Chapter II

REVIEW OF BACAMPICILLIN

Bacampicillin

Physicochemical Properties (48,52,53)

Chemically, Bacampicillin is 1-ethoxy-carbonyl-oxyethyl-6-D(D-α-aminophenylacetamido) penicillanate. It is the α-ethoxycarbonyloxyethyl ester of ampicillin and usually available as hydrochloride salt. (Figure 4) It's chemical name is 4-Thia-1-azabicyclo [3.2.0] haptane-2-carboxylic acid, 6-[(aminophenylacetyl) amino]-3,3-dimethyl-7-oxo-,1-[(ethoxycarbonyl) oxy] ethyl ester, monohydrochloride, [2S- [2α, 5α , 6β (S)]]

Structural formula: $C_{21}H_{27}N_3O_7S \cdot HCl$

Molecular weight : 501.98

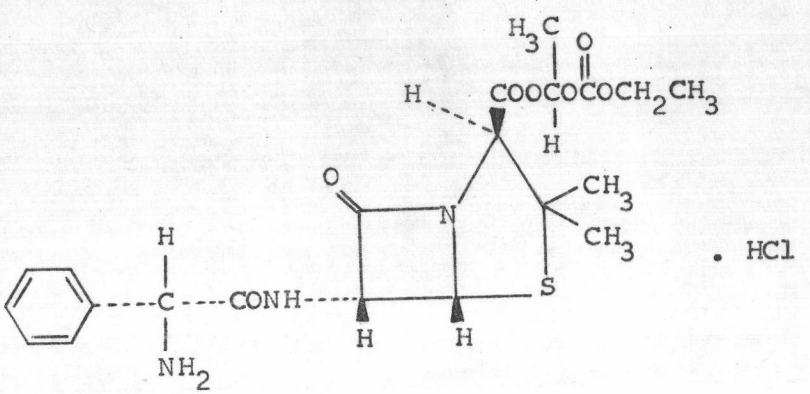

Figure 4 Structure of bacampicillin hydrochloride

Bacampicillin hydrochloride is a white crystalline powder, m.p. 171-176°, $[\alpha]_D^{20}$ + 161.5°. Bacampicillin is a weak acid with pKa equal to 6.8. Bacampicillin hydrochloride 1.44 g is approximately equivalent to 1 g of ampicillin. LD_{50} in mices (mg/kg) : 8529 orally, 176 i.p., 9475 s.c., 184 i.v.

Solubility: 1 in 15 of water, 1 in 7 of alcohol and 1 in 10 of chloroform.

Practically insoluble in ether.

Stability: In vitro, it is stable at both gastric and neutral pH (7.4) The hydrolysis is greatly enhanced in vivo or in the presence of biological fluids e.g., tissue homogenates, sera (27). On hydrolysis bacampicillin is converted to ampicillin, acetaldehyde, ethanol and carbondioxide as shown in Figure 5.

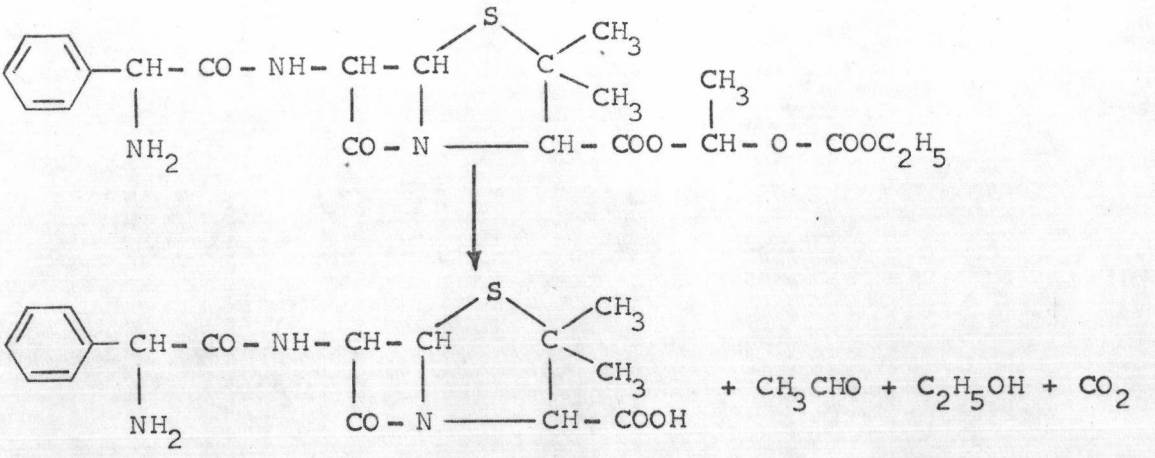

Figure 5 Enzymatic hydrolysis of bacampicillin

Antibacterial Activity (2,27,54)

