Penetration of antibiotics into bone

The need to deliver effective concentration of antibiotics to bone occurs in several areas of orthopaedic practice. Patients who are undergoing total joint replacement (Ericson, Lidgren et al., 1982); patients who have either acute or chronic osteomyelitis (Blockey & McAlister, 1979; Lidwell et al., 1980); patients who have sustained compound fractures (Patzakis, Harvey & Ivler, 1974; Gustillo & Anderson, 1976).

The route by which these antibiotics are administered can be either systemically or locally, the latter by means of incorporation into the bone cement (Buchholz & Engelbrecht, 1970; Wahlig et al., 1978). In order that the antibiotic reaches bone in effective concentrations following a systemic injection, there needs to be an adequate blood supply and flow to the bone. Brookes et al. (1961) have described the blood supply of a diaphyseal bone and have shown that the pattern of flow is centrifugal in direction and Kelly & co-workers have shown that the two systems, the marrow and cortical flows, run in parallel to each other (Kelly & Janes, 1968; Lopez-Curto, Bassingthwaighte & Kelly, 1980).

In normal bone, water soluble minerals leave the capillaries by the process of passive free diffusion, dependent on the molecular weight of the molecule (Cofield, Bassingthwaighte & Kelly, 1975; Davies, Bassingthwaighte & Kelly, 1976; Hughes et al., 1977; Lemon et al., 1980). Fat-soluble molecules however pass freely through the thin capillary wall (Kelly, 1973). Once outside the capillaries in bone, there is a fluid space, which has been estimated to be 11 ml/100 ml of bone (Morris et al., 1982). This space separates the vessel walls from the bone cells, the collagen and the hydroxyapatite.

Changes in bone blood flow lead to alterations in mineral exchange, so that with high flows, the extraction falls, whilst at low flows the extraction increases. However, in the same experiments, it was shown that whilst at low flows the exchange is flow dependent, at high flow it is diffusion limited (McCarty & Hughes, 1983). In experimental animals bone blood flow has been measured, using the microsphere technique described by Lunde & Michelson (1970) and it has been demonstrated that flow varies to different bones, some bones in the skeleton having a higher flow than others (Tothill et al., 1984).

Following an experimental osteotomy, the bone blood flow increases, reaching a maximum two weeks after the event (Paradis & Kelly, 1976), but the extraction of small molecules remains constant during this time, suggesting an increase in capillary surface area from dilatation and recruitment (Hughes et al., 1979). The blood flow to bone can also be altered by means of vasoactive drugs and it has been shown that noradrenaline increases the resistance in bone and reduces the flow, whilst ATP causes the reverse effect (McCarty et al., 1985).

With these facts available, it is possible to examine the penetration of antibiotics into bone. Clearly antibiotic penetration at capillary level is dependent on molecular size, protein binding, fat solubility, partition coefficients and the pH of the solution (Lunke, Fitzgerald & Washington, 1981) have shown by the use of outflow dilution techniques, that the antibiotic cefamandole enters bone. They have also measured the volume of distribution of cefamandole and demonstrated its presence in the interstitial fluid space. We have studied the extraction of cefazidime using outflow dilution techniques in the canine tibia and found that about 50% of the injected dose of the antibiotic was extracted into bone at normal flows (Hughes et al., 1984).

In a recent communication to the 13th International Congress of Chemotherapy, Larsson, Larsson & Holm (1983) examined the importance of capillary flow in antibiotic penetration and demonstrated the flow dependence of antibiotics in bone. This supports our previous study of flow dependence of solutes in bone (McCarty & Hughes, 1983) and indeed complies with Renkin's theory of transcapillary exchange (Renkin, 1968).

If the antibiotic is given locally in the bone cement as has been pioneered by Buchholz, it presumably diffuses out of the cement structure over a period of time. The antibiotic that is released is then potentially capable of diffusing across the bone substance, through the fluid spaces and this centrifugal movement of large molecules has been shown to occur in bone (Owen, Howlett & Triffitt, 1977). Whilst diffusion of smaller molecules such as ethylene diphosphonate in cortical bone has also been
osteomyelitis. Fitzgerald (1983) has developed an experimental model with subacute osteo-
cement. It is doubtful though that bone can be saturated with an antibiotic, any more than can any other tissue, as the principles of both flow and diffusion are important factors governing solute transport. Therefore antibiotics enter bone and the capillaries should become more permeable, a greater concentration of the antibiotic could reach bone over a given period of time. On the other hand in chronic osteomyelitis there is often a mechanical block to antibiotic penetration, in the form of dead bone or fibrous tissue membranes, although antibiotics have been assayed in pus in chronic osteomyelitis following systemic administration (Hughes, Nixon & Dash, 1981). It seems much more sensible that in chronic osteomyelitis, following adequate surgery, locally applied antibiotics are administered, particularly if incorporated into bone cement to allow a slow release of an antibiotic from cement. Fitzgerald (1983) has developed an experimental model with subacute osteomyelitis, to study just such a process. He found that though gentamicin impregnated Palacos® bone cement provided excellent protection from infection in contaminated wounds, it was not effective in the treatment of established osteomyelitis.

On the other hand Klemm (1976) constructed cement beads which contain gentamicin, specially for the treatment of patients with chronic osteomyelitis. The efficacy of these has been demonstrated, experimentally by Wahlig et al. (1978), in patients undergoing revision for infected total hip replacement by Josefsson, Lindbergh & Wiklander (1981) and in patients with established deep infection in a controlled trial who responded as well and were easier to manage than those treated with wound washouts (Hedstrom et al., 1980).

Following compound fractures, when in the initial stages, the bone blood flow is decreased, prior to its later rise, the bone vascular system is shut down and then the mineral extraction may be entirely flow dependent. In that case high dose antibiotics need to be given systemically for a period dependent on the severity and extent of the skin loss, and tissue damage, in order to reach the bone spaces. These processes of antibiotic penetration suppose that when the antibiotics reach the fluid spaces in bone it is here that they meet and destroy pathogenic organisms. This point and indeed others are areas that require further examination and research.

S. P. F. HUGHES, F. M. ANDERSON, Departments of Orthopaedic Surgery and Bacteriology, University of Edinburgh, Edinburgh, Scotland.

References


**Bacterial kinetic studies in infection**

It is well known that most patients with urinary tract infection respond rapidly to a fluid diuresis or a minimal dose of virtually any antimicrobial agent. There is an important minority of patients with chronic recurrent symptomatic infections who have persistent bacteriuria in spite of receiving an appropriate antibiotic. Investigation of such individuals may reveal an obvious focus of infection such as a renal calculus or an abnormal urinary tract, for example a large residual volume in the bladder. Some have no radiographic abnormality although all show abnormalities on scanning electron microscopy of bladder biopsies (Elliott, Slack & Bishop, 1984).

One non-invasive approach to the investigation of such patients is to observe their response to a