CHAPTER 4

POPULATION ANALYSIS OF PHARMACOKINETIC PARAMETERS OF CAPTOPRIL

4.1 INTRODUCTION

The specialised study of the mathematical relationship between a drug dosage regimen and the resulting plasma drug concentration is known as pharmacokinetics (Mac Kichan and Comstock, 1986). Pharmacokinetic study is a major advance in the understanding of how drugs are absorbed, distributed and eliminated. Several physiological (eg. maturation of organ function in infants) and pathological process (eg. heart failure, renal failure) dictate dosage adjustment in individual patients. These processes modify specific pharmacokinetic parameters. The two basic parameters are clearance (CL), which is a measure of the ability of the body to eliminate the drug, and volume of distribution, which is a measure of the apparent space in the body available to contain the drug.

Individual compartmental modeling provide a mathematical equation and a set of parameter values that yield a detailed description of the plasma concentration time curve. The predicted plasma concentrations are then determined by the model based parameters. Usually, a pharmacokinetic program is used in assisting the computation of the parameters.

Besides compartmental analysis, noncompartmental analysis is also commonly used to characterise the plasma concentration-time curve. Then estimation of the interindividual variability of the pharmacokinetic parameters can be determined using descriptive statistic. Although commonly used, noncompartmental analysis has certain limitations. These limitations may include approximations introduced by calculation of the trapezoidal area

under the curve (AUC) and inconsistencies in estimating the terminal elimination rate constant (λ_z).

The purpose of this standard two stages analysis is to determine from the bioequivalence studies, the variability of the pharmacokinetic parameters (CL, K, and $t_{1/2}$) of captopril in healthy population.

4.2 METHOD

Non compartmental method was used to determine from the captopril pharmacokinetic parameters, using Win Nonlin professional version 2.1. The slope of the terminal elimination phase was calculated from the least-squares regression of the natural logarithm of plasma concentration versus time over the last four to five points.

The basic calculations are based on the area under the plasma concentration versus time curve (AUC, zero moment) and the area under the first moment curve (AUMC), the latter being the entire area under the plot of concentration and time versus time to infinity. Both the AUC and AUMC are calculated using the trapezoidal rule.

$$AUC_n^2 = \Delta t * \frac{C_1 + C_2}{2} \quad \text{..... (eqn.1)}$$

$$AUMC_n^2 = \Delta t * \frac{t_1 * C_1 + t_2 * C_2}{2} \quad \text{..... (eqn.2)}$$

The portion of the AUC in the tail t = T is estimated as (C_T/K) where C_T is the concentration at time T which is the last point; K is the terminal rate constant. For AUMC, the estimate for the extrapolate area after the last point at t = T to t = ∞ is $(C_T + k) * (T + 1/k)$

Mean residence time, MRT is the time that the drug stay in the body and is expressed as

$$MRT = \frac{AUMC}{AUC} \quad \text{..... (eqn. 3)}$$

Apparent clearance for extravascular dosing is expressed as

$$CL/F = Dose / AUC\infty \quad \text{..... (eqn. 4)}$$

and apparent volume of distribution for extravascular dosing based on terminal phase is expressed as

$$V_z / F = Dose / k * AUC\infty \quad \text{..... (eqn.5)}$$

Finally, the half-life ($t_{1/2}$) is defined as the time taken for the plasma concentration to fall to half its value

$$t_{1/2} = \frac{\ln 2}{k} \quad \text{.....(eqn. 6)}$$

Population analysis

Standard two stages analysis is used for the population analysis, in which the individual values will be used to construct the mean, spread and variability using statistical program SPSS 10.

4.3 RESULT

A total of 66 individual parameters of CL / F, $t_{1/2}$ and K from bioequivalence studies were analysed using SPSS 10. The result from the descriptive statistics of the parameters, CL / F, $t_{1/2}$ and K are shown in Table 4

