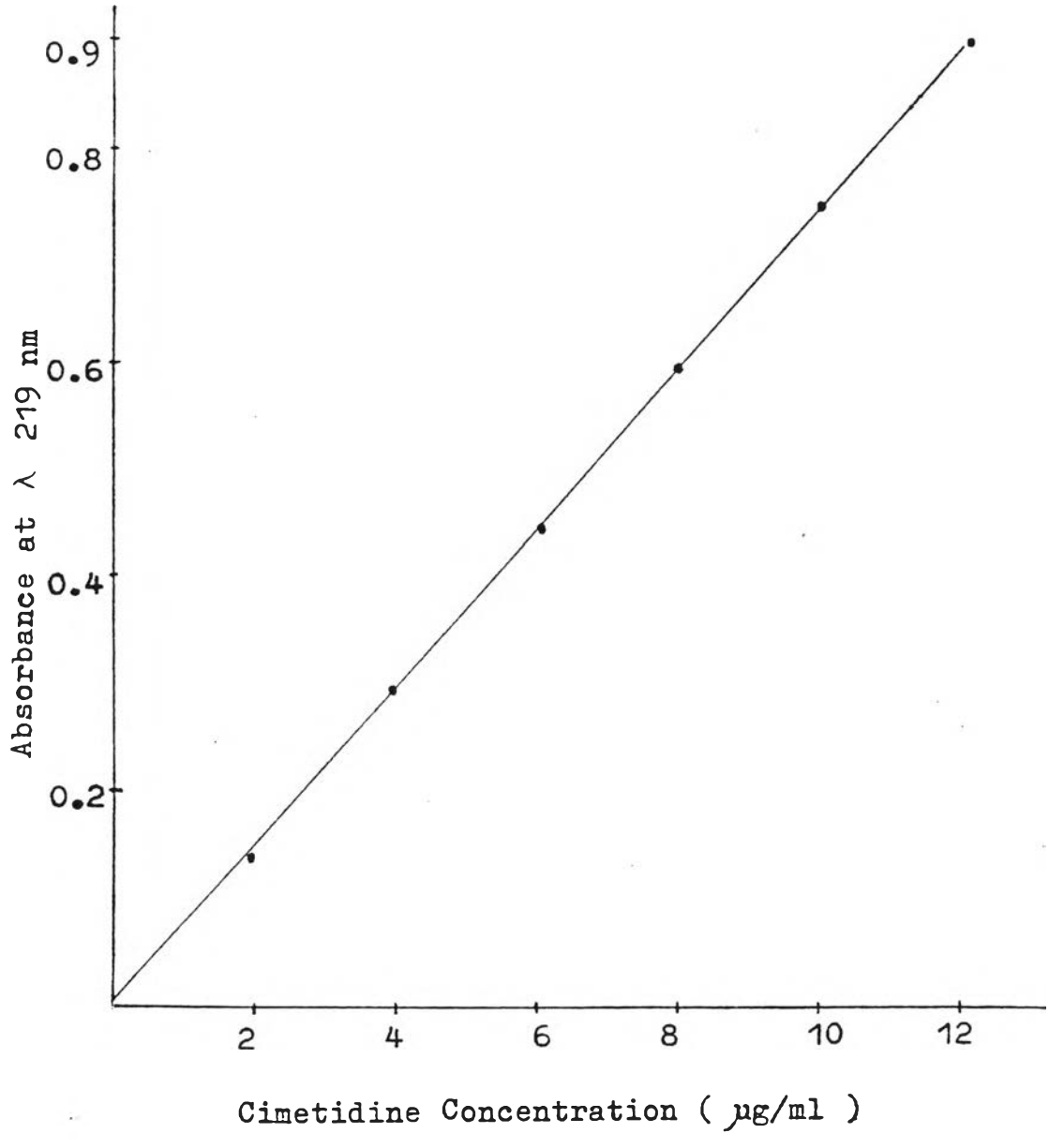

Figure 9 Typical standard curve for cimetidine concentrations in 0.1 N sulfuric acid

Table 13 Typical Standard Curve Data for Cimetidine Concentrations in Carbondioxide-Free Deionized Water Estimated Using Linear Regression[1]

