

# PROPULSIVE LOAD ADMINISTRATION AND BACAMPICILLIN

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## SYNOPSIS

**Propulsive load dosage for antibiotics is a term applied to intermittent dosage which enables establishment of a better buffering capacity than continuous intravascular infusions. The major factors explaining why propulsive load dosing is effective are the antibacterial post-antibiotic effect (APAE), post-antibiotic leucocyte enhancement (PALE), post-antibiotic repressed adhesion (PARA), and pharmacokinetic extravascular persistence (PEP). These properties all apply to ampicillin, and its prodrug bacampicillin is preferable to other aminopenicillins for pharmacokinetic reasons. This prodrug produces particularly high peak area under the serum curve (PAUC), which is one decisive factor in establishing high extravascular concentrations of an antibiotic. Bacampicillin is subject to nearly complete absorption and high extravascular levels which are maintained longer than those in serum. Bacampicillin is thus an alternative preferable to ampicillin when the infecting microbe is ampicillin sensitive.**

## INTRODUCTION

By the term propulsive load dosing we understand intermittent dosage of antibiotics with high doses at time intervals rather than as continuous infusions. Load dosing applies to oral doses like tablets or intravenous rapid bolus doses. By the word propulsive, we convey the concept that load dosing enables optimal and good extravascular penetration of the antibiotic. At first impulse, one might think that maintenance of antibiotic concentrations constantly above a minimum inhibitory level (MIC) were ideal and that this were safer than dosage loads like tablets or injections given at certain time intervals. We shall expand on the reasons why intermittent administration, i.e. propulsive load dosing functions well. In this context, we shall deal with the theoretical and practical explanations behind why intermittent dosage of antibiotics entails effective therapy. We refer to ampicillin delivered by bacampicillin as an example of propulsive dosing.

Dosage of antibiotics has the inherent purpose of giving the substance such a way that it may penetrate most effectively into sites of infection. The degree of success is determined to a considerable extent by the pharmaceutical characteristics of the dosage form. Important are also pharmacodynamic and pharmacokinetic properties of the antibiotic.

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**BIOPHARMACEUTICAL PROPERTIES OF AMPICILLIN DOSAGE**

Let us first consider the biopharmaceutical properties of ampicillin. During the 70-ies and 80-ies, ampicillin has become available as a prodrug, e.g. in the form of bacampicillin. This is synthesized from ampicillin by attachment of an ester group at the carboxy group to the molecule (Figure 1). This changes the chemical properties of the antibiotic. Important is higher lipid solubility (Figure 2) (1) of bacampicillin than either plain ampicillin or amoxycillin. This leads to a more effective delivery of ampicillin from bacampicillin than when given as traditional ampicillin.

The better cumulative absorption has been demonstrated at different levels of the gastrointestinal tract by radioactive labelling of the antibiotics (2) (Table 1). Bacampicillin is at the same time less degradable in the acid stomach contents (3) (Figure 3). Thus more intact, active ampicillin is released from bacampicillin than from plain ampicillin. Higher serum concentration levels appear after bacampicillin when it is compared with the identical molar dose of ampicillin given in cross-over fashion to the same subjects (4) (Figure 4).

**Table 1. Absorption of <sup>35</sup>S-ampicillin and <sup>35</sup>S-bacampicillin at different levels of the gastrointestinal tract. Adapted from (2).**

	Level of aspiration (cm)	Cumulative absorption (%)	
		Ampicillin	Bacampicillin
Stomach	50	13	20
Doudenum	90-105	22	65
Jejunum	140-200	31	71

By saying that bacampicillin is a prodrug, we mean that it is a preliminary form used for dosage purposes only. It is hydrolysed to deliver ampicillin and thereby able to mediate enhanced absorption of ampicillin, i.e. to improve the biopharmaceutical properties of ampicillin. Prodrugs are dosage forms intended only for delivery of the active drug. Bacampicillin can, accordingly, only be used to treat infections caused by ampicillin sensitive bacteria. Bacampicillin as such is antibacterially inactive and separate antibiotic suceptibility testing beyond the sensitivity to ampicillin is not required.

The quantitatively better absorption from bacampicillin makes this form more economical in the sense that a higher portion of the dose is absorbed. In addition, less antibiotic reaches the colon with consequent lesser changes in the faecal flora. Loose stools accompany bacampicillin therapy relatively rarely. In comparative double blind studies in 463 patients the frequency of diarrhoea has been 0.7% after bacampicillin compared to 12% after plain ampicillin (5). Comparison of the overall side effects of major aminopeni-

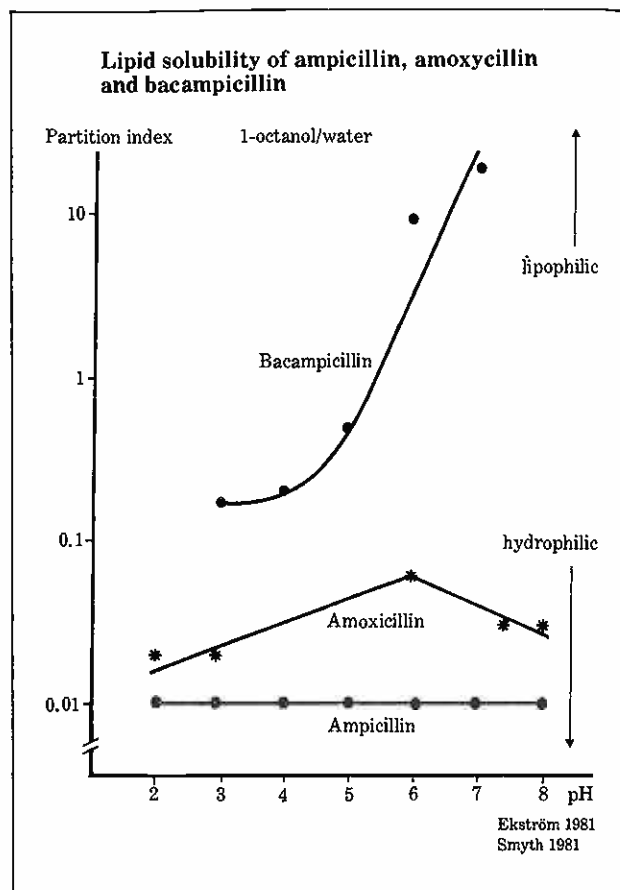


Figure 2. Lipid solubility of ampicillin, amoxycillin, and bacampicillin. Adapted from (1).

cillins are shown in Table 2. Let us now return to the main principles of propulsive load dosing.

