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Pharmacokinetics of antibiotics in natural and experimental superficial compartments in animals and humans

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Transcapillary exchange of antibiotics and other small molecules is diffusion driven and occurs in the capillary beds of the tissues. Small polar molecules are ionized at physiological pH and diffusion is pore-mediated. More lipophilic substances can also leave capillaries by the transcellular route. Splanchnic tissues have fenestrated capillary walls while somatic tissues have mainly micropores in their capillary walls. Under normal physiological conditions the ratio of capillary surface area to volume of fluid present (SA/V) is very large (> 100) and the rate of exchange of substances between capillaries, interstitial fluid and tissue fluid is extremely rapid. The structure of the interstitial space or ground substance, linking the capillary to the tissue cells, is designed to regulate the exchange of water, albumen and other solutes between the plasma and tissues. Interstitial space fluid (tissue fluid) is not simply an ultrafiltrate of plasma and has a specific chemical imbalance with plasma. Some antibiotics bind to serum albumen and it is claimed that this impairs their ability to penetrate into tissue fluids. However, the reduced concentration of albumen in the tissue fluid, relative to the plasma, is the main reason why percentage tissue penetration data based on total levels present are misleading and perpetuate the misconception that highly bound antibiotics (> 80%) have a reduced penetration potential.

The majority of infections are localized in extracellular fluid. Several models have been developed to sample serially the extracellular compartment. They have yielded diverse concentration/time profiles even for the same antibiotic at similar sites (skin and subcutaneous tissues). It has been shown that the various profiles are a direct consequence of compartment SA/V, which can range from > 100 to < 10. In the preclinical situation, the blister model has proven popular and reproducible but it should be remembered that the delayed profile seen is an artefact of blister geometry (SA/V < 10). On the evidence available it is likely that bacterial infections, in the presence of acute inflammation, will enhance the rate of entry of agents, while the reverse is true in areas of chronic inflammation where pathological barriers are already in place.

Introduction

The study of the factors influencing the pharmacokinetics of antibiotics in extravascular compartments in laboratory animals and humans is essential for the establishment of meaningful treatment regimens, and in the assessment of new therapeutic molecules. Since bacterial infections, models of which are the subject of this supplement, are normally located in the aqueous phase of the interstitial space of tissues' extracellular fluids, it is in these fluids that we have to attain effective antibiotic concentrations.

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This review will concentrate on the penetration of antibiotics into the interstitial space of tissues where the endothelial walls of the capillary beds are porous, and the tissues themselves have no capacity for active transport or specialized drug exclusion mechanisms. It will outline the function, ultrastructure and physiochemical properties of capillaries and the interstitial space and how these relate to the handling of antibiotics. The methods and models devised for the procurement of interstitial fluid in humans and animals will be briefly examined and finally major factors governing the pharmacokinetics of antibiotics in natural systems and experimental models, e.g. tissue geometry, serum binding and the role of infection, will be presented and discussed.

Function and ultrastructure of capillary walls

Function

The pump assisted vascular system ensures that blood is moved around the body. The capillaries ensure that the blood reaches every part of the body where it is required. Nutrients and gases leave the vascular compartments through the capillary walls and enter the interstitial space. From here they enter the interstitial fluid of tissues and organs where they are translocated to the individual cells. Simultaneously, excretory products are removed from the cells, exported into the capillaries and then transported back to the excretory organs. Thus there is a constant exchange of water and solutes between tissue cells and the blood via fluid in the interstitial space. The exchanges of water are controlled by Starling's forces (Starling, 1896), and the exchange of solutes by the laws of simple diffusion as described by Fick (1855). Other factors affecting the transcapillary exchange of antibiotics are blood flow through the exchanging capillary beds, the rate of transfer across the capillary walls, pKa and lipophilicity. In general polar substances will move through the capillary wall pores and microchannels while more lipophilic substances will in addition pass directly though the endothelial wall.

Ultrastructure

Capillaries are the terminal manifestations of the endothelial tubes of the vascular system with highly simplified tunicae. On anatomical evidence, Krstic (1991) has shown that capillaries can be subdidived into three types depending on the integrity of their endothelial cell walls, namely, continuous, fenestrated or sinusoidal. Brief descriptions are as follows.

Continuous. Here the tunica intima consists of a continuous layer of flattened endothelial cells covered with the basal lamina and a considerable presence of flattened overlying pericytes, also covered by the basal lamina. The endothelial cells have tight junctions, and numerous microvesicles (50–70 nm diameter) are distributed in the endothelium; these can fuse to form microchannels connecting the internal and external endothelial surfaces. These capillaries are generally found in muscle, central nervous system, adipose tissues, etc (Figure 1).