In the ester form, the compound per se lacks of antibacterial activity. After oral administration, it is rapidly absorbed by the upper gastrointestinal tract and is extensively hydrolysed by non-specific esterase enzymes to ampicillin, the active compound. The antibacterial spectrum and in vivo activity are essentially that of ampicillin itself. In vitro studies demonstrated that most strains of the following gram positive bacteria are susceptible: α- and β- hemolytic streptococci, pneumococci, non-penicillinase producing staphylococci and enterococci, including various gram negative bacteria e.g. Haemophilus influenzae, Escherichia coli, Proteus mirabilis, Neisseria gonorrhoeae, Samonella and Shigella species. Theoretically, because of the higher serum and urine levels attained, it might be expected to be more active in vivo than equimolar doses of oral ampicillin against susceptible bacterial species with borderline sensitivity to ampicillin. Like ampicillin, bacampicillin has no activity against penicillinase producing bacteria, Pseudomonas and most strains of Klebsiella.

Preclinical Studies (27,54)

In vitro, In vivo Hydrolysis

Bodin, et al. (27) demonstrated that bacampicillin was comparatively stable in neutral phosphate buffer, pH 7.4 and simulated gastric juice, pH 1.2. The hydrolysis was greatly enhanced in the presence of 10 percent human serum, rat serum or

canine serum. The results were consistent with the rapid and extensive hydrolysis investigated in rats and dogs.

In vivo Oral Absorption

The oral absorption of equimolar doses of bacampicillin compared with ampicillin was investigated in rats and dogs. In rats as well as dogs, the peak plasma levels of ampicillin were substantially higher and the area under the curves indicated more than three times larger in bioavailability of bacampicillin than ampicillin.

Penetration into Tissue Fluids (27)

The penetration of ampicillin after oral administration of bacampicillin was studied in rats using tissue cages model. The mean transudate ampicillin levels were two to three times higher and last longer after administration of bacampicillin than ampicillin. Similarly, the kidney and liver homogenates showed three to four times higher levels of ampicillin following bacampicillin administration than ampicillin. The higher initial blood levels attained after bacampicillin administration resulted in a correspondingly higher tissue penetration.

Clinical Evaluations

Therapeutic efficacy, Adverse reactions and Tolerance

Several extensive investigations and documentations concerning the therapeutic efficacy of bacampicillin in

various types of infections including adversed drug reactions and tolerance have been reported. Some of those are briefly summarized as follows:

Bergogne-Berezin, et al. (45) investigated the penetration of ampicillin after oral single dose of 800 mg bacampicillin in 28 hospitalised patients with bronchopulmonary infections such as pneumonia and bronchitis. They showed that ampicillin concentrations attained in bronchial secretions were sufficiently high to inhibit most current pathogenic bacteria e.g., gram positive cocci and non-penicillinase producing Haemophilus influenzae and suggested that bacampicillin was a useful drug in acute bronchopulmonary infections.

A comparative clinical study in 271 patients suffering from acute exacerbation of chronic bronchitis investigated by Maesen (46) showed that for this infection, bacampicillin 800 mg given orally t.i.d for 7-10 days was superior to ampicillin 556 mg given t.i.d for 10 days, amoxycillin 750 mg given t.i.d for 10 days and pivampicillin 700 mg given q.i.d for 7 days, as regard to its excellent clinical responses with relatively low untoward effects and good tolerance. The corresponding evaluations were reported by Davies (55) who found that bacampicillin 800 or 1600 mg given orally to 16 patients showed clinical advantages over ampicillin 1 g or more in patients with acute exacerbation of chronic bronchitis.

In acute otitis media, Virtanen (42) reported that after oral administration of bacampicillin 800 mg twice a day to 40

patients, the ampicillin concentrations in middle ear effusions at 12 hours after administration was as high as 0.6 mcg/ml compared with 0.1 mcg/ml in serum. The dosage regimen was therefore well suited to the treatment of this infection.

Sorri, et al. (43) showed that after given bacampicillin 1200 mg orally two times a day to 30 patients subjected to radical maxillary sinus surgery for chronic sinusitis, the clinical responses showed satisfactory improvement, though one of the patients vomitted and another one suffered from diarrhoea.

Hallander, et al. (41) presented their experiences with 68 patients with acute peritonsillitis. They evidenced that bacampicillin 200 mg upto 800 mg given twice a day showed the same satisfactory clinical responses as ampicillin 500 mg given three times per day.