**PROPULSIVE LOAD DOSING, PRINCIPAL ELEMENTS**

Propulsive dosing is successful because it establishes high concentrations in the foci of infection and entails establishment of a buffering capacity beyond the time period when concentrations in serum are above MIC. This is due to four factors:

1. Antibacterial post-antibiotic effect — APAE
2. Post-antibiotic leucocyte enhancement — PALE
3. Post-antibiotic repressed adhesion — PARA
4. Pharmacokinetic extravascular persistence — PEP

We shall look at each factor separately.

**ANTIBACTERIAL POST-ANTIBIOTIC EFFECT**

The antibacterial post-antibiotic effect involves the obser-

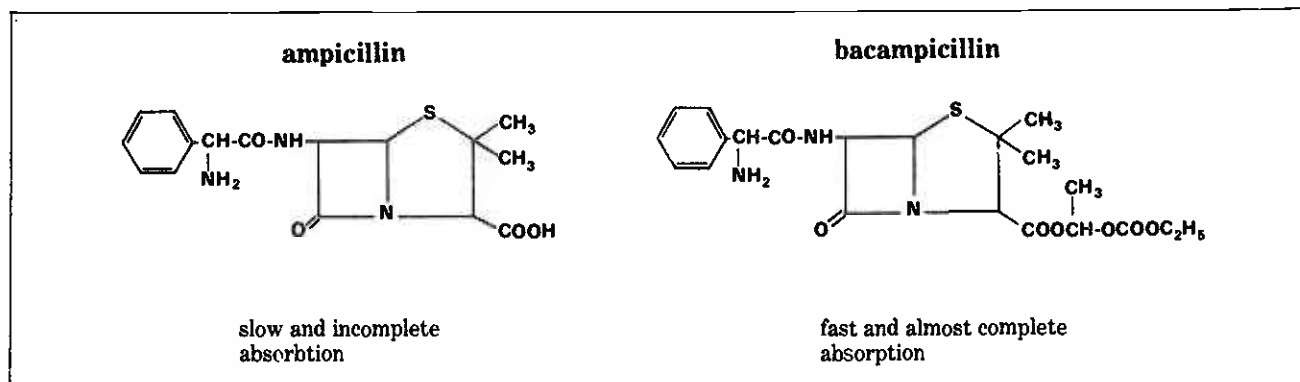


Figure 1. Chemical formulas of ampicillin and bacampicillin.

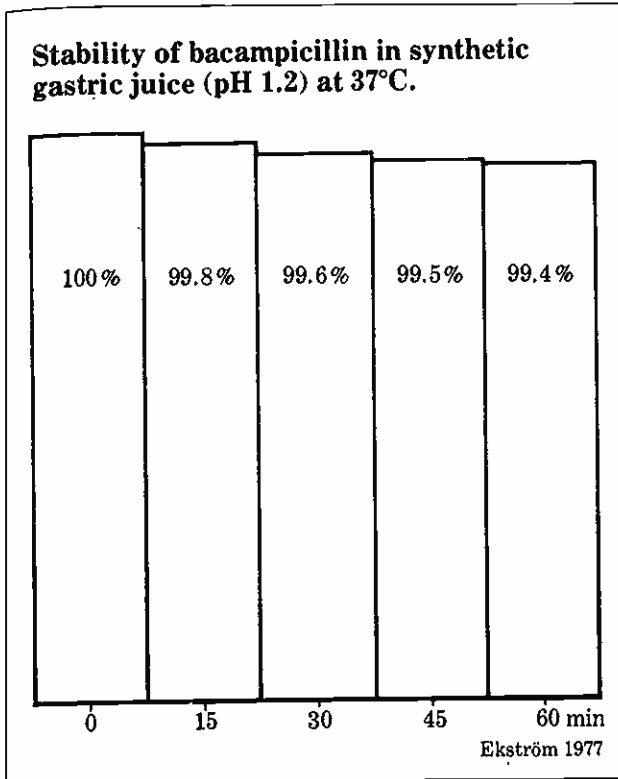


Figure 3. Stability of bacampicillin in synthetic gastric fluid. Adapted from (3).