Fenestrated. Again a single layer of flattened endothelial cells with a continuous basal lamina, tight junctions but fewer pericytes. In addition to microvesicles and microchannels there are pores (50–80 nm diameter) directly linking the internal and external surfaces. These pores are frequently grouped to form sieve plates with 20–60 pores/μm^2. Fenestrated capillaries have actin fibrils in their cytoplasm and are therefore contractile. These capillaries are found mostly in kidneys and the endocrine glands. The

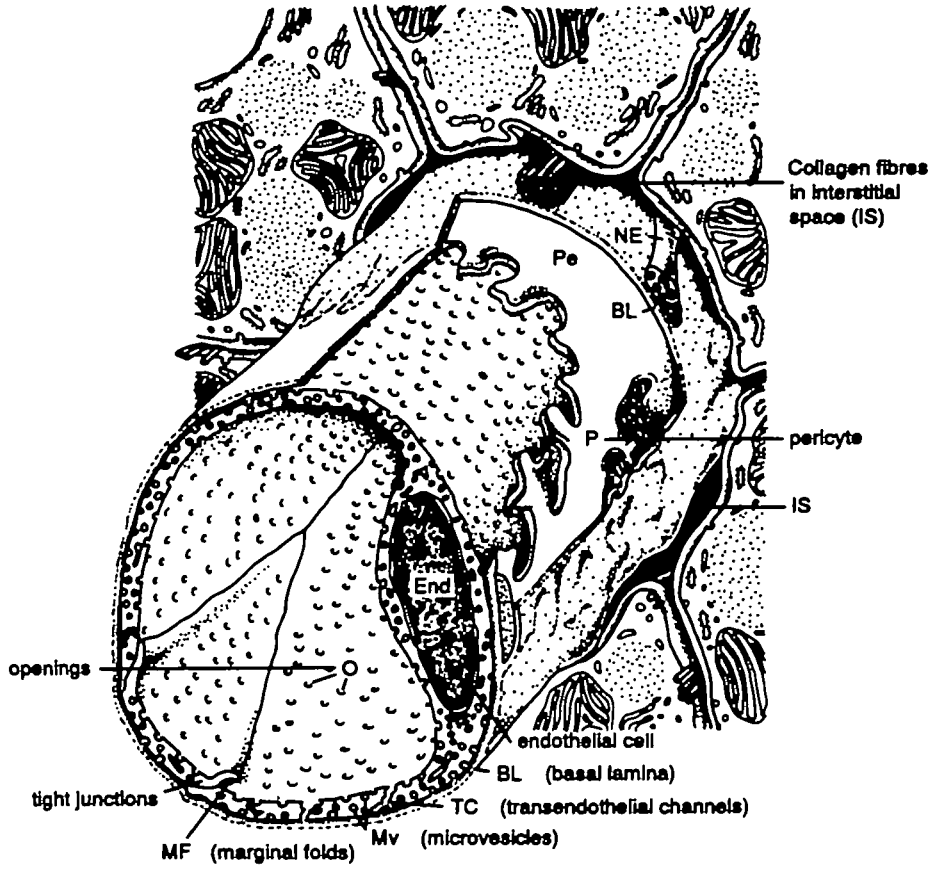

Figure 1. Representation of a continuous capillary in brown adipose tissue (rat) (cf. Krstic (1991)).

exchange of substances between plasma and tissue fluid is greatly enhanced by the presence of the endothelial pores or fenestrations (Figure 2).

Sinusoidal. These exhibit a single layer of flattened endothelial cells with tight junctions, and a virtual absence of basal lamina or pericytes. In addition to microvesicles and pores there are large holes (0·5–3·0 μm diameter) occurring regularly over the entire surface. These capillaries are mostly found in the adrenal cortex, pituitary gland, spleen and liver, and offer a minimal permeability barrier to the exchange of substances between the secretory tissues and the plasma.

Under normal physiological conditions the body provides a considerable capillary surface area (SA) within the interstitial space of tissues to service a relatively small unit volume (V) of interstitial space fluid; consequently the SA/V ratio is greatly in excess of 100. It is not surprising that drug transfer between capillary blood and interstitial space is alleged to be a very fast process (Gibaldi & Perrier, 1982). It has been proposed by Stec & Atkinson (1981) that small polar molecules will exchange between plasma and tissue fluid more rapidly with fenestrated capillaries, which are associated with the splanchnic bed, than with continuous capillaries, which are mainly associated with the capillary beds of skeletal muscle and other somatic tissues (Figure 3).