Standard No.	Concentration (µg/ml)	Absorbance at λ 217	Inversely estimated[2] concentration (µg/ml)	%-Theory[3]
1	0.50	0.044	0.45	90.40
2	1.00	0.087	0.98	98.50
3	2.00	0.169	2.00	100.00
4	3.00	0.248	2.98	99.40
5	4.00	0.341	4.13	103.40
6	6.00	0.494	6.03	100.50
7	8.00	0.645	7.90	98.80
8	10.00	0.815	10.01	100.10
			Mean	98.90
			S.D.	3.75
			C.V.[4]	3.79 %

1. $r^2 = 0.999$

2. Inversely estimated concentration = $\frac{\text{Absorbance} - 6.826\times10^{-3}}{8.139\times10^{-2}}$

3. % Theory = $\frac{\text{Inversely estimated concentration}}{\text{Concentration}} \times 100$

4. C.V. = $\frac{\text{S.D.}}{\text{Mean}} \times 100$

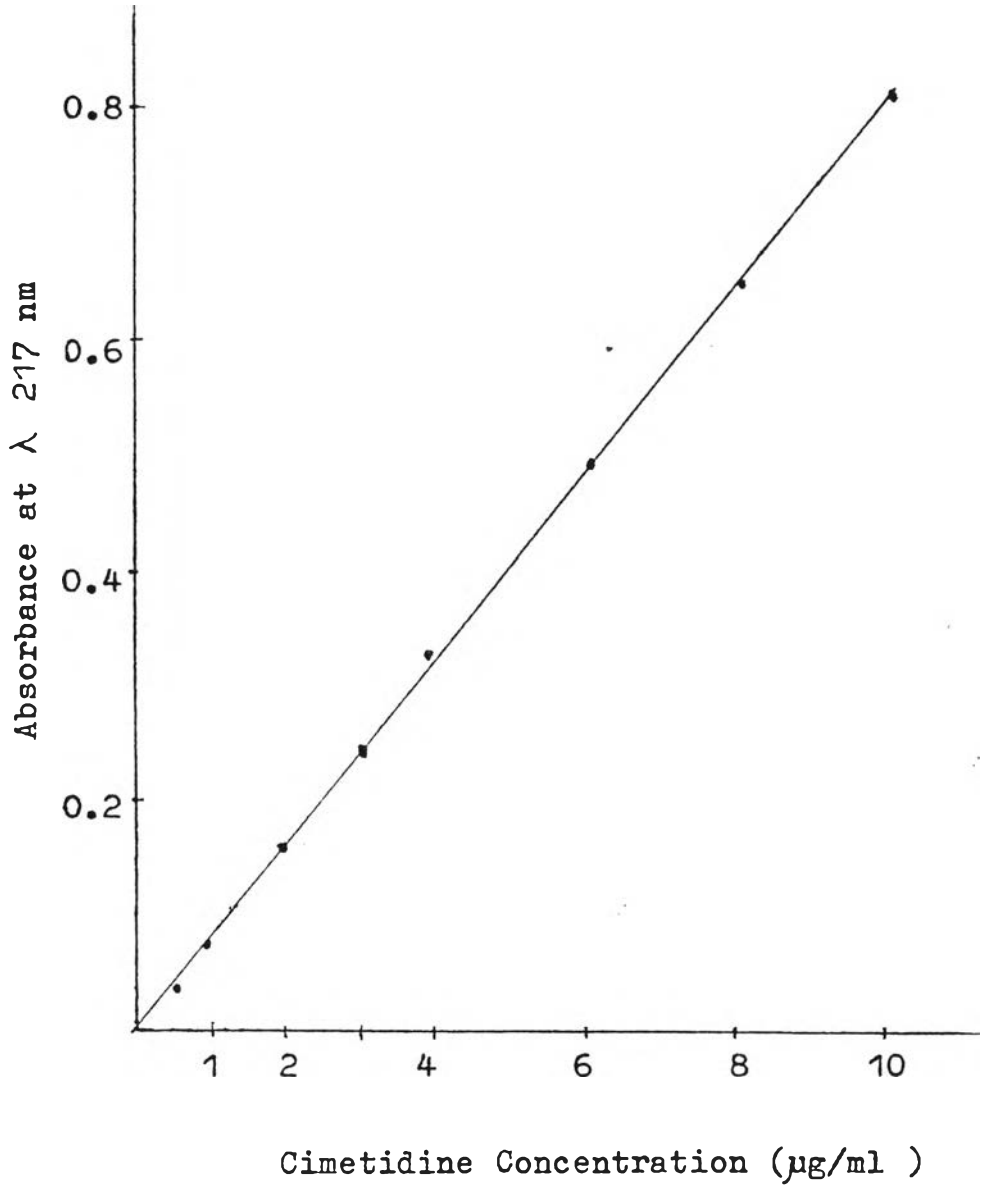

Figure 10 Typical standard curve for cimetidine concentrations in carbondioxide-free deionized water