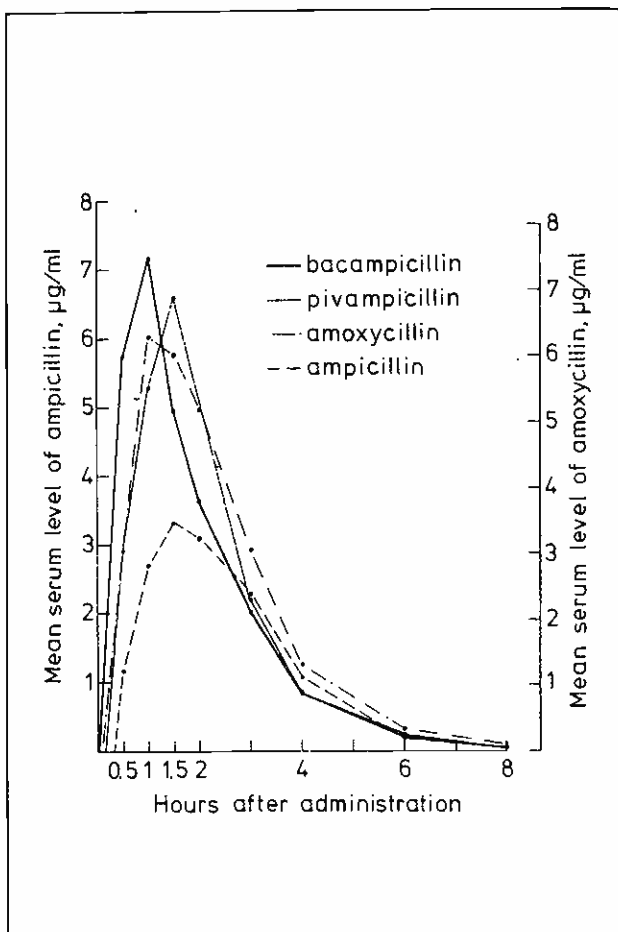


Figure 4. Concentrations of ampicillin after cross-over administration of equimolar doses (equivalent to 280 mg ampicillin and 400 mg bacampicillin) to the same healthy volunteers of bacampicillin, ampicillin, and pivampicillin ester, and amoxycillin. Adapted from (4).

Table 2. Side effects of aminopenicillins. Adapted from (5).

	Diarrhoea	Gastric	Rash	Total
Ampicillin	12.0	2.7	5.5	20.2%
Pivampicillin	1.4	7.4	3.4	12.2%
Talampicillin	5.7	6.1	2.4	14.2%
Bacampicillin	1.2	2.6	2.4	6.2%

vation that an interval of time elapses from the time when the antibiotic is removed (or the concentration of the antibiotic drops below the minimum inhibitory concentration of the antibiotic) till full bacterial recovery, i.e. uninhibited bacterial multiplication. This has been demonstrated with *Escherichia coli* exposed to ampicillin at concentrations which are gradually diminished at the same rate as in the body (6). In Figure 5, the X-axis is a time axis indicating the gradually smaller concentrations; an interval of approximately 1 hour proceeds after the concentration drop below the minimum inhibitory concentration (MIC) before complete resumption of growth activity. The same phenomenon is shown when *E. coli* is exposed to constant levels of the antibiotic for different periods of time (7) (Figure 6). The effect is similar when pneumococci are exposed to ampicillin (8) (Figure 7), both when the antibiotic is removed by centrifugation and by penicillinase. This phenomenon has been observed also with other bacteria and other penicillins. A lag time before resumed uninhibited bacterial multiplication has been observed e.g. with staphylococci and flucloxacillin (9) (Figure 8). The postantibiotic effect is longer with Gram-positive organisms than with Gram-negative bacteria indicating that they require a longer time before full recovery after exposure to antibiotics. The antibacterial post-antibiotic effect is one aspect of the inherent buffering capacity of propulsive load dosing.

#### POST-ANTIBIOTIC LEUCOCYTE ENHANCEMENT

Another significant role of the antibiotics is the observation that they may enhance the normal defence mechanisms (10). This enables antibiotics, to enhance the ability of leucocytes to remove and kill phagocytized bacteria, even at concentrations below antibacterially inhibitory levels (Figure 9). This has become known as the post-antibiotic leucocyte enhancement (PALE). This phenomenon contributes to an extended support of the body's own combat against the microbes.

#### POSTANTIBIOTIC REPRESSED ADHESION

In hollow organs like the urinary tract, bronchial tree, or vagina, attachment of the bacteria to the epithelial cells enhances the ability of the microbes to invade tissues, i.e. cause infections. When the bacteria are exposed to sub-inhibitory concentrations, i.e. below MIC, though, adhesion of microbial cells is inhibited (11). Thus to some extent and under given conditions, even subinhibitory antibiotic concentrations contribute to the eradication of bacteria. This interaction corresponds to what we understand by the post-antibiotic repressed adhesion (PARA) of bacteria to epithelial cells. This continues for a relatively long time because production of substances on the bacterial surface corresponding to the receptor sites of attachment are secondary to the vital processes of bacterial life such as cell generation.

These three phenomena, APAE, PALE and PARA explain why propulsive load dosing produces an extended period of antibacterial activity, i.e. a buffering period which prolongs the antibacterial effect even after subinhibitory antibiotic concentrations have been reached. The extended effect in these three factors are complemented by extended periods of persistence of the antibiotic in extravascular sites.

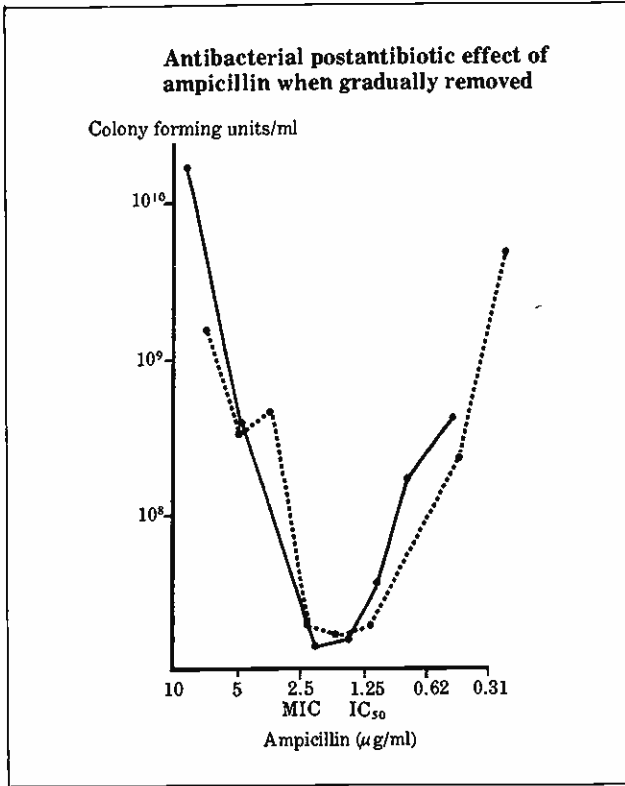


Figure 5. Kill and regrowth of *Escherichia coli* exposed in vitro to ampicillin at concentrations diminishing with a half-life of 1 hour. Two experiments. Time along X-axis shown by the concentrations present in the bacterial culture. Adapted from (6).