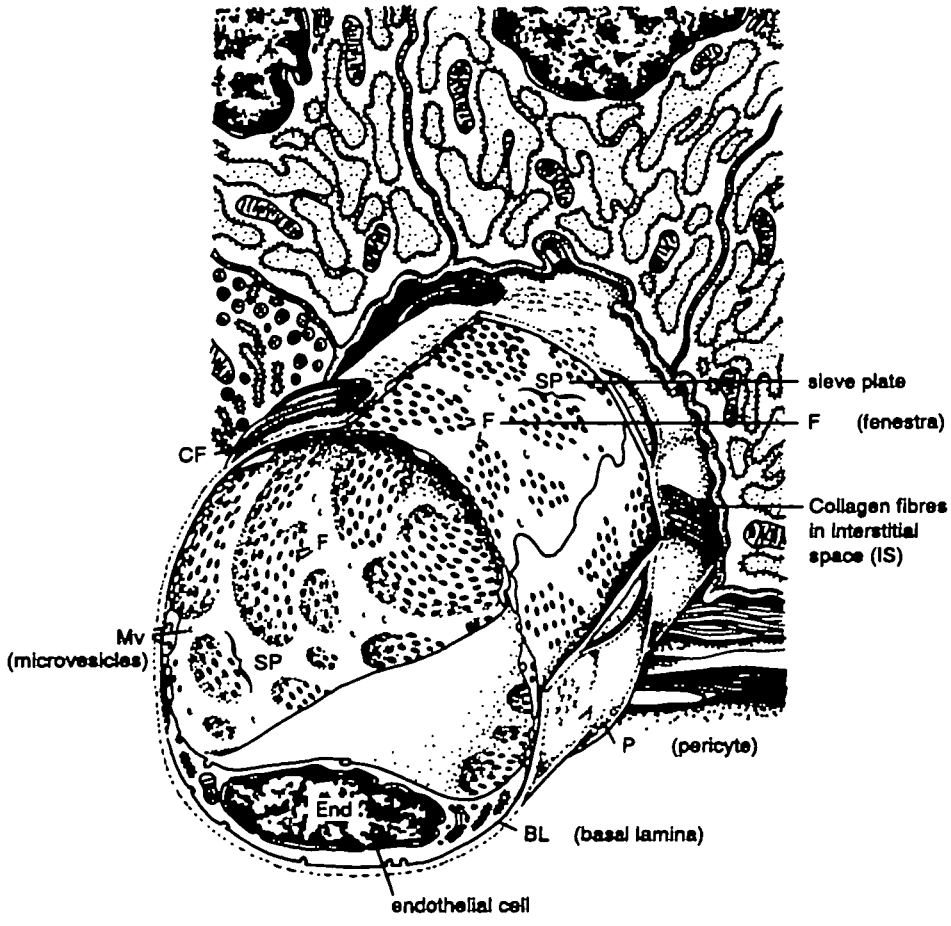

Figure 2. Representation of a fenestrated capillary, thyroid gland (human) (cf. Krstic (1991)).

Function, ultrastructure and physicochemical properties of interstitial tissue space

The function, ultrastructure and physicochemical properties of the important but largely 'forgotten organ' (Katz, 1980), known as the interstitial space, have been reviewed by Katz (1980) and Laurent (1972). The remainder of this section summarizes points important to this presentation.

Function

The primary function of the interstitial space is to provide a tissue in which to regulate the transport of water and solutes between capillaries and the tissues.

Structure

Katz (1980) proposed three phases to the interstitial space: extracellular fluid, dissolved macromolecules and the structural matrix. Other workers, cited by Gilanyi *et al.* (1988), have subsequently suggested two phases, namely an immobile 'water poor, colloid rich'

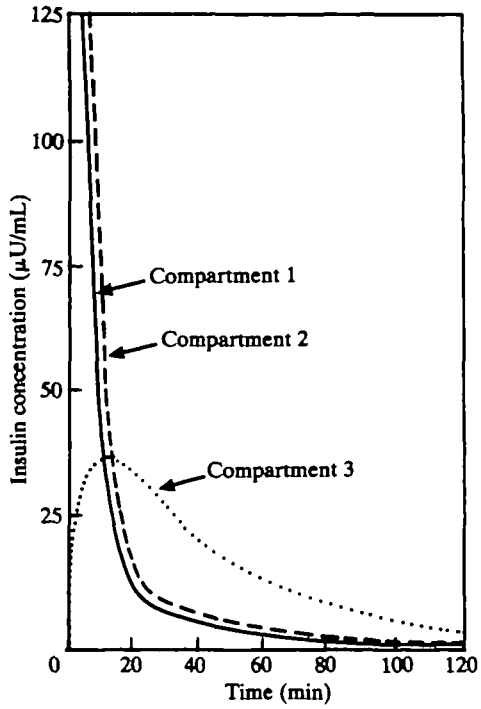

Figure 3. Measured plasma concentrations of insulin in compartment 1 (plasma volume) after intravenous injection of a 25 mU per kg dose and computer-derived estimates of insulin concentration in presumed splanchnic (compartment 2) and somatic (compartment 3) components of interstitial fluid (cf. Atkinson, Ruo & Frederiksen (1991)).

and a mobile 'water rich, colloid poor' microphases, or more recently a single phase system consisting of a glycoaminoglycan-containing gel-like matrix embedded in a matrix of collagen fibres. For convenience we will consider the three phase system proposed by Katz (1980). The first phase, that of extracellular fluid, comprises water and dissolved ions and small molecules. The second phase encompasses dissolved macromolecules, mostly serum proteins at concentrations of 30–80% of that seen in the serum depending on factors such as disease, tissue anatomy and location. The third phase is the network of cross-linked long chain proteins, e.g. collagen and elastin, and polysaccharides, e.g. glycoaminoglycans and mucopolysaccharides (Figure 4). The polysaccharide, hyaluronic acid, can have an unfolded length of 10 μm and has been described as a large water-imbibed coil containing 1000 times more water than organic material, with a diameter of 5000 Å (Laurent & Gergely, 1955).