For uncomplicated gonorrhoea, Ricia, et al. (56) reported that there was no significant difference in clinical responses following oral administration of ampicillin 3.5 g or bacampicillin 1.6 g each with probenecid 1 g to 83 patients with culture-positive uncomplicated gonorrhoea. Although, the equimolar dose of bacampicillin is only one-third of ampicillin, it was as effective as the standard oral regimen of ampicillin for urogenital gonococcal infections. Whilst, Wallin, et al. (57) found that a single oral dose of bacampicillin 800 mg with probenecid 1 g could be constituted an effective treatment for uncomplicated gonorrhoea. It was extremely well tolerant and only 4.6 percent of side effects. In patients with gonococci showing reduced

sensitivity to ampicillin, a 1.6 g single dose of bacampicillin was required.

Muller, et al. (58) compared bacampicillin 800 mg with ampicillin 2 g given orally t.i.d. for 10 days in 100 hospitalized patients with upper or lower urinary tract infections. They found that bacampicillin regimen, with respect to clinical responses and tolerance was superior to ampicillin. These results were parallel to those of the pyeonephritis model studied by Ritzerfeld (59).

Grafford and Nilsson (60) summarized ten clinical studies with impressive number of patients, suffering from upper or lower respiratory tract infections or with urogenital infections. The patients were treated with bacampicillin 400 or 800 mg twice or three times daily. They noted more than 90 percent satisfactory clinical response in all patient groups. The result therefore suggested that a twice daily dosage regimen of bacampicillin was sufficient for these infections. However, for severe cases, the doses of 1200 or 1600 mg twice a day should be considered.

Adverse Drug Reactions

Since bacampicillin is completely converted to ampicillin invivo, the therapeutic effects and adverse drug reactions are essentially that of ampicillin. Typical untoward effect is the effect of the compound on the ecology of the normal flora. Gastrointestinal disturbances, diarrhoea or loose stool are consequently occurred (16). Exanthema is also reported as the common

side effect following ampicillin administration (2). Bacampicillin, reported by Ekstrom, et al. (61), emerged lower incidence of side effects than ampicillin. The total frequency of diarrhoea, gastric upsets and skin reactions were 1.2, 2.3 and 2.2 percent respectively. These adverse reactions were considered to be no or very little clinical importance. The results were consistent with the figures reported by Bergan (62) who summarized those figures from several clinical presentations showing that the frequency of diarrhoea, upper gastrointestinal distress and exanthema after bacampicillin administration were 1.2, 2.6 and 2.4 percent respectively.

Bacampicillin and other ampicillin esters appeared to have lower incidence of diarrhoea, when compared with ampicillin since the higher degree of gastrointestinal absorption resulted in the lesser effect of ampicillin on bowel flora (4). Moreover, the esters have in theory no antibacterial activity before absorption. This would seem to be confirmed by the studies of Heimdahl (63) who showed that bacampicillin 400 mg given orally t.i.d for 7 days did not greatly influence the normal microflora on the mouth, throat and colon. The higher incidence of upper gastrointestinal disturbances following oral administration of pivampicillin and talampicillin compared with bacampicillin display as a crucial role for their limited uses.

Tolerance

After oral absorption, bacampicillin was hydrolysed enzymatically to liberate ampicillin and the side chain moiety which breaks down to acetaldehyde, ethanol and carbondioxide as previously shown in Figure 5. On the other hand, formaldehyde and phthalic acid are formed as a by-product after hydrolysis of pivampicillin and talampicillin respectively (28,29). On the first thought, one may speculate theoretically that toxic effects rationally occur from these released-side chains or one may question that the differences in frequency of side effects especially upper gastrointestinal distress e.g. nausea, vomitting as well as epigastric pain may due to different foreign compounds. This theory is merely hypothetical, however. The body is well able to cope with the small amount of these released-side chains presented at a reasonable rate. The types and severities of side effects reported after oral administration of bacampicillin were not different from those seen after administration of ampicillin. Moreover, they are reduced in frequency following administration of the former (4). The well tolerance of bacampicillin at up to 3200 mg daily was reported by several investigators. Maesen and Davies (46) evidenced an excellent tolerance after oral administration of bacampicillin 1600 mg twice daily for 10 days in 16 patients with acute exacerbations of chronic bronchitis. Koldestam, et al. (40) showed that following oral administration of bacampicillin 800 mg and pivampicillin 700 mg t.i.d. for 10 days, bacampicillin pronounced higher tolerance than pivampicillin. Also, the duration of

symptoms considering all side effects was relatively shorter after discontinued the treatments. Although, in severe infections, the higher doses of bacampicillin were recommended, Grafford and Nilsson (60) suggested that the trend towards an increased frequency of adverse reactions with increasing doses would have little clinical significance.