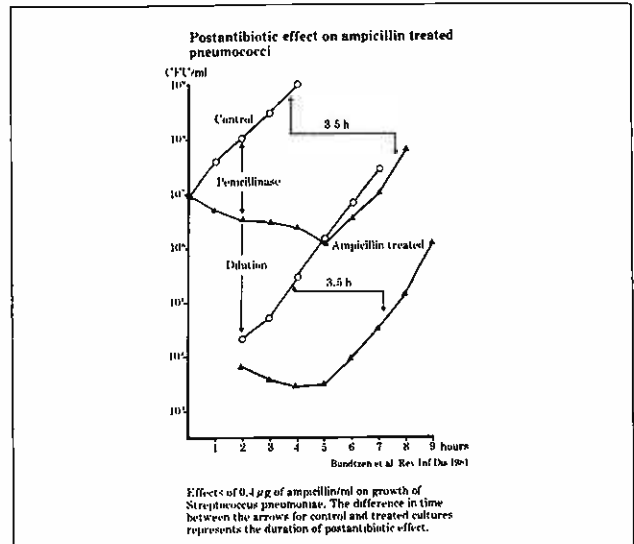


Figure 7. The effect of pneumococci exposed to ampicillin at 0.4 mg/l for 2 hours when the antibiotic was removed by centrifugation or addition of penicillinase. Adapted from (8).

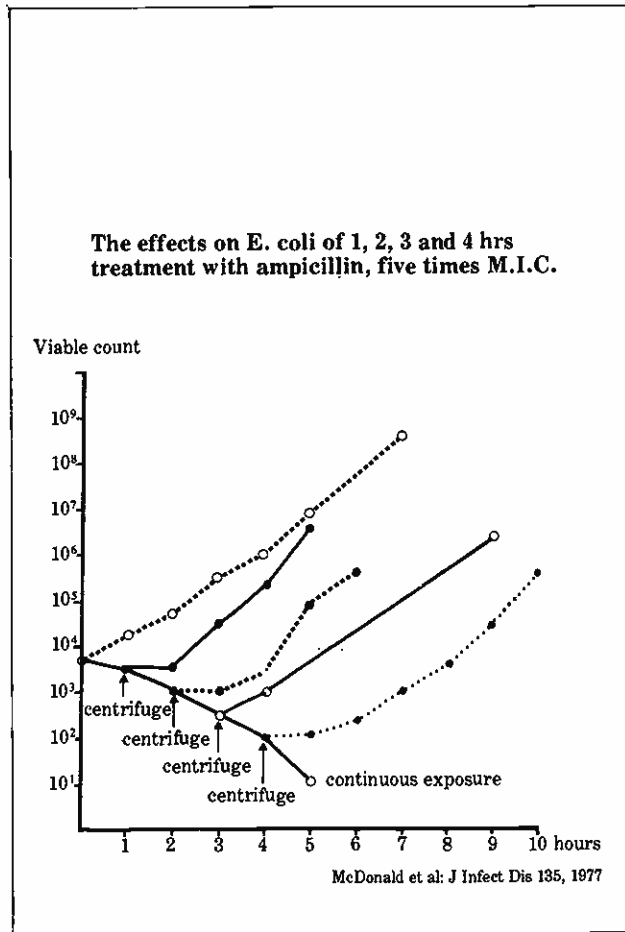


Figure 6. The effects of *Escherichia coli* exposed to ampicillin at five times its minimal inhibitory concentration for 1, 2, 3, and 4 h. Adapted from (7).

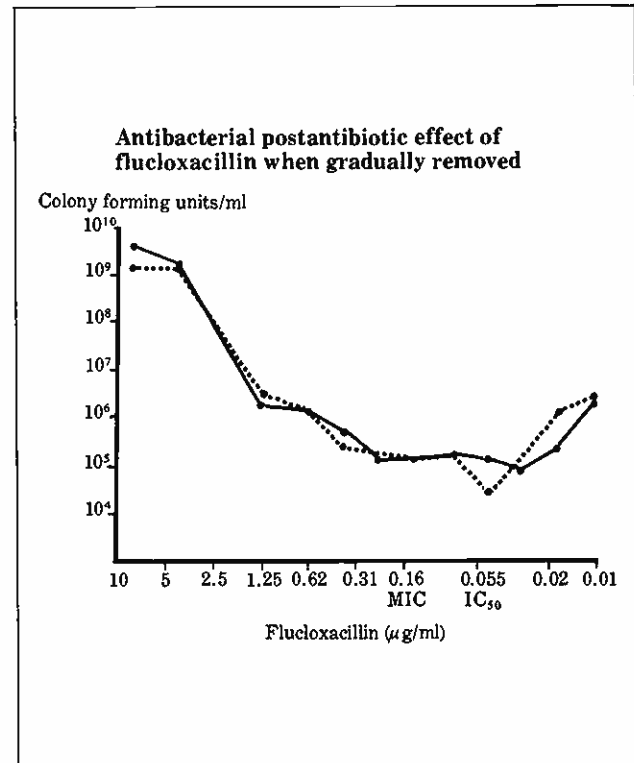


Figure 8. Kill and regrowth of *Staphylococcus aureus* exposed in vitro to flucloxacillin at concentrations diminishing with a half-life of 1 hour. Two experiments. Time along X-axis shown by the concentrations present in the bacterial culture. Adapted from (9).