Properties

The connective tissue polysaccharides are polyelectrolytes and carry carboxyl and sulphate groups which are dissociated at physiological pH. This polyelectrolyte characteristic is important for the transport of ions in connective tissues, for interactions with other macromolecules and for the frequently reported but recently disputed (Gilanyi *et al.*, 1988) electroyte imbalance of particularly sodium and chloride ions seen between

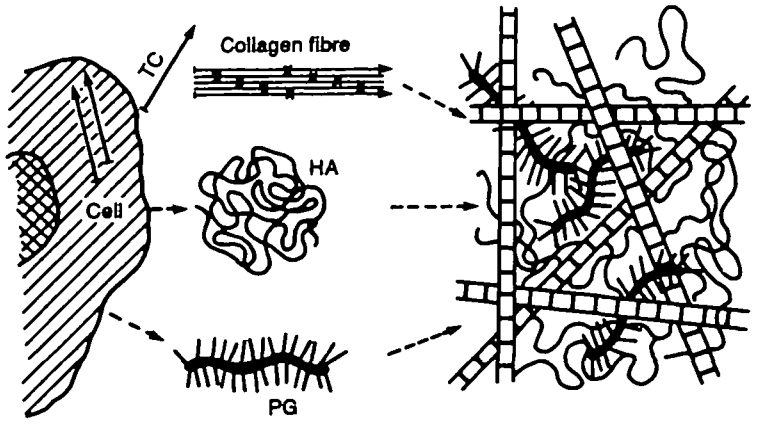

Figure 4. Demonstration of the formation of interpenetrating collagen-polysaccharide networks in the extracellular space. Fibroblasts synthesize procollagen molecules which extracellularly turn into tropocollagen (TC). The latter polymerize into collagen fibres. The cells also excrete hyaluronic acid (HA) and proteoglycan (PG) molecules and these polysaccharides from a gel-like structure together with the collagen fibres (cf. Laurent (1972)).

interstitial fluid and plasma. The network or matrix formed mainly by polysaccharides will be kept expanded by self-generated osmotic forces and it is the properties of this network that determine many of the functions of the interstitial space or ground substance. The interstitial space consists of narrow communicating aqueous channels through the network which impedes the bulk or convective flow of water. Although bulk flow is strongly hindered by the polysaccharide network to approximately 1/10 of that seen in adjacent segments of the vascular tree, there is minimal hindrance to the diffusion of water molecules or solutes in the narrow aqueous channels. Because bulk flow is so inefficient, water and solutes travel the few microns separating the capillaries and cells predominantly by diffusion. The movement of large solute molecules such as proteins is also hindered but in proportion to the size and shape of the molecule and the concentration of polysaccharides in the matrix. Thus the space available for the location of macromolecules in a polymer network is considerably reduced. This induced sterical exclusion is a function of the concentration of polymer in the matrix and the size of the particular macromolecule. Sterical exclusion can explain why, under normal conditions, the concentration of plasma proteins in interstitial fluids, while varying between the interstitial fluid compartments, is less than that seen in the plasma.

It can be concluded that interstitial connective tissues have specific structural, osmoregulatory and translocatory functions which are reflected in their composition. Although the extracellular, extravascular, fluid content of subcutaneous tissue and skeletal muscle is considerable (10 and 25 L/75 kg body weight, respectively), the vast majority is bound up in the ground substance with free water only available as minute water channels and biofilms. It can be shown that interstitial tissue fluid is not simply an ultrafiltrate of serum and the chemical imbalance seen with plasma, regarding protein content and the concentrations of particular ions, is brought about by the presence and concentration of specific matrix molecules in the ground substance. Because interstitial connective tissue plays a vital role in the translocation of substances between tissues and cells it is designed, under conditions of normal hydration, to respond quickly to changes in blood composition and is therefore in intimate contact

with the capillaries of the lymph and vascular systems. Knowledge of the factors governing the exchange of antibiotics between the tissue interstitium and plasma is of considerable interest to physicians and will be discussed further in this review.

Model systems for studying the pharmacokinetics of antibiotics in interstitial fluid

The relationship between antibiotic concentrations in plasma and tissues, has been the subject of much debate. Much of the early work was completed on excised tissues or wound exudates and informed opinion at that time suggested that tissue levels were substantially lower than concurrent plasma levels and persisted for longer periods of time (Kunin, 1981). We now know that these data are, in the main, erroneous because of problems of interpretation and methodology (Gerber, Frimodt-Möller & Craig, 1980; Cars & Ögren, 1985). In recent years various approaches have been used to study concentrations of antibiotics in the tissue fluids of animals and humans.