Table 4.1 Descriptive statistics for CL / F, $t_{1/2}$ and K

Subject Number	CL/F (l/hr.kg)	$t_{1/2}$ (h)	K (h^{-1})
1	1.6	2.589	0.268
2	1.3	2.783	0.249
3	2.8	3.235	0.214
4	1.5	2.884	0.240
5	2.1	2.446	0.283
6	2.6	1.714	0.405
7	1.7	2.026	0.342
8	1.9	3.282	0.211
9	1.6	4.636	0.150
10	2.6	1.684	0.412
11	1.6	5.888	0.118
12	1.3	2.594	0.267
13	2.5	3.643	0.190
14	2.4	1.596	0.434
15	1.6	1.924	0.360
16	1.7	1.643	0.422
17	1.8	2.671	0.260
18	2.0	5.404	0.128
19	2.0	2.779	0.249
20	2.7	4.205	0.165
21	2.1	3.212	0.216
22	5.6	2.529	0.274
23	2.8	2.477	0.280
24	1.5	2.431	0.285
25	1.9	1.991	0.348
26	1.8	2.421	0.286
27	2.6	1.702	0.407
28	1.7	2.152	0.322
29	1.6	1.886	0.368
30	1.8	3.779	0.183
31	2.0	1.722	0.403
32	1.3	5.809	0.119
33	1.9	1.635	0.424
34	1.3	2.408	0.288
35	0.2	2.107	0.329
36	1.5	2.084	0.333
37	1.4	1.358	0.510
38	1.8	2.645	0.262
39	1.2	1.656	0.419
40	2.0	1.862	0.372
41	1.8	3.010	0.230

Subject Number	CL/F (l/hr.kg)	$t_{1/2}$ (h)	K (h^{-1})
42	1.9	1.193	0.581
43	1.3	3.140	0.221
44	1.4	1.979	0.350
45	2.2	2.118	0.327
46	1.9	2.514	0.276
47	1.6	2.000	0.347
48	2.6	2.678	0.259
49	2.1	2.504	0.277
50	1.5	2.919	0.238
51	1.2	3.957	0.175
52	1.3	2.200	0.315
53	1.3	3.269	0.212
54	2.0	1.737	0.399
55	1.9	2.275	0.305
56	3.0	2.327	0.298
57	3.5	3.600	0.193
58	1.8	1.187	0.584
59	3.8	3.281	0.211
60	2.9	6.349	0.109
61	2.0	1.196	0.580
62	1.8	3.945	0.176
63	4.5	4.199	0.165
64	2.1	3.111	0.223
65	2.8	6.784	0.102
66	2.0	4.650	0.149
Descriptive statistic: n = 66			
Mean	2.03	2.81	0.29
Median	1.91	2.51	0.28
Minimum	0.18	1.19	0.10
Maximum	5.57	6.78	0.58
Std. dev.	0.80	1.25	0.11
Variability (CV %)	39.00	44.00	38.00
Lower quartile	1.58	1.98	0.21
Upper quartile	2.23	3.27	0.35
Skewness	1.89	1.37	0.68

Table 4.2 shows the mean value of clearance, half-life and elimination rate constant determined by descriptive statistics for the 66 subjects. Published data of the values of clearance, half-life and elimination rate constant is shown in Table 4.3. Figure 4.1, 4.2 and 4.3 show the superimposed histogram model for the clearance, half-life and elimination constant, respectively.

From the descriptive statistics analysis, the clearance, half-life and elimination rate constant values are within the values which were reported in literature. For the clearance, our result 0.23 l/hr.kg (range: 0.18 – 5.57) is very close to the result by Massana *et al.*1997 and Jankowski et al. 1994. The results by Jankowski *et al.* are reported in l/hr. If this result divided by the weight of subjects (range from 60 –70 kg), the result will not differ so much with our result which is 1.40 to 1.63 for CL/F = 97.77 and 1.04 to 1.22 for CL/F = 72.92. Three early literatures by Duchin *et al.* (1981), Richer *et al.* (1984), and Creasey *et al.* (1986) have a lower CL as compared to others. This might be due to the assay sensitivity at that time might not be as good as recent study. However, the values are still within our present study lower range.

For the half-life, present study value is 2.81 (range: 1.19-6.78) which is longer compared to the literature. This is because five to seven subjects in the present study have a long half-life compared to the others. Hence these high values influenced the mean results. If we refer to the range, our value is quite close to the literature (refer to table 4.3). This long half-life is also reflected in our K values, when they are lower compared to literature. This is because the half-life ($t_{½}$) and elimination rate constant (K) are inversely related.

Table 4.2 Captopril pharmacokinetic parameters for all subjects (n = 66) in the 4 sets of bioequivalence studies carried out.

Parameters	Mean	Range	SD
Clearance (l/h/kg)	2.03	0.18 – 5.57	0.04
Half-life (h)	2.81	1.19 – 6.78	1.25
Elimination rate constant (h^{-1})	0.29	0.10 – 0.58	0.11

SD = Standard deviation

Table 4.3 Published data of the values of clearance (CL), half-life ($t_{1/2}$) and elimination rate constant (K).