**PHARMACOKINETIC EXTRAVASCULAR PERSISTENCE**

Perhaps the most important aspect of propulsive load dosing is the phenomenon of pharmacokinetic extravascular persistence (PEP). PEP has been observed for all antibiotics with a serum half-life below some 1 — 2 h, for instance for ampicillin from bacampicillin. This involves the potential of ampicillin to penetrate into the extravascular space (12). It has been shown by studies on peripheral lymph (13) (Figure 10) that the extravascular foci have peak concentrations below those in serum, that the extravascular peaks appear somewhat later than in serum, and that the concentrations are maintained for longer periods of time than that observed in serum itself. The longer duration of

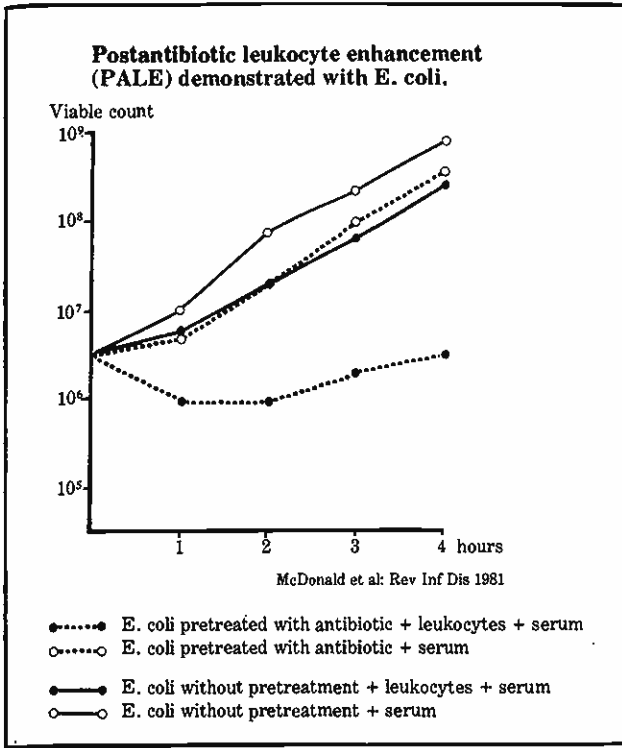


Figure 9. The effect on viable counts (log colony forming units/ml) of *Staphylococcus aureus* treated for 10 minutes with 10 times the minimal inhibitory concentration of benzylpenicillin. After removal of the antibiotic, the bacteria were exposed to serum along (○ - - - - ○), or leukocytes + serum (● - - - - ●). Controls were untreated cells exposed to serum alone (○ - - - - ○) or to serum + leukocytes (● - - - - ●). Adapted from (10).

antibiotics extravascularly corresponds to what we have described as pharmacokinetic extravascular persistence.

Ampicillin from bacampicillin penetrates more readily into the extravascular space than e.g. erythromycin or mecillinam (13, 15). The better penetration assessed from the relationship between the area under the antibiotic concentration curve (AUC) in peripheral lymph relative to AUC of serum levels. The AUC of peripheral lymph has been 80% of the serum value for ampicillin from bacampicillin (14) compared to 35% for erythromycin (15).

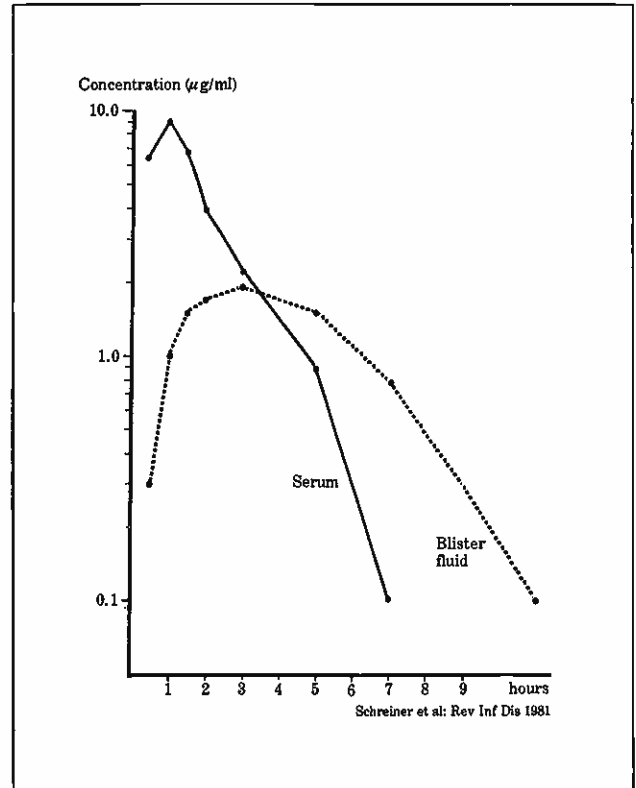


Figure 11. Concentrations of ampicillin from bacampicillin in serum and suction skin blisters in healthy human volunteers. Adapted from (16).

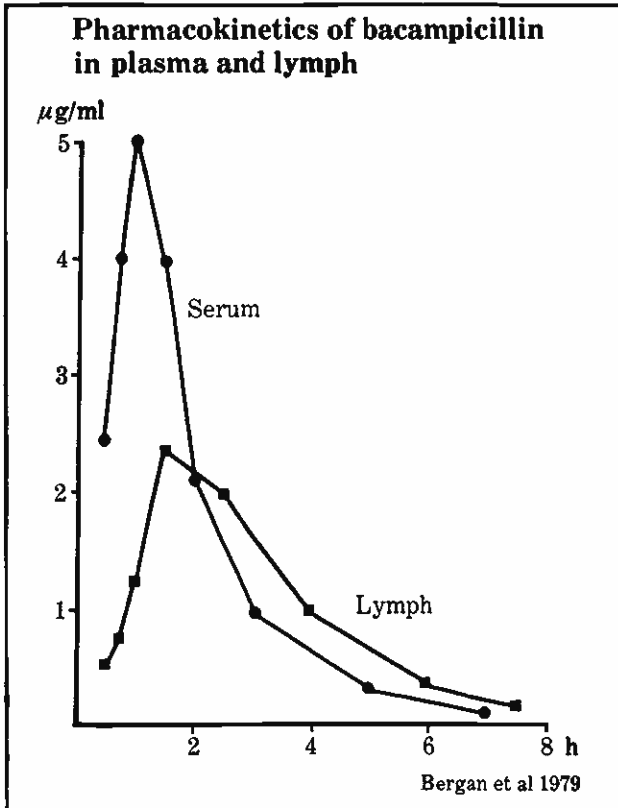


Figure 10. Concentrations of ampicillin from bacampicillin in serum and peripheral lymph in healthy human volunteers. Adapted from (13).