Removal of tissues or fluid

The most direct system is to obtain pieces of tissue by biopsy. Equally, it is easy to remove samples of peritoneal fluid with paper discs (Wise *et al.*, 1981; Corbett *et al.*, 1985). These techniques are possible in humans undergoing elective surgery but it is not always practical to obtain a whole time course of samples from the same donor and also a reproducible system for extracting interstitial fluid from biopsy samples has not been devised. For obvious reasons these techniques are unsuitable for preclinical studies.

Indirect measurements

A knowledge of the structure of a given tissue, and how different classes of compound partition into its extracellular fluid and total tissue water (Ryan & Cars 1980, 1983; Cars & Ögren, 1985; Cars & Ryan, 1988) plus antibiotic plasma or homogenate concentrations, are sufficient data from which to calculate extracellular concentrations, but only in the post-distribution phase (Schentag, Swanson & Smith, 1985; Nix *et al.* 1991*a*,*b*).

Direct measurements

All other models in current use are simply variations on the theme of how to collect serial samples of interstitial fluid from tissues, and the majority have for convenience concentrated on the skin and subcutaneous interstitial space as a source of fluid.

The different types of model have been reviewed and categorized many times (Holm, 1978; Raeburn, 1978; Bergeron & Brousseau, 1986; Wise, 1986*a*). Each model has been modified several times and each change has been the basis of several publications. The models can be broadly classified as natural or artificial. Natural, where the interstitial fluid is present as a biofilm and consequently has to be absorbed and collected on cotton threads or paper discs, and artificial, where much larger volumes are accumulated to assist serial sampling, e.g. blisters, tissue cages and saline-containing chambers. The suction blister technique is widely used and is very convenient; however, it must be remembered that the concentration/time profiles attained are unique to compartments where the SA/V is very low. Also, a recent study by Bruun

et al. (1991) has shown that the peak levels attained are dependent on whether the blisters are created before or after drug administration; higher peak levels were seen when blisters were produced after drug administration.

Factors influencing the penetration of antibiotics into tissues

There have been several reviews dealing with factors influencing the distribution of antibiotics into tissues based on theoretical considerations and data obtained in experimental models (Barza, 1981, 1990; Bergan, 1981; Barza & Cuchural, 1985; Ryan, Cars & Hoffstedt, 1986; Nix *et al.*, 1991*a,b*). Many of the factors relate to the chemical properties of the antibiotic used (solubility, binding to serum proteins, pKa) while other factors are more host dependent and relate to type of tissue and capillary, blood flow, infection, etc. Below are outlined some of the major factors governing the distribution of antibiotics into natural interstitial tissue fluid compartments and those that have been generated in experimental model systems.

Compartment geometry

Under normal conditions of hydration the interstitial space in tissues is in dynamic equilibrium with the vascular system regarding exchange of gases and nutrients (see previous section). Molecules only have to travel small distances; consequently the ratio of capillary surface area (SA), to the volume (V) of extracellular fluid they service is large (SA/V $>$ 100; Figures 1 and 2). Van Etta *et al.* (1982, 1983), using visking tubing sacs, demonstrated that the SA/V ratio is important and can profoundly alter the concentration/time profiles seen. Other workers, using different models, and sampling fluid from the skin and subcutaneous compartments, have published a wide range of tissue fluid concentration/time profiles for a wide range of antibiotics. In a recent review Ryan (1985) analysed the kinetic profiles for several antibiotics obtained from a variety of models in animals and humans. Because of the extensive literature the analysis was restricted to eight reports where two or more models were tested simultaneously. This selection ensured a reduction in bias introduced by experimental technique, assay systems and choice of antibiotic. The results demonstrated conclusively that variation in SA/V ratio was a major factor in determining the kinetics of antibiotic concentrations in tissue fluids and fully explained differences previously reported between models. In compartments where the SA/V ratio was high ($>$ 100) i.e. natural compartments, the antibiotic concentration/time profiles resembled those seen in the plasma, while in compartments where the SA/V was low ($<$ 10), as seen in the artificial compartments, e.g. tissue cages, fibrin clots, blister fluids, the profiles were changed and showed reduced peak levels, increased time to peak values and delayed elimination relative to concurrent plasma kinetics.

Protein binding

The importance of serum protein binding on the distribution of antibiotics into extravascular sites has been the subject of much discussion, review and experimental work using several model systems (Rolinson & Sutherland, 1965; Merrikin, Briant & Rolinson, 1983; Ögren & Cars, 1985; Wise, 1986*b*; Cars, 1991). In the previous sections concentrations of antibiotics in plasma and interstitial space fluid have been expressed in terms of total drug present, which is the combination of total and free antibiotic.

