CHAPTER V

DISCUSSION

The drugs used in this study were those of commercially available tablets. On the molar basis, a 400-mg bacampicillin tablet is equivalent to ampicillin 278 mg, it was only a rough estimation as an equivalent dose of 250 mg ampicillin. Therefore, in the assessment of the results, this inequivalence in molar doses should sometimes be taken into consideration.

1. Comparison of Some Bioavailability Parameters and Pharmacokinetic Parameters Obtained from This Study with Those Previously Reported

1.1 Bioavailability Parameters

Some meaningful criteria used for assessment of the bioavailability of drugs via oral route of administration are: the peak serum concentrations, the peak time, the area under the serum concentration-time curve and the percentage urinary recovery of drug. In this study, the mean individual peak serum concentration (the value obtained from pointing out the peak concentration of each subject, then averaged) of ampicillin after oral administration of ampicillin 250 mg was 2.04 mcg/ml reached at 1.68 hours after ingestion. The peak of the mean serum concentrations (the value obtained from considering the concentration at each sampling time as the mean of 14 subjects,

then pointed out the peak concentration) was 1.74 mcg/ml and the peak time was 1.5 hours. It is suggested that if the individuals reach their peak values at different times after administration, the peak of the mean serum concentrations is not always a correct estimate of the actual peak concentrations achieved and the mean individual peak concentration can be considered more accurately. However, in comparing the peak concentrations obtained in this study with those previously reported, the peak of the mean serum concentrations was used, since it was more commonly reported in those previous studies. The peak of the mean serum concentrations after oral administration of ampicillin 250 mg obtained in this study was slightly lower, but occurred earlier, than 2.6 mcg/ml and 3.5 mcg/ml reached at about 2 hours reported by Ekstrom, et al.(54) and Sutherland, et al.(25) respectively. The percentage urinary revocery of ampicillin after oral administration of ampicillin 250 mg was 33% in this study which was comparable to 33% and 37% reported by Knudsen and Rolinson (12) and Sutherland et al. (25)

The peak concentrations attained after oral administration of ampicillin 500 mg have been reported in a wide range e.g., Kunin and Finkelberg (79) reported a very low value of 1.5 mcg/ml while Ehrnebo, et al. (39) reported a rather high value of 6.7 mcg/ml. However, the most common values reported were ranging from 2.4 to 4.5 mcg/ml (10-14, 21, 34, 43, 80). The peak of the mean serum concentrations found in this study was 3.2 mcg/ml which was approximately midpoint of the usually reported range. The peak time observed in this study was 1.5 hours which corresponded to those 1.5 - 2 hours commonly reported.

However, some observers noted the peak time to be three hours after administration (47,81). This delayed peak time, probably caused by the non-strictly fasting state of the patients participated in their studies. The AUC_0^∞ in this study was found to be 10.97 hr. mcg/ml, this figure agreed closely with 11.1 hr. mcg/ml and 12.4 hr. mcg/ml cited by Simon, et al. (71) and Lode, et al. (14). The percentage urinary recovery was 31 percent which was comparable to those 30.6 and 33.8 percent reported by Ferrara and Zanon (34), Gordon, et al. (10) and Lode, et al. (14). All bioavailability parameters obtained after oral administration of ampicillin 500 mg were closely resembled those reported by Gordon, et al. (10) whose study involved a test population and the experimental design that was practically identical to ours.

Following a single oral administration of bacampicillin 400 mg, the peak of the mean serum concentrations was 5.41 mcg/ml and the peak time was 45 minutes. It was somewhat lower but occurred earlier with respect to those 6.8 - 8.9 mcg/ml reached at about 1 hour previously reported (33,35,37,41). The area under the serum concentration-time curve and the percentage urinary recovery observed in this study were 9.93 hr. mcg/ml and 62 percent respectively. They were slightly smaller than the earlier findings i.e., the area under the serum concentration-time curve earlier reported was 13.7 - 13.9 hr. mcg/ml and the percentage urinary recovery ever reported was ranged from 70 to 83 percent (33,37,41). This small discrepancies may reflect biological variation in different tribe and race of the subjects.

After oral administration of bacampicillin 800 mg, the peak of the mean serum concentrations of 9.5 - 16.5 mcg/ml and the peak time of about 1 hour have been reported (34,38,39,41,67,71). The corresponding values obtained from this study were 10.55 mcg/ml and 45 minutes respectively. The area under the serum concentration-time curve was 22.4 hr. mcg/ml which was smaller than 25.7 - 28.6 hr. mcg/ml reported by Verbist (21) and Croydon and Sutherland (19). The percentage urinary recovery was 54 percent compared to that 57 percent reported by Simon, et al. (71).