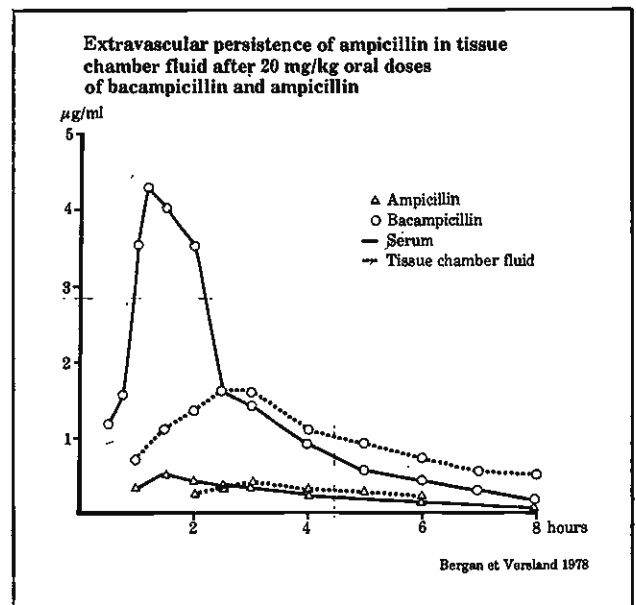


Figure 12. Extravascular persistence of ampicillin in tissue chamber fluid after doses of 20 mg/kg body weight of ampicillin or bacampicillin to mini-pigs. Adapted from (17).

The fact that PEP has been demonstrated in lymph is important since lymph represents drainage directly from the extracellular tissue fluid and thus truly reflects concentrations in unmanipulated tissues, i.e. in the barrier zone around an infected focus. Other experimental models have shown the same general pattern as observed in lymph. This applies e.g. to suction skin blisters (16) (Figure 11), subcutaneously implanted tissue cages (17) (Figure 12), skin chambers mounted on top of scarified skin, implanted fibrin clots, wound fluid, and abscess fluid (12). These experimental models, though, represent deeper compartments. This means that the maximum concentrations reached in them are below those in lymph. Longer duration or slower elimination of ampicillin from bacampicillin has also been demonstrated in body locations where this agent is therapeutically relevant, such as the middle ear (18) (Figure 13), lung tissue (19) (Figure 14), and bronchial secretion (20) (Figure 15). Observations like these support the strategy of propulsive dosage with a compound like bacampicillin which produces high serum peaks.

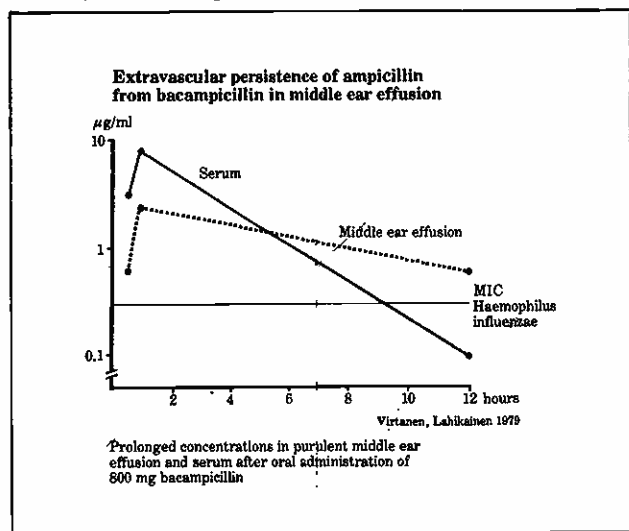


Figure 13. Persistence of ampicillin from bacampicillin in middle ear effusion compared with serum levels. Adapted from (18).

This relates to the major point of the theory underlying propulsive dosing. A high area under the serum concentration curve around the peak — the peak area under the serum curve (PAUC) is decisive. The PAUC is the major propulsive factor in penetration into extravascular parts of the body. A high peak area under the serum curve is the propulsive force responsible for the delivery of ampicillin from bacampicillin into the infected focus. The area under the concentration curve of the infected focus is directly proportional to the area under the serum curve (12). This follows from pharmacokinetic theory and equations, but has also been demonstrated to occur in practice (12). Figure 16 shows the same dose of benzylpenicillin given intravenously either as high bolus doses or by continuous infusion (21) and demonstrates that the former propulsive bolus dosing produces higher extravascular concentrations in interstitial tissue fluid and subcutaneously implanted fibrin clots. Similar findings have been observed with ampicillin and aminoglycosides (12, 21, 22).