This is misleading since it implies that all the drug present is free for distribution or antibacterial action, while in fact only the free drug is mobile and active. In the normal rapidly equilibrating situation that exists between interstitial space fluid and plasma the free drug concentration/time profiles for both compartments will be practically identical regarding peak levels attained, time to peak and rate of elimination. However, owing to sterical hindrance the concentration of albumen (the main serum protein responsible for binding antibiotics) could be three to four times lower in interstitial space fluid than in plasma. Therefore for a relatively highly bound drug (> 80%), the concentration/time profiles based on total drug present will be substantially different for plasma and interstitial space fluid, despite the fact that the concentrations of free antibiotic will be practically identical. It has become customary to calculate the area of the antibiotic concentration/time profile (AUC), and to use the ratio of AUC(T)/AUC plasma × 100 to calculate the % penetration of a drug into compartment T. In the case of rapidly equilibrating compartments, where the SA/V ratio is high, the length of the observation is not as important as for compartments with a low SA/V. Here the relative AUCs should be calculated to infinity or at least to the next dosing period and it is worth noting that most experimental pharmacokinetic studies are conducted only using a single shot of antibiotic. More meaningful data are obtained after several doses to obtain a steady state or during continuous infusion studies when plasma and tissue fluid concentrations should be uniform.

In their review, Bergeron & Brousseau (1986) drew attention to the inverse relationship, based on relative AUCs, between antibiotic penetration into extravascular sites and the degree of serum binding of the antibiotics concerned based on data obtained for eleven β-lactam antibiotics evaluated in blister, lymph and cotton thread models ($R = -0{\cdot}74085$). They also noted an inverse relationship (AUCs) with twelve agents in the fibrin clot model ($R = -0{\cdot}7748$), but could only show a poor correlation ($R = 0{\cdot}3694$) in data abstracted from tissue cage models, again with twelve β-lactam antibiotics. They noted that the high protein content and presence of a thick granulomatous sheath in the tissue cage model might impede the exchange of antibiotics. In a recent report Bergan, Engeset & Olszewski (1987) reviewed accumulated data on fifteen β-lactams concerning their penetration (AUC) into the peripheral lymph of volunteers, and he also reported an inverse relationship, with an excellent correlation ($R = -0{\cdot}92$). Reworking the data produced by Wise and his colleagues (see listing in Redington, Ebert & Craig, 1991) with the cantharidine blister model and a selection of eighteen β-lactams, we see a familiar inverse relationship between penetration (AUCs) and degree of serum binding which would suggest that highly bound antibiotics have impaired penetration into tissue fluids.

However, Cars (1991) proposed that differences in albumin content between serum and tissue fluids are probably the most important factor explaining the inverse relationship between protein binding and the degree of penetration seen. Citing the work of Odar-Cederlöf & Borgå (1976), he observed that the difference in concentration (total) of drugs in tissue fluids and serum will become more pronounced when the albumin level in the tissue fluid decreases and the degree of protein binding of the antibiotic increases. Since the fluids derived in the different models vary significantly in their protein content, this would have the effect of making the term '% tissue penetration', for a given antibiotic, more or less dependent on the model used for its calculation! It should be remembered that under steady state (at equilibrium) conditions, the mean concentration (CSS) of free drug in the serum and extravascular fluids

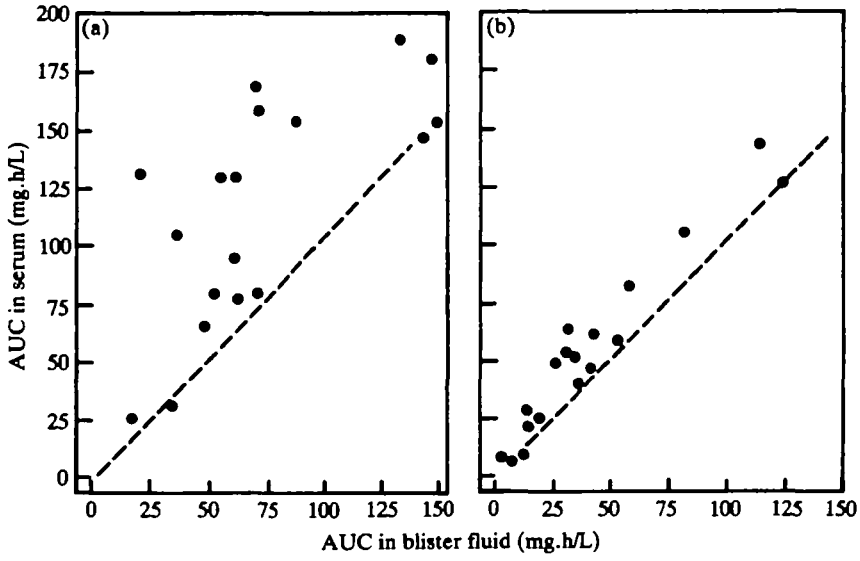

Figure 5. Relation between the AUC in serum and that in blister fluid for total (a) and free (b) drug. Data on 18 β-lactam antibiotics were obtained from Wise and colleagues (cf. Redington *et al.* (1991)).