1.2 Pharmacokinetic Parameters

Few previous pharmacokinetic studies of ampicillin and bacampicillin have been reported since most of the earlier studies concentrated on the assessment of the bioavailability of drugs i.e., only the bioavailability parameters were considered and reported. The pharmacokinetic parameters obtained from this study were slightly different from those reported by other investigators. The factors possibly responsible to the differences were the subjects participated in the studies, the differences in their races, ages, weight and normal habits, the mathematical model applied and the assumptions used to interpret the data.

Braga and Fraschini (38) reported that the AUC_o^∞ after an oral dose of bacampicillin 800 mg in patients with acute exacerbation of chronic bronchitis was 30.3 ± 13.07 hr. mcg/ml whereas the AUC_o^∞ of 22.4 ± 2.40 hr. mcg/ml was observed in the present study. The peak serum levels, the peak time and the

overall elimination rate constant were in good agreement. It was also noted that the serum levels at 8 hours after administration was 0.2 mcg/ml which was substantially higher than 0.08 mcg/ml observed in this study. The persistent of serum levels in those patients probably due to the reservation of the drug in the inflammed tissues thereafter, rendered the higher AUC_o^∞ than those observed in the healthy subjects.

Since, the calculation of the volume of distribution and the total clearance usually based upon the fraction of ampicillin absorbed, the variation in the reported values of these parameters may partly due to the reason that the fraction of ampicillin absorbed were varied from one study to the others. In this study, the fraction of ampicillin and bacampicillin absorbed were assumed to be 0.48 and 0.91 respectively. These values were taken from the average of the previously reported data (13,32,39,71). In addition, some pharmacokinetic parameters e.g. the absorption rate constant and the overall elimination rate constant obtained after single oral administration of bacampicillin 400 mg found in this study differed from those reported by Rozencweig, et al. (33). The plausible explanation for the discrepancies is that a 3-compartment pharmacokinetic model was applied in Rozencweig's study.

The absorption rate constant obtained after oral administration of ampicillin 500 mg was 1.17 hr^{-1} which was higher than 0.60 - 0.89 hr^{-1} previously reported (13,14,20,71). The overall elimination rate constant and the serum half-life were 0.63 hr^{-1} and 1.15 hr. They were comparable to those 0.61 hr^{-1}

and 1.14 hr. reported by Eshelman, et al. (20).

The absorption rate constants obtained after oral administration of bacampicillin 400 and 800 mg were 3.40 hr^{-1} and 2.70 hr^{-1} whereas the corresponded values previously reported were 2.25 hr^{-1} (35) and 1.80 hr^{-1} (38) respectively. The overall elimination rate constants obtained after oral administration of bacampicillin 400 and 800 mg were 0.72 hr^{-1} and 0.74 hr^{-1} respectively. They were slightly different from 1.0 hr^{-1} and 0.69 hr^{-1} previously reported (35,38). Braga and Fraschini (38) reported that the apparent volume of distribution (V_d) and the total clearance (Cl_T) after oral administration of bacampicillin 800 mg were 48.4 litres and 31.2 litres/hour. They were higher than the values observed in the present study (33.3 litres and 24.2 litres/hour). In comparison, the AUC_o^∞ reported by Braga and Fraschini (38) was also higher than the AUC_o^∞ found in this study while the overall elimination rate constant was nearly the same. The difference in the observed values of V_d and Cl_T obtained in this study and those previous findings (38) may partly due to the difference in the fraction of ampicillin absorbed used to calculate these parameters.

2. Comparison of Ampicillin Serum Concentration Profiles and Pharmacokinetic Parameters Obtained after Oral Administration of Ampicillin 250 and 500 mg and Bacampicillin 400 mg

The ampicillin serum concentration profiles after oral administration of ampicillin and bacampicillin were markedly different. Whereas, bacampicillin showed a steep, rapid rise

in serum concentrations until reaching the maximum levels, the serum concentration profiles of ampicillin showed a delayed rise but more persistent levels as illustrated in Figure 9. The oral absorptions of ampicillin and bacampicillin after a single oral dose were compared using the following parameters : the mean individual peak concentration, the peak time, the area under the serum concentration-time curve and the percentage urinary recovery of drug. The mean individual peak concentration attained after oral administration of bacampicillin 400 mg was 5.98 mcg/ml which was significantly higher than 2.04 mcg/ml and 3.93 mcg/ml obtained after oral administration of ampicillin 250 and 500 mg respectively. More rapid oral absorption after ingestion of bacampicillin was marked by the earlier peak time when compared with those of ampicillin. The peak time after oral administration of bacampicillin 400 mg was 0.82 hour while they were 1.68 hours and 1.71 hours after ingestion of ampicillin 250 and 500 mg. The AUC_0^∞ and the percentage urinary recovery confirmed that the absorption of bacampicillin was more complete than ampicillin. After oral administration of bacampicillin 400 mg, the AUC_0^∞ and the percentage urinary recovery were 9.93 hr. mcg/ml and 62.43 percent respectively whereas the values obtained after oral administration of ampicillin 250 mg were 5.51 hr. mcg/ml and 32.02 percent respectively. The differences in these values between the two treatments were approximately two fold, though the doses were virtually equivalent in the molar basis. It was therefore undoubted that bacampicillin, the ester form was absorbed more rapidly and more completely from gastrointestinal tract than ampicillin itself. This would support the view that