Table 14 Typical Standard Curve Data for Cimetidine Concentrations in Human Plasma Estimated Using Linear Regression[1]

Standard No.	Concentration (µg/ml)	Area Ratio (Cimetidine/ Procainamide)	Inversely estimated[2] concentration (µg/ml)	% - Theory[3]
1	0.25	0.0979	0.25	101.70
2	0.50	0.2779	0.46	92.30
3	1.00	0.7769	1.04	103.60
4	2.00	1.6349	2.02	101.20
5	3.00	2.4496	2.96	98.70
6	4.00	3.3593	4.01	100.20
7	5.00	4.2200	5.00	100.00
			Mean	99.70
			S.D.	3.60
			C.V.[4]	3.61%

1. $r^2 = 0.999$

2. Inversely estimated concentration = $\frac{\text{Area ratio} + 0.1229}{0.8684}$

3. % Theory = $\frac{\text{Inversely estimated concentration}}{\text{Concentration}} \times 100$

4. C.V. = $\frac{\text{S.D.}}{\text{Mean}} \times 100$

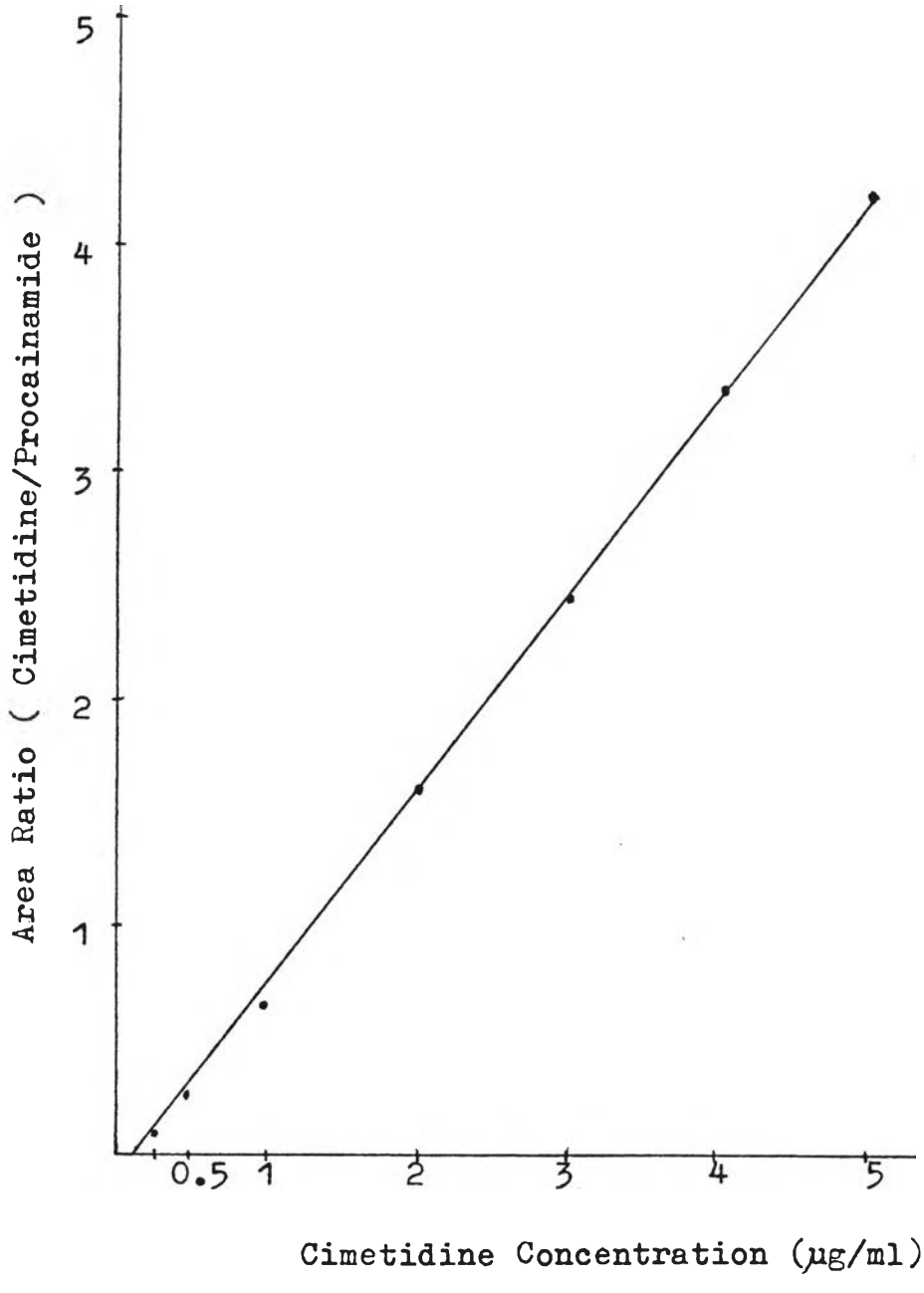

Figure 11 Typical standard curve for cimetidine concentrations in human plasma

APPENDIX C

SUBJECTS

Table 15 Physical Characteristics of the Subjects

Subject No.	Sex	Age (yr)	Weight (kg)
1	M	19	61
2	M	20	56
3	M	20	58
4	M	21	61.5
5	M	22	52
6	M	20	51
7	M	22	58
8	M	20	59
9	F	27	51
Mean		21.22	56.39
S.D.		2.39	4.14

Table 16 Biochemical Laboratory Results

Test	Normal value	Subject 1	2	3	4	5	6	7	8	9
BUN	5-25 mg%	10.2	13.8	13.9	13.0	11.7	15.0	9.7	17.9	9.8