over the dosing period are equal (Barza, 1990), even though peak levels attained in the two compartments can be different, because of the prevailing SA/V ratio in the tissue compartment, providing there is no active transport or destruction of drug in the extravascular site. This implies that over the dosing interval the percentage penetration of a drug, calculated on the relative AUCs of free drug, should be approaching 100% regardless of the degree to which it is bound to serum. This fact is not obvious from conventional plots of percentage penetration (AUC total drug) where an inverse relationship is often portrayed. Recently, Redington *et al.* (1991) reviewed the data published by Wise and colleagues regarding the penetration of eighteen β-lactam antibiotics into the fluid of cantharadine induced blisters. They were able to show an excellent correlation between the AUCs for free drug in plasma and blister fluid (Figure 5). They further observed that the route of drug elimination in the kidney has a major impact on the pharmacological effects of serum binding and confirmed that for antibiotics eliminated by tubular secretion (active transport), in addition to glomerular filtration, the main effect of increasing serum protein binding is to decrease the AUC of free drug in the serum and blister fluid. For drugs eliminated by glomerular filtration (passive transport), the main pharmacological effect of high serum binding (> 80%) is effectively to increase the AUC for total drug with little or no effect on the AUCs of free drug in the serum and blister fluid.

It is possible to make some generalizations on the effect of serum binding on the penetration of antimicrobial agents into extravascular interstitial space. Only free drug is available for antibacterial activity and distribution into tissue fluids. If the concentrations of albumin in plasma are considerably greater than corresponding concentrations in tissue fluids, then the main effect of high binding (> 80%) will be to distort enormously the total amounts of antibiotic in each compartment, which will compromise the calculation of % penetration ratios. At equilibrium the mean concen-

tration of free drug in serum and tissues over a given dosing period will be equal, and the % penetration ratio of free drug will approach 100%, even though the concentration/time profile in the vascular and tissue compartments can be dissimilar. Data showing an inverse relationship between percent penetration into tissues and serum binding are misleading, in that they imply that highly bound antibiotics (> 80%) will have impaired tissue penetration. A high degree of serum binding, in the absence of active transport excretory mechanisms such as tubular secretion, will effectively reduce the amount of free drug in the serum and extend the elimination half life.

Infection

There is considerable experimental and theoretical evidence available on the major factors influencing the distribution of agents into specific compartments of the healthy body and these have been discussed in the previous sections. These compartments have strictly controlled physiological windows in which to function and any significant departure will induce symptoms of clinical disease. In the area of the treatment of infectious disease we have an added factor to contend with, that of the body's response to invading microorganisms which we try to augment with antimicrobial agents, and the establishment and subsequent isolation of infective foci. For theoretical reasons, infection will dilate capillaries and increase vascular supply to the infected region, this will assist the entry of host cells and antimicrobials into the area with accompanying changes to the surrounding milieu. These changes can range from subtle changes, in pH, fluid and protein content in acute infections to, in chronic disease, suppuration and granulation leading to decreased vascular supply and necrosis. A whole range of pathological and physiological scenarios can be envisaged covering mild self-limiting infections, suppurating wounds and end-stage abscess formation. There is a paucity of experimental evidence from which to unravel factors important in the rate of entry (penetration) of antimicrobial agents into infected foci. Basically two approaches have been made. The first involves endotoxin (LPS) induced local inflammation, and the second involves inducing infections in model systems used, or developed primarily, to study antibiotic penetration into healthy tissue (tissue cages, synovial fluid, granuloma pouches, etc). The data from the literature, including those cited by Clarke (1989) and Bengtsson *et al.* (1991) but excluding reports where infections were induced with bacteria producing significant amounts of antibiotic hydrolysing enzymes, have been analysed and summarized in the Table.

Local inflammation

LPS effects where observed, were seen to have a positive effect on the rate of entry of drugs. For example in one of two reports dealing with LPS induced synovitis, Firth *et al.* (1988) found accelerated penetration of ampicillin and kanamycin in horses, but Shoaf *et al.* (1986), showed no enhanced entry in calves of trimethoprim/sulphadiazine. Again while there was no enhancement of ampicillin entry into LPS-inoculated suction blisters in humans (Schreiner, Bergan & Hellum, 1981), there was an increase in the rate of entry of oxytetracycline into LPS inoculated tissue cages in calves (Bengtsson *et al.*, 1991).

Table. The effect of aseptic/septic inflammation on the pharmacokinetics of antibiotics