the ester group attached to ampicillin molecule could provide higher lipid solubility and render better penetration of the molecule through the intestinal wall.

The pharmacokinetic parameters can be obtained by fitting the data to a one-compartment open model. There were small discrepancies in some parameters e.g., the peak concentrations and the peak time between the model output and those obtained experimentally, since the mathematical model usually based upon several assumptions which is not always fully satisfy in practice. At the same time, the fit of the model to the measurements will not be perfect due to the measurement errors.

In addition to the peak time, the absorption rate constant obtained after oral administration of ampicillin and bacampicillin could substantiate the more rapid oral absorption of the later than the former. The absorption rate constant obtained after oral administration of bacampicillin 400 mg was two times higher than those observed after oral administration of ampicillin 250 and 500 mg. The overall elimination rate constant, the serum half-life, the apparent volume of distribution and the total clearance obtained after oral administration of bacampicillin 400 mg were closely resembled those obtained after the administration of ampicillin. Statistical analysis revealed no significant difference in these values between the different treatments.

Some pharmacokinetic parameters e.g., the absorption rate constant, the overall elimination rate constant, the serum half-

life and the urinary excretion rate constant could be obtained from urinary excretion data. Theoretically, these parameters should have the same values as those obtained from serum data. In comparing the pharmacokinetic parameters obtained after oral administration of bacampicillin with those obtained after ingestion of ampicillin, the parameters obtained from urinary excretion data were in agreement with those obtained from serum data i.e., the absorption rate constant obtained after oral administration of bacampicillin was substantially higher than those obtained after the administration of ampicillin while the overall elimination rate constants and the serum half-lives were not significantly different.

The similarities in the observed values for distribution and elimination pharmacokinetic parameters of ampicillin and bacampicillin would support the view that bacampicillin is essentially ampicillin in vivo, i.e., it is hydrolysed to ampicillin, the active compound, by enzymes present in sera or gastrointestinal mucosa, the later perhaps hydrolysed the drug while it is being absorbed through the mucosa.

3. Dose-Drug Concentration Response

After oral administration of two progressive doses of ampicillin 250 and 500 mg and bacampicillin 400 and 800 mg, only two pharmacokinetic parameters changed with doses, the peak serum concentrations and the area under the serum concentration-time curves which indicating the difference in the amount of drug entering the general circulation. The results showed that the

peak serum concentrations and AUC_o^∞ for both ampicillin and bacampicillin seemed to be increased in a linear function with the increased dose, whereas the pharmacokinetic parameters of distribution and elimination appeared to be remain unchanged with the increased dose. The mean individual peak concentrations were 2.04 mcg/ml and 3.93 mcg/ml and the AUC_o^∞ were 5.51 hr. mcg/ml and 10.97 hr. mcg/ml after oral administration of ampicillin 250 and 500 mg. After oral administration of bacampicillin 400 mg and 800 mg, the mean individual peak concentrations were 5.64 mcg/ml and 11.26 mcg/ml and the AUC_o^∞ were 9.27 hr. mcg/ml and 22.36 hr. mcg/ml respectively. Similarly, the pharmacokinetic parameters obtained from urinary excretion data appeared to be unchanged with the increased doses. However, only two progressive doses of drugs were studied, it is not possible to definitely conclude that the kinetics of drugs is not dose-dependent. If the doses are further increased, the saturation of the transport systems might occur and the non-linear relationship between dose and the above mentioned two pharmacokinetic parameters may happen.