Pharmacokinetic Studies

1. Absorption

An extensive study exibited absorption characteristics of bacampicillin after ingestion was accomplished by Swahn (63, 64). By labelling the drugs with radioactive compound, $\left[S^{35}\right]$ ampicillin and $\left[S^{35}\right]$ bacampicillin were obtained. After administration of the labelled drugs to normal volunteers, 60-89 percent of the labelled bacampicillin was absorbed by the time the compound reached the upper jejunum while 24-45 percent of the labelled ampicillin was absorbed by the same time. The liberation to ampicillin from the ester was so rapid that unchanged bacampicillin could not be found in the blood 10 minutes after ingestion. Also, complete liberation to ampicillin was evidenced by the inability to detect the parent compound in urine. The results also showed that 39 percent of labelled ampicillin but only 14 percent of labelled bacampicillin was detected in feces, implying better absorption of the later than the former. The uptake of labelled bacampicillin throughout the gastrointestinal tract was 20 percent by stomach, 65 and 75 percent by duodenum and proximal jejunum respectively.

The bioavailability of ampicillin after oral bacampicillin administration was reported by many investigators (33-38). All of them agreed that intestinal absorption of bacampicillin was faster and more complete than ampicillin. The peak serum concentrations after ingestion of bacampicillin 400 mg occurred within 1 hour were 7.5 - 9.9 mcg/ml compared with 2.8 - 3.7 mcg/ml reached at about 1.5 - 2 hours after equimolar dose of ampicillin. The area under the serum concentrations-time curves (AUC) as well as the percentage urinary recovery of ampicillin which provided a measurement of bioavailability were evidently increased after administration of bacampicillin, e.g. Jannerfeldt (66) reported the AUC was 13.9 and 9.2 hr. mcg/ml after administration of bacampicillin 400 mg and ampicillin 278 mg respectively. The corresponding results 15.5 and 10.3 hr. mcg/ml were reported by Sjovall, et al. (35). Moreover, a pharmacokinetic comparison of oral bacampicillin and parenteral ampicillin in equimolar doses studied by Bergan (66) showed that bacampicillin 800 mg given orally rendered the same peak serum concentrations and bioavailability as equimolar dose of ampicillin given intramuscularly, i.e., the mean peak serum concentrations were 11.1 and 10.3 mcg/ml following bacampicillin and ampicillin administration respectively. The bioavailability of bacampicillin was 87 percent while the bioavailability of ampicillin was only 71 percent. However, they were higher than the 40-55 percent bioavailability of oral ampicillin previously reported.

1.1 Dose-drug concentration Relationship

In order to acheive the effectiveness of antibiotic chemotherapy, the concentrations of active drug in the focus of infections must exceed a certain minimum inhibitory concentration. Although the exact relation between the concentration of active drug in the focus of infections and the serum concentrations is not yet known, it was demonstrated that the concentration of drug in the focus of infections was decisively depended both on the peak serum concentrations (68,69) and the area under the serum concentrations-time curves (70). On this respect, the serum concentrations must reach or exceed a certain levels to be able to render adequate concentrations at site of infections. The effectiveness of antibiotic chemotherapy was therefore assumed closely related to the concentrations of drug in serum. It seemed worthwhile to study the relationship between the increased doses and the corresponding increased in serum concentrations, because it would be relevant as a basis for determining an adequate dosage in clinical situations. Dose-related changes in the only two pharmacokinetic variables, the peak serum levels and the AUC.

The relevant study of dose-drug concentration relationship was presented by Sjovall (15) who administered single doses of 400, 800, 1200 and 1600 mg of bacampicillin orally to nine healthy volunteers. There seemed to be a linear increase in peak concentrations up to 800 mg, but with a higher doses the increase in peak concentrations was somewhat less than proportional. With regard to AUC, there seemed to be a linear function

of all the doses studied. Studies of dose-drug concentration relationship of ampicillin, amoxycillin and ampicillin esters e.g., bacampicillin, pivampicillin and talampicillin by several investigators were also summarized and illustrated in table. Bacampicillin as well as the other ampicillin esters showed proportionally increased in peak serum concentrations and AUC with the increased doses. In contrast to its esters, the peak serum concentrations and AUC after oral administration of ampicillin are far less than proportional which implied that one can only partially compensate for the poor absorption of oral ampicillin by increasing the oral dose. Moreover, the compensation is limited by the higher incidence of side effects due to larger amount of unabsorbed drug in the gastrointestinal tract (16).