Focus of inflammation/ infection	Source of inflammation/ infection	Animal	Antibiotic	Rate of drug entry			Reference
				enhanced	no change	reduced	
Synovium	LPS	horse	P,A	√			Firth *et al.* (1988)
Synovium	LPS	calf	T/S		√		Shoaf *et al.* (1986)
Blister	LPS	human	P		√		Schreiner *et al.* (1981)
Tissue cage[a]	LPS	calf	O	√			Bengtsson *et al.* (1991)
Pericardium[b]	*Staphylococcus aureus*	dog	P,C,A	√			Tan *et al.* (1974)
Lymph[b]	*Streptococcus pyogenes*	rabbit	P		√		Roberts *et al.* (1979)
Tissue chamber[b]	*S. aureus*	rabbit	C		√		Gerding *et al.* (1987)
Granuloma pouch[a]	*S. aureus*	rat	C			√	Nishida & Murakawa (1977)
	Escherichia coli						
Tissue cage[a]	*Klebsiella pneumoniae*	rabbit	Q			√	Rylander & Norrby (1983)
	Bacteroides fragilis						
Tissue cage[a]	*K. pneumoniae*	rabbit	M,A			√	Rylander *et al.* (1981*a*,*b*)
	B. fragilis	rabbit					
	Proteus spp.	rabbit					
Tissue cage[a]	*S. aureus*	rabbit	C			√	Gerding *et al.* (1987)
Tissue cage[a]	*E. coli*	rabbit	C			√	Holm, Ekedahl & Bergholm (1978)

[a]Chronic inflammatory response induced before infected.
[b]Acute inflammatory response as a consequence of infection.
Key to antibiotics: A, C, O, P, M, Q, T/S indicate aminoglycosides, cephalosporins, tetracyclines, penicillins, metronidazole, quinolones, and trimethoprim sulphadiazine respectively.

Local infection

This category has been further subdivided into acute infections in naive tissues where the inflammatory response is a consequence of infection, or acute infections initiated in areas of chronic inflammation.

Acute infections in naive tissues. Tan *et al.* (1974) induced acute staphylococcal pericarditis in dogs and six days later compared the rate of entry of β-lactams and aminoglycosides into infected and non-infected sites. He found that the ratio of pericardial fluid antibiotic concentrations to concurrent plasma concentrations over several time points was higher in infected animals. Roberts, Futrell & Sande (1979) compared concentrations of penicillin G and nafcillin in the peripheral lymph of infected and non-infected rabbits and could find no differences in the peak values attained, although in the presence of inflammation penicillin G equilibrated more rapidly and naficillin less rapidly than in uninfected animals. Using a rather more artificial model involving visking sacs, Gerding *et al.* (1987) could find no effect of infection on antibiotic penetration.

Infection in areas of chronic inflammation. Work in granuloma pouches induced in rats (Nishida & Murakawa, 1977), showed that there was a reduction in the rate of entry of cefazolin into pouches infected 24 h previously compared with data obtained immediately after infection, indicating that the acute infection exacerbated an already chronically inflamed focus. Several other workers have shown similar reductions in cephalosporin, quinolone and aminoglycoside influx attributable to acute infections in chronically infected tissue cages (Holm, 1978; Rylander *et al.*, 1981*a,b*; Gerding *et al.*, 1987). The reasons for the reduced influx has been discussed by Rylander *et al.* (1981*b*), and Barza (1981) cites several references dealing with non-enzymic binding and inactivation by constituents of pus. It is worth noting that Holm (1978) reported that although the rate of entry of cephaloridine was reduced in infected tissue cages, the rate improved as the bacterial population was reduced, again indicating the role bacteria play under these conditions.

From the data presented and from theoretical considerations, it is possible to confirm that inflammation will improve the rate of entry of drugs into sites of relatively high and low SA/V ratios. The presence of bacteria in acute infections will also enhance drug entry, providing they do not elaborate antibiotic destroying enzymes, and this will be most evident in the absence of chronic inflammation. However, in the presence of chronic inflammation involving granulation where the dynamics of drug exchange are already compromised, acute bacterial infection will reduce the rate of entry of drugs. Since the majority of infections in human and veterinary medicine likely to require treatment with antibiotics are acute and in well vascularized areas of the body, further experiments in models of acute infection, in the absence of chronic inflammation are needed to establish firmly the effect of infection on drug disposition in tissues.

In the clinical situation physicians are most likely to initiate antibacterial therapy with the dual intention of arresting the disease process and preventing its spread to naive tissue. Here they can be guided by plasma levels which in the absence of chronic disease will reflect prevailing tissue concentrations (Ryan *et al.*, 1986).

Conclusions

Information on host factors and drug properties influencing the pharmacokinetics of antibiotics in tissue fluids and superficial compartments can be gained from physio-

logical, anatomical and biochemical studies, and from information gleaned from experimental models, not all of which have strict clinical counterparts. From the review conducted here on some of the factors involved, several conclusions can be drawn. Interstitial space is an important tissue in its own right, and interstitial tissue fluid is not simply an ultrafiltrate of plasma. Concentrations of antibiotics in tissues and tissue fluids are a consequence of the type of tissue, its function, the predominant capillary type, and prior and prevailing plasma antibiotic concentrations. Drug transfer is diffusion driven through pores or transcellularly, depending on pKa. Of the three variable factors reviewed in some depth, compartment geometry, infection and protein binding, the host generated factors, such as specific compartment geometry and infection, are important in that they can influence local tissue levels without changing prevailing plasma concentrations. On the other hand, protein binding, a compound specific property, affects both plasma and tissue concentrations alike and its main effect is to exaggerate total levels present, particularly those in the plasma.

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