4. Effect of Food on Oral Absorption of Bacampicillin

Earlier studies have shown that the oral absorption of ampicillin is influenced by food (20,47,82). However, the contrary result was reported by Klein (11) since, in his study, the drug was not promptly administered with food. A number of investigators did suggest that food did not affect the oral absorption of bacampicillin as well as other ampicillin esters. The observations in this study corresponded very well with those

of others. All pharmacokinetic parameters obtained either from serum data or urinary excretion data after oral administration of bacampicillin in fasting state and those obtained when bacampicillin was ingested with meal showed no significant difference. The mean individual peak concentrations obtained after oral administration of bacampicillin 400 mg in fasting state was 6.33 mcg/ml which was comparable to 7.07 mcg/ml obtained after the administration of bacampicillin with meal. The peak times were 0.96 hour and 0.89 hour after ingestion of bacampicillin with and without meal respectively. The AUC_0^∞ and the percentage urinary recovery too, were not affected by food. They were 10.59 hr. mcg/ml and 58.22 percent respectively after the administration of bacampicillin in fasting state and 11.46 hr. mcg/ml and 57.32 percent respectively after the drug was taken with meal. The slightly higher observed values obtained after bacampicillin was concurrently administered with food than those obtained in fasting state may partly due to high intersubject variation in oral absorption of bacampicillin, when administered with food, which was reflected by the high coefficient of variation (C.V. = 0.50). It is of interest that most of the earlier studies noted the higher peak concentrations and the shorter peak times obtained after oral administration of bacampicillin with food than those obtained after the drug was administered in fasting state, though not to the extent of statistically significant difference. However, those studies proposed that the explanation for this phenomena was remain obscure.

5. Comparison of Some Pharmacokinetic Parameters Obtained from Serum Data with Those Obtained from Urinary Excretion Data

The attempts to define the pharmacokinetic aspects using urinary excretion data can be accomplished by the method of urinary excretion rate plot and the sigma-minus plot. A plot of the logarithm of urinary excretion rate versus time yields a bi-exponential curve, the terminal portion of which is linear. The overall elimination rate constant can be obtained from the slope of this terminal linear segment whereas the Y-intercept of this linear curve represents the urinary excretion rate constant. By applying the feathering method to the curve, the absorption rate constant is obtained. On the other hand, the overall elimination rate constant can be estimated from the slope of the sigma-minus plot. Theoretically, the estimation of the overall elimination rate constant from the urinary excretion rate plot is not convenient due to the fluctuations in the rate of drug elimination. The sigma-minus method is considered to overcome the problem since this method is less sensitive to fluctuations in drug elimination rate (74). However, the findings in this study did not agree with the fore-mentioned suggestion. In comparison, the pharmacokinetic parameters obtained from the urinary excretion rate plot were more consistent with those obtained from serum data than the other method. The overall elimination rate constants obtained after oral administration of bacampicillin 400 mg using the urinary excretion rate plot and the sigma-minus plot were 0.79 hr^{-1} and 0.96 hr^{-1} whereas the value calculated from the serum data was 0.72 hr^{-1}. After oral administration

of ampicillin 250 mg, the overall elimination rate constant calculated from serum data was 0.63 hr^{-1} compared to 0.63 hr^{-1} and 0.79 hr^{-1} obtained from urinary excretion rate plot and the sigma-minus plot respectively. The statistical comparison between some parameters obtained from serum data and those obtained from urinary excretion data (either by the urinary excretion rate plot or the sigma-minus plot) could be further accessible in Table 21. Based on the results described above, it may be suggested that the urinary excretion rate plot can be used appropriately to describe the pharmacokinetic appearance of the drug whenever the urinary excretion data is used.

Conceptually, the pharmacokinetic parameters obtained from urinary excretion data should have the same values as those calculated from serum data. In the present study, most of the parameters obtained from urinary excretion data were closely resembled those obtained from serum data. However, the small discrepancies existed between the absorption rate constants obtained after oral administration of bacampicillin 400 or 800 mg calculated from urinary excretion data and those obtained from serum data ($p < 0.05$). In the case, the absorption rate constants may not be accurately determined since bacampicillin was absorbed very rapidly, only a few data points in the early absorptive phase were allowed to calculate the absorption rate constant. Hence, by collecting blood samples or urine samples in the early absorptive phase more frequently, it is expected that the absorption rate constants obtained from urinary excretion data will be closely in agreement with those obtained from serum data. Unfor-

tunately, the frequent collection of urine samples was not convenient in practice, moreover the mistaken information was obtained whenever the collecting interval of urine samples was less than 15 minutes. This findings may suggest that the estimate of the absorption rate constants using urinary excretion data was not always satisfactory especially for the drug which its oral absorption was very rapid.

Howsoever, since no significant difference between the pharmacokinetic parameters of ampicillin or the elimination pharmacokinetic parameters of bacampicillin obtained from serum data and those obtained from urinary excretion data was observed, it was thereafter possible to study the pharmacokinetics of ampicillin or the elimination pharmacokinetics of bacampicillin by means of complete urine collection instead of collecting blood periodically. In this study, urine collection was carried out until 8 hours after administration. The plots of the cumulative amount of drug excreted in urine versus time had levelled off, indicating that urine collection was complete. This finding supported Knudsen, et al. (12) who noted that 97 percent of ampicillin excreted in urine appeared within 8 hours after administration.