	CL /F(l/hr.kg)	$t_{1/2}$ (h)	K (h^{-1})	n	Dosing/ frequency	Formulation	Population
Duchin *et al.* (1981)	0.76 ± 0.08	1.93 ± 0.20	-	5	10mg/ single	intravenous	Caucasian
Richer *et al.* (1984)	0.69 ± 0.08	0.66 ± 0.13	-	10	72mg*a/ single	Oral form	Caucasian
Creasey *et al.* (1986)	0.19 ± 0.02	1.4 ± 0.1	-	12	100mg/ single	Tablet	Caucasian
Jankowski *et al.* (1994)	72.92 ± 18.53*b	1.11 ± 0.34	0.67 ± 0.18	12	25mg/ single	Oral form	Caucasian
Jankowski *et al.* (1994)	97.77 ± 22.34*b	1.03 ± 0.19	0.69 ± 0.11	12	50mg/ single	Oral form	Caucasian
Massana *et al.* (1997)	2.36 ± 0.67	1.01 ± 0.92	1.60 ± 0.69	12	100mg/ single	Tablet	Caucasian
M.E Franklin *et al.*(1998)	-	1.58 ± 0.41	0.47 ± 0.12	20	100mg/ single	Tablet	Caucasian
Present study, Zamri *et al.* (2000)	2.03 ± 0.80	2.81 ± 1.25	0.29 ± 0.11	66	12.5 – 25mg/ single	Tablet	Oriental

- = no result presented

*a = dose base on average weight of 1 mg/kg.

*b = unit in l/hr, assume average weight of 70 kg than the CL/F would be 1.04 to 1.40 l/hr.kg

The normal curve line superimposed on the frequency histogram (Figure 4.1, 4.2 and 4.3) confirmed that all the parameters, eg. clearance, half-life and elimination rate constant were uni-modally distributed with a slight skew as shown by the skewness value for the parameters which deviate slightly from 1 as shown in Table 4.1. Consequently, the distribution plot shows that the present population pharmacokinetic parameters is uni-modal without distinctive subpopulations of example, rapid or slow metabolisers for captopril.

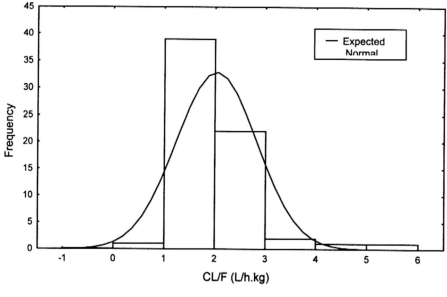

Figure 4.1 Superimposed Histogram plot with fitted normal curve of frequency of observation versus clearance

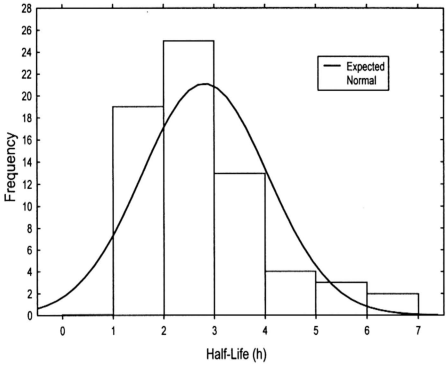

Figure 4.2 Superimposed Histogram plot with fitted normal curve of frequency of observation versus half-life

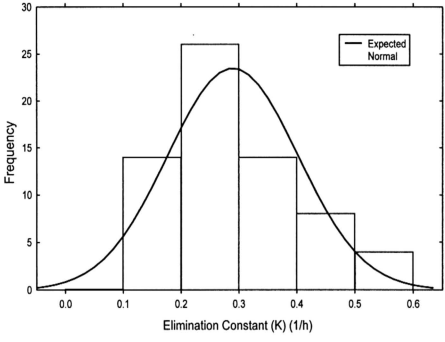

Figure 4.3 Superimposed Histogram plot with fitted normal curve of frequency of observation versus elimination constant

4.4 DISCUSSION AND CONCLUSION

From the descriptive statistics and the frequency histogram, we can conclude that all of the pharmacokinetic parameters such as clearance, half-life and elimination rate constant are uni-modlly distributed and all these values are in agreement with the literature values. There does not appear to be any distinctive subpopulations of for example, rapid or slow metabolisers for captopril within the population studies.