Indeed, the success of propulsive load dosing in many respects depends upon the ability of the dose to render high serum peaks. This is the reason why it is important that bacampicillin produces relatively high serum concentrations. The serum AUC is higher after bacampicillin than after equimolar doses of other aminopenicillins like amoxicillin and ampicillin (Figure 4). After comparable recom-

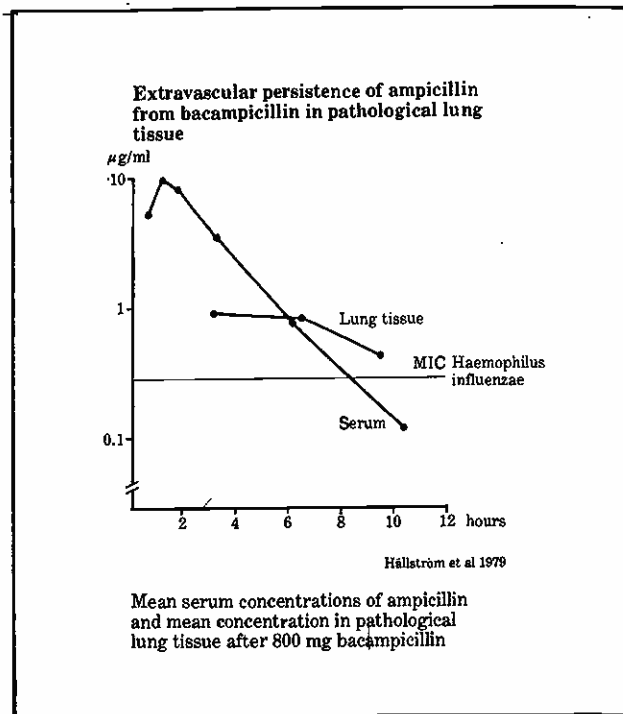


Figure 14. Persistence of ampicillin from bacampicillin in lung tissue compared with serum levels. Adapted from (19).

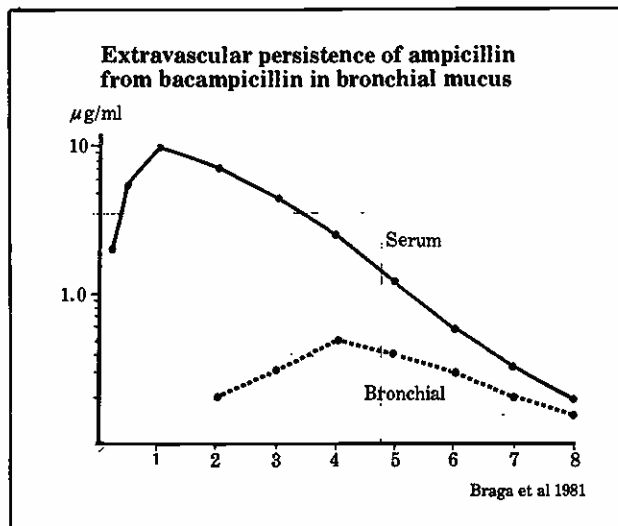


Figure 15. Persistence of ampicillin from bacampicillin in bronchial mucus compared with serum levels. Adapted from (20).

mended therapeutic doses of 400 mg bacampicillin and 500 mg plain ampicillin the former results in higher serum levels (23) (Figure 17). Indeed, the concentration curve after bacampicillin resembles that of a corresponding equimolar intramuscular dose as has been shown in another crossover study (24) (Figure 18).

All the four basic phenomena which we have discussed, antibacterial post-antibiotic effect, post-antibiotic leucocyte enhancement, post-antibiotic repressed adhesion, and pharmacokinetic extravascular persistence, explain why propulsive load dosage is a successful mode of antibiotic administration. Figure 19 shows when these principles become relevant in relationship to the concentrations in serum and extravascular levels. Figure 20 summarizes the interplay between body concentrations effected by propul-

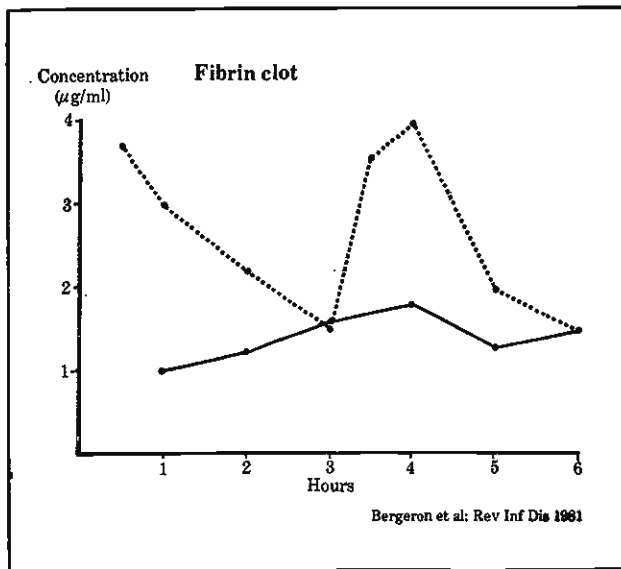
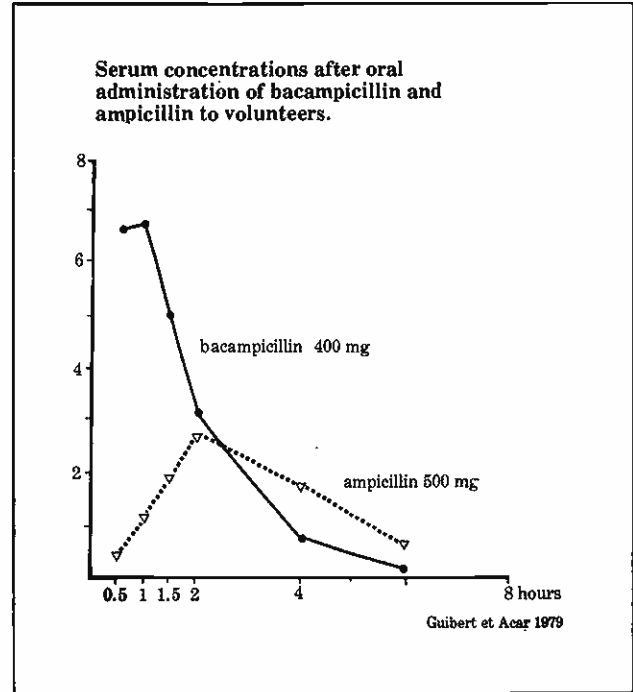
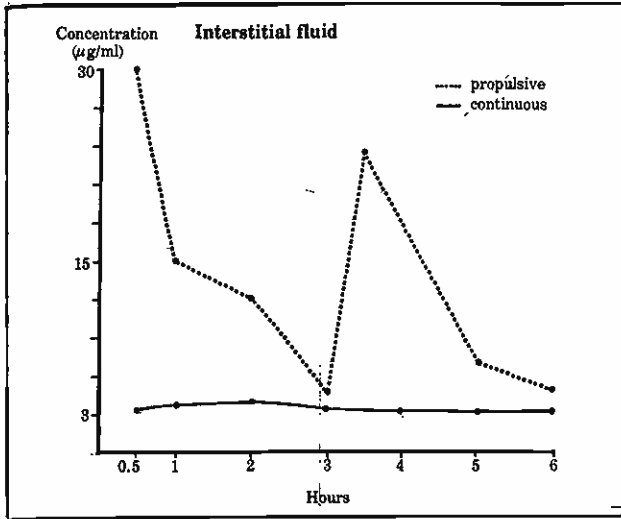