CREA	0.9-1.7 mg%	1.25	1.37	1.50	1.50	1.25	1.06	1.10	1.25	0.90
B	0.8-1.5 mg%	1.05	0.80	0.90	0.88	1.00	1.00	0.80	0.82	0.81
DB	0.2-0.8 mg%	0.20	0.30	0.30	0.30	0.30	0.22	0.10	0.20	0.10
LB	0-1.3 mg%	0.85	0.40	0.40	0.58	0.70	0.78	0.60	0.32	0.21
A.P.	40-115 U/L	105	74	80	62	85	62	85	85	62
SGOT	4-19 U/L	6	6	6	4	12	6	10	7	5.3
SGPT	2-17 U/L	5	3	6	3	9	4.5	6.5	14	5

Table 17 Hematological Laboratory Results

Test	Results Subject 1	2	3	4	5	6	7	8	9
RBC count (mill/mm^3)	5.06	4.81	4.32	4.39	4.83	4.75	4.51	5.42	3.60
WBC (cell/mm^3)	6,650	4,600	6,100	7,600	4,950	6,650	8,850	5,350	5,200
Hemoglobin (gm %)	15.0	15.0	16.3	15.2	16.0	14.0	16.0	15.0	12.5
Hematocrit (%)	45	45	46	45	47	45	46	46	38
Neutrophils (%)	54	34	44	43	32	61	59	53	54
Lymphocytes (%)	46	61	49	56	56	39	33	45	46
Monocytes (%)	-	2	3	1	-	-	5	-	-
Eosinophils (%)	-	3	4	-	11	-	3	2	-
Basophils (%)	-	-	-	-	1	-	-	-	-
Blood grouping	B	O	A	B	O	A	O	B	AB

APPENDIX D

STATISTICS

1. Mean ($\bar{X}$)

$$\bar{X} = \frac{\sum X}{N}$$

2. Standard Deviation (S.D.)

$$S.D. = \sqrt{\frac{\sum (X - \bar{X})^2}{N - 1}}$$

3. Standard Error of The Mean (SEM)

$$SEM = \frac{S.D.}{\sqrt{N}}$$

4. Testing Concerning the Difference of Two Means

(by Student's t-test)