1.2 Effect of Food

The study of the influence of food on the oral absorption of bacampicillin was scarcely reported. The four-way crossover studies by Pfizer Pharmaceuticals, unpublished data (37) showed that food neither decreased the extent of absorption nor delayed the peak concentrations in serum. It was striking that the serum levels were greater when bacampicillin was taken with food, though not to the extent of statistical significance. The peak serum levels after ingestion of 400 mg of bacampicillin reached at 1 hour was 6.11 ± 0.72 mcg/ml without food and 6.61 ± 0.81 mcg/ml with food. Similarly, the peak serum levels after ingestion of bacampicillin 800 mg was 11.09 ± 0.80 mcg/ml without food and 12.72 ± 0.83 mcg/ml with food.

2. Distribution

Studies of the distribution and concentrations ofampicillin attained in human tissues after oral administration of bacampicillin were reported by several investigators. The substantially higher peak serum concentrations due to the better oral absorption of bacampicillin than ampicillin contributed the corresponding higher concentrations in the extravascular fluids (57). A comparative studies of ampicillin and bacampicillin penetration into body fluids e.g., skin blister fluids, saliva and tears as reported by Simon et al. (71) showed that the ratio of the mean peak ampicillin levels in the skin blister fluids, saliva and tear fluids after the administration of bacampicillin compared to those obtained after the administration of ampicillin were 4:1, 3:1 and 2:1 respectively. The corresponding results were obtained by Tan et al. (36) who compared the diffusibility into interstitial fluids of ampicillin to that of bacampicillin using a skin window technique. The levels of ampicillin in interstitial fluids found after bacampicillin administration were substantially higher than those attained after ampicillin.

Recently, Braga and Fraschini (38) evaluated the kinetic of diffusion of bacampicillin in progressive logarithmic doses: 800, 1200 and 1800 mg into bronchial secretions. They noted a linear correlation between the increased doses and the peak serum levels as well as the increased doses and the bronchial secretion peaks. The better bioavailability of bacampicillin was reflected by the higher ampicillin levels reached in bronchial secretions. In comparison, the percentage ratio of AUC of bronchial secretions

to AUC of serum was 4-6 percent after bacampicillin administration while it did not exceed 3 percent after ampicillin. This ratio was consistent with 2.5 - 6.0 percent reported by Bergogne-Berezin et al. (45) who followed ampicillin concentrations attained in serum and bronchial secretions in 17 patients with acute bronchopulmonary infections after oral administration of bacampicillin 800 mg. The same range of ratio approximately 3-8 percent was cited by Davies and Maesen (55). They also noted that the levels of ampicillin in bronchial secretions after oral administration of bacampicillin were considerably higher than those attained after administration of ampicillin i.e., the mean peak sputum concentrations were 0.25, 0.45 and 0.85 mcg/ml obtained after oral dose of ampicillin 1 g, bacampicillin 800 and 1600 mg respectively.

The distribution of ampicillin after oral administration of bacampicillin 800 mg into both normal and pathological lung tissues was studied by Hallstrom et al. (72). The results showed that the mean concentration in pathological lung tissues was above the MIC (0.25 mcg/ml) of Haemophilus influenzae and sustained for more than 9 hours after administration. The mean concentration in normal lung tissues exceeded 0.25 mcg/ml for at least 8 hours. According to Virtanen and Lahikainen (42) the peak ampicillin concentrations in middle ear effusions were 2.4 ± 0.4 mcg/ml following an oral dose of bacampicillin 800 mg. At 12 hours the levels were as high as 0.6 ± 0.2 mcg/ml, exceeding the MIC of about 90 percent of Haemophilus influenzae strains. Concentrations of ampicillin in urethra and cervical secretions

after oral administration of bacampicillin in 48 patients with uncomplicated gonorrhoea were investigated by Kallings et al (73). The median concentration in the male urethra after a single 800-mg dose of bacampicillin plus probenecid 1 g was 3.2 mcg/ml by 2 hours after administration. In the female urethra, the median concentration of ampicillin was 2.3 mcg/ml at 2 hours. The median concentration in cervical secretions was 1.6 mcg/ml at 1 hour and increased to 2.9 mcg/ml at 2 hours.

3. Elimination

The elimination of ampicillin from blood is very rapid. The small quantities are eliminated in bile, but by far the largest proportion of an absorbed dose excreted unchanged into urine by active transport through tubular cells in addition to glomerular filtration (4). Following oral administration of bacampicillin to healthy volunteers or patients with presumably normal renal function, about 57-80 percent of active ampicillin was recovered in urine within 6 hours. The plasma half-lives are variously reported as 0.5 - 1 hour. (33-35,38,67).