Figure 16. Comparison between concentrations of benzylpenicillin in fibrin clots and interstitial tissue fluid when the same dose is given either as propulsive load dosing (.....) or by continuous intravenous dosing (——). Adapted from (21).

Figure 17. Serum concentrations of ampicillin after administration of 500 mg ampicillin or 400 mg bacampicillin orally. Adapted from (23).

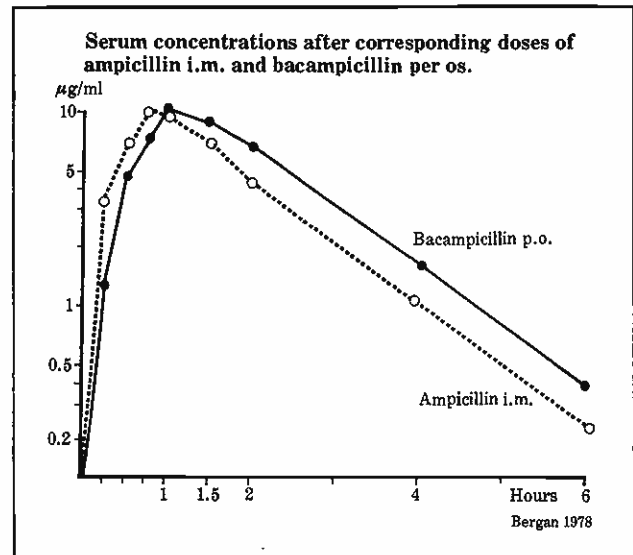


Figure 18. Serum concentrations of ampicillin after cross-over dosing to the same 10 healthy volunteers of equimolar doses of bacampicillin orally or 500 mg ampicillin intramuscularly. Adapted from (24).

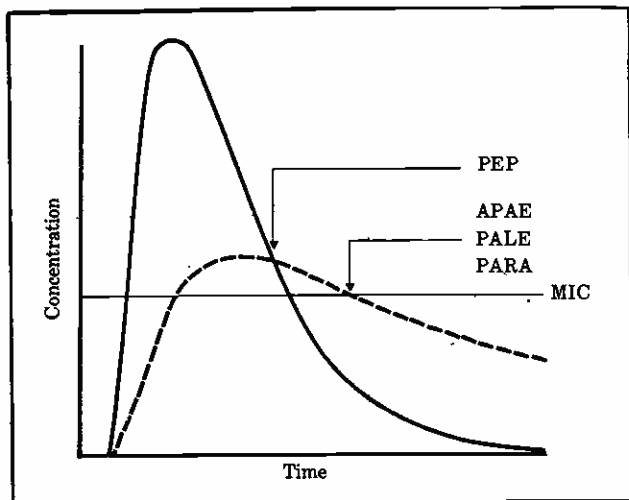


Figure 19. Time relationship between PEP = pharmacokinetic extravascular persistence, APAE = antibacterial post-antibiotic effect, PALE = post-antibiotic leucocyte enhancement, and PARA = post-antibiotic repressed adhesion. Concentrations of antibiotic in serum (—) and in extravascular focus (---) are indicated.

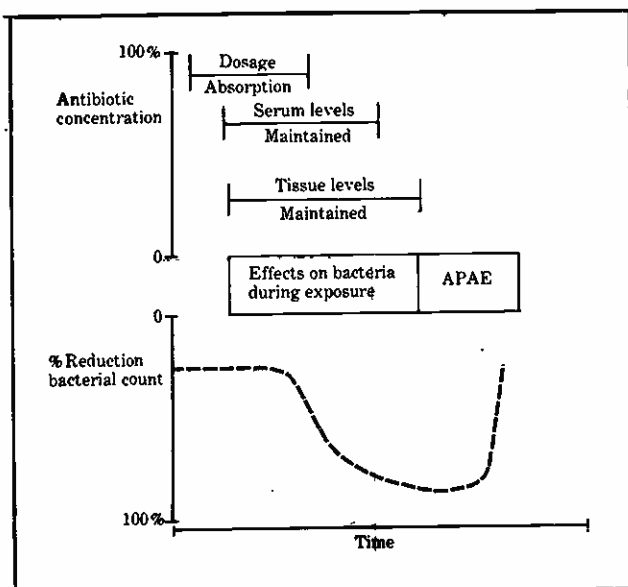


Figure 20. Propulsive load dosing: pharmacokinetic and bactericidal effects.

sive load dosing and reduction in bacterial count numbers after one single dose. An ample buffering capacity is incorporated into the principle of propulsive load dosing, for which bacampicillin has inherently favourable properties when ampicillin therapy is indicated because of the relatively high peak area under the curve reached after bacampicillin.

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