Let μ_1, μ_2 = Population means

X_1, X_2 = Sample means

σ_1^2, σ_2^2 = Population variances

s_1, s_2 = Sample standard deviation

N_1, N_2 = Sample size

The null hypothesis $H_o : \mu_1 = \mu_2$

The alternative hypothesis $H_a : \mu_1 \neq \mu_2$

The statistic t was given as $t = \frac{(\bar{X}_1 - \bar{X}_2) - (\mu_1 - \mu_2)}{S_p}$

First homogeneity of variance is tested for using the F test, which is defined as follows:

$$F = \frac{(s_1)^2}{(s_2)^2}$$

where $(s_1)^2$= the larger of the two sample variances

$(s_2)^2$= the smaller of the two sample variances

With this test we are evaluating the null hypothesis of no difference between the two population variances. If the F is not significant, the null hypothesis stands.

4.1 if $\sigma_1^2 \neq \sigma_2^2$

The statistic t was given as

$$t = \frac{\bar{X}_1 - \bar{X}_2}{S_p}$$

Where S_p^2 was the pooled variance

$$S_p^2 = \frac{(s_1)^2}{N_1} + \frac{(s_2)^2}{N_2}$$

With degree of freedom

$$df. = \frac{\left(\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}\right)^2}{\frac{\left(\frac{s_1^2}{N_1}\right)^2}{N_1-1} + \frac{\left(\frac{s_2^2}{N_2}\right)^2}{N_2-1}}$$

4.2 if $\sigma_1^2 = \sigma_2^2$

The test statistic for this case was

$$t = \frac{\bar{X}_1 - \bar{X}_2}{S_p}$$

Where the pooled variance

$$S_p^2 = \left(\frac{1}{N_1} + \frac{1}{N_2}\right)\left[\frac{(N_1-1)\, s_1^2 + (N_2-1)\, s_2^2}{N_1+N_2-2}\right]$$

And degree of freedom

$$df. = N_1 + N_2 - 2$$

Comparing this t value with $t_{(Tab)}$ for $\frac{\alpha}{2}$ that is obtained from the table.

5. Analysis of Variance (ANOVA)

Table 18 Analysis of Variance for Completely Randomized Design.

Source of Variation	Sum of Squares	df.	Mean Square	Variation Ratio
Among-groups	$\sum_{j=1}^{k} n_j(\bar{X}_{\cdot j} - \bar{X}_{\cdot\cdot})^2$	k-1	$\frac{SS_{among}}{k-1}$	V.R. = $\frac{MS_{among}}{MS_{within}}$
Within-group	$\sum_{j=1}^{k} \sum_{i=1}^{n_j} (X_{ij} - \bar{X}_{\cdot j})^2$	N-k	$\frac{SS_{within}}{N-k}$	
Total	$\sum_{j=1}^{k} \sum_{i=1}^{n_j} (X_{ij} - \bar{X}_{\cdot\cdot})^2$	N-1		

where X_{ij} = Observed value i at Treatment j

$i = 1, 2, \ldots, n$

$j = 1, 2, \ldots, k$

$T_{\cdot j} = \sum_{i=1}^{n_j} X_{ij}$

$\bar{X}_{\cdot j} = \frac{T_{\cdot j}}{n_j}$

$T_{\cdot\cdot} = \sum_{j=1}^{k} T_{\cdot j}$

$\bar{X}_{\cdot\cdot} = \frac{T_{\cdot\cdot}}{N}$

$N = \sum_{j=1}^{k} n_j$

Comparing the V.R. value with the critical value F obtained from table at degree of freedom (k-1) and (N-k).

If $F > F_{(Tab)}$, we reject the null hypothesis that $u_1 = u_2 = u_3 = \ldots = u_k$ and accept the alternative hypothesis.

If F is not significant, the null hypothesis stands.

APPENDIX E

NONCOMPARTMENT ANALYSIS BASED ON STATISTICAL MOMENT THEORY

Noncompartmental methods for the estimation of certain pharmacokinetic parameters are usually based on the estimation of the area under a plot of drug concentration versus time. Noncompartmental methods have been used to estimate bioavailability, clearance, apparent volume of distribution, and the fraction of a dose of a drug that is converted to a specific metabolite, base on data following single doses of drug and metabolite. These methods do not require the assumption of a specific compartmental model for either drug or metabolite. In fact, these methods can be applied to virtually any compartmental model, provided that we can assume linear pharmacokinetics.

