Elution and antibacterial activity of meropenem from implanted acrylic bone cement

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Sir,

Meropenem has good tissue penetration and broad-spectrum bactericidal activity. Often employed to treat multi-resistant Gram-negative organisms, meropenem was active against 98.7% of 1657 clinical surveillance Enterobacteriaceae isolates collected in the United States in 2005.[1] Its stability permits combination with polymethylmethacrylate (PMMA) bone cement. We present here the first published account of the use of meropenem-loaded PMMA in human prosthetic joint infection.

The patient, a 66 year-old with insulin-requiring type 2 diabetes, polymyalgia rheumatica (treated with 10mg prednisolone daily) and nodular prurigo, kindly gave written informed consent to publication. She was 170cm tall and weighed 102kg. She had had her left hip replaced for osteoarthritis at another institution in 1996. This prosthesis had functioned excellently for over 10 years before becoming unstable; cup revision in September 2006 was complicated by formation of an infected haematoma. The joint was replaced again in October 2006 and the patient put on a long antibiotic course. Recurrent dislocation led to further socket revision in July 2007. The patient was referred to our specialist hip revision service with continuing instability in late 2008. On 17th February 2009, both components were revised. Seven operative tissue specimens were sterile. Antibiotic prophylaxis was with 48 hours of vancomycin and gentamicin.

Post-operatively she developed a wound haematoma. The wound started to discharge and she returned to theatre on 10th March for a washout; the components were retained and the wound closed. Five of five tissue specimens grew *Klebsiella pneumoniae* susceptible to co-amoxiclav, cefotaxime, piptazobactam, carbapenems, ciprofloxacin, amikacin and trimethoprim, but resistant to amoxicillin and gentamicin. Intravenous co-amoxiclav 1.2g thrice daily was administered from 10th to 27th March, followed by oral co-amoxiclav 625mg thrice daily until 20th April.

Infection persisted, and extensive osteomyelitis developed in the proximal femur. A decision was made to proceed to one-stage revision. Both joint components and the proximal femur were replaced on 21st April. One of three acetabular specimens grew *K. pneumoniae* (susceptibilities as above), while two of three grew *Morganella morganii* susceptible to the cephalosporins, piptazobactam, carbapenems, ciprofloxacin, amikacin and gentamicin, and resistant to co-amoxiclav, colistin and trimethoprim. From 24th April through 12th May the patient received 1.2g co-amoxiclav intravenously thrice daily.

On 12th May, a large abscess connected superficial and deep tissues. This was washed out. The acetabular component was removed. 10g meropenem was crushed in a sterile vacuum mixing bowl (Optivac® Fusion™, Biomet, Bridgend); two 40g mixes of sterile orthopaedic bone cement (Palacos, Biomet; each mix containing 1.8g gentamicin and 1.8g clindamycin preloaded by the manufacturer) were added. The resulting cement was used to fix the replacement acetabular prosthesis. A third cement mix combined with 5g meropenem was used to coat the stem. Intravenous meropenem and amikacin and serial vac dressings were initiated. Samples of pus, fluid and hip tissue each grew scant *K. pneumoniae* susceptible to ciprofloxacin, cephalosporins, ertapenem and meropenem but resistant to co-amoxiclav, piptazobactam, gentamicin and amikacin.

On 13th May, drain fluid was collected. An ISO susceptibility test agar plate was seeded with the patient's *K. pneumoniae* isolate; a second plate was seeded with fully susceptible *Escherichia coli* strain ATCC 25922. 20µL of drain fluid was placed at the centre of each plate. Plates were incubated aerobically at 36°C for 18 hours. Inhibition zones suggested that antibacterial activity in the vicinity of the prosthesis was sufficient to inhibit growth of the patient's *K. pneumoniae* (and therefore also her more susceptible *M. morganii*).

An aliquot of 13th May drain fluid was sent to the UK Antimicrobial Reference Laboratory, Bristol, where its meropenem concentration was measured (by high performance liquid chromatography) at 73.5mg/L. Drug levels in pre- and post-meropenem-dose serum samples (also collected on 13th May) were considerably lower (9.3mg/L and 12.5mg/L respectively), suggesting that meropenem was eluting from the cement. The accepted meropenem susceptibility breakpoint is 4mg/L.[2]

The patient received intravenous meropenem 1g thrice daily until 30th July, with intravenous amikacin 1g daily for the first two postoperative weeks. By 30th July, she was well and mobilising, and was discharged home off antibiotics.

Antibiotic loading of PMMA is routine practice in joints with suspected or proven infection. The aim is to achieve high antibiotic levels at the site of infection while minimising systemic toxicity. The antibiotic used must be heat stable (since cement polymerisation is strongly exothermic) and water soluble (to allow diffusion from cement to tissues). The most common antibiotics used are gentamicin, vancomycin, and cefazolin, either alone or in combination.[3] Unfortunately, this patient's *Klebsiella* isolate was gentamicin-resistant, cefazolin is not available in the UK, and other cephalosporins are not heat stable. Previous studies have suggested that meropenem elutes from small PMMA discs *in vitro*,[4-5] but the present report is the first to provide useful *in vivo* data. Meropenem should be considered for inclusion in bone cement in patients with difficult-to-treat prosthetic joint infections.

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Transparency declarations

None to declare.

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