Statistical Moments

The application of statistical methods to pharmacokinetics was reported in 1979 by Yamaoka et al. (51) and Cutler (52). In 1980, Riegelman and Collier (53) applied statistical moment theory to the evaluation of drug absorption.

The time course of drug in plasma can usually be regarded as a statistical distribution curve. Irrespective of the route of administration, the zero and the first

moments are defined as follows:

$$AUC = \int_0^\infty C\,dt \qquad \text{Eq. 7}$$

$$MRT = \frac{\int_0^\infty tC\,dt}{\int_0^\infty C\,dt} = \frac{AUMC}{AUC} \qquad \text{Eq. 8}$$

Where MRT is the mean residence time of a drug in the body. AUC and MRT are termed the zero and first moment, respectively, of the drug concentration-time curve.

In the usual single-dose pharmacokinetic study, blood sampling is stopped at some time t* when drug concentration, C*, is measurable. Hence, estimation of the area under the blood level-time curve from zero time to infinity, AUC, must be carried out in two steps. The area under the curve from zero time to t* is calculated by means of the trapezoidal rule. To this partial area we must add the area under the curve from t* to infinity, which is usually estimated as follows:

$$\int_{t^*}^\infty C\,dt = \frac{C^*}{\lambda_n} \qquad \text{Eq. 9}$$

Where λ_n is 2.303 times the slope of the terminal exponential phase of a plot of log drug concentration versus time. The sum of the two partial areas is AUC.

The same approach must be used to estimate total AUMC. The area under the first moment curve from t* to infinity is estimated as follows:

$$\int_{t^*}^{\infty} tC\,dt = \frac{t^*C^*}{\lambda_n} + \frac{C^*}{\lambda_n^2} \qquad \text{Eq. 10}$$

Bioavailability

Bioavailability often refers to the fraction (F) of an oral dose that actually reaches the systemic circulation. Since the availability of an intravenous dose is usually unity, we can estimate F as follows:

$$F = \frac{AUC_{oral}}{AUC_{i.v.}} \cdot \frac{Dose_{i.v.}}{Dose_{oral}} \qquad \text{Eq. 11}$$

Equation 11 assumes equal clearances in the oral and intravenous studies. The fraction of the oral dose available relative to a standard other than an intravenous injection (F_{rel}) may be estimated by means of a similar equation.

For example, the $[AUC]_o^{\infty}$ after oral dosing of Brand A and after intravenous administration were 11.2593 and 7.4901 μg-hr/ml, respectively . Average dose of cimetidine Brand A was 402.67 mg and was 200.68 mg for cimetidine injection.

Therefore, $F_{ab} = \frac{11.2593}{7.4901} \cdot \frac{200.68}{402.67} = 0.75$

and if $[AUC]_o^{\infty}$ after oral administration of Brand B was 10.7195 μg-hr/ml with the dose of 391.29 mg

$$F_{rel} = \frac{10.7195}{11.2593} \cdot \frac{402.67}{391.29} = 0.98$$

Half-Life

The first moment of the blood level-time curve, mean residence time, is the statistical moment analogy of half-life. In effect, the MRT represents the time for 63.2 % of the administered dose to be eliminated.

$$t_{1/2} = 0.693\ MRT_{i.v.} \qquad \text{Eq. 12}$$

Where $MRT_{i.v.}$ calculated by equation 8, would be 1.89 hours. Therefore,

$$t_{1/2} = 0.693\ (\ 1.89\ ) = 1.31 \text{ hours}$$

Absorption Kinetics

Statistical moment methods for estimating rates of absorption after oral administration of a drug are based on differences in mean residence times after different modes of administration. In general,

$$MAT = MRT_{oral} - MRT_{i.v.} \qquad \text{Eq. 13}$$

Where MAT is the mean absorption time. When drug absorption can be described by a single first-order process,

$$MAT = 1/K_a \qquad \text{Eq. 14}$$

Where K_a is the apparent first-order absorption rate constant.

Since MRT_{oral} = 3.34 hours, $MRT_{i.v.}$ = 1.89 hours

Therefore MAT = 3.34 - 1.89 = 1.45 hours

and K_a = 1/1.45 = 0.69 $hour^{-1}$

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