Thermal Stability of "End of the Line" Antibiotics When Used in Polymethylmethacrylate Bone Cement

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Purpose: "End of the line" antibiotics such as amikacin, meropenem, and minocycline are used systemically to treat multidrug-resistant gram-negative infections; however, their use in polymethylmethacrylate (PMMA) is not routine and has not been well documented. One barrier to inclusion of alternative antibiotics in PMMA is the high polymerization temperatures of this material. The purpose of this study is to quantify the thermal stability of selected antibiotics using clinically relevant PMMA bead and tibial spacer models.

Methods: Polymerization temperatures of Simplex PMMA were measured in a 1-cm custom bead mold and 8 × 5 × 3 cm tibial spacer (Stage One) model at 30-second intervals. Maximum temperatures for each time point were used to generate thermal profiles that were programmed into a thermocycler (C1000 Touch, Bio-Rad). Stock solutions of antibiotics were made (USP reference standards of Tobramycin, amikacin, meropenem trihydrate, and minocycline hydrochloride). Tobramycin validated the methodology given its known thermal stability. Each antibiotic solution was subjected to one of the 2 thermal profiles followed by immediate incubation at 37°C to mimic clinical implantation. Samples were removed from incubation at 8 time points across 28 days for testing of microbiologic activity. The minimum inhibitory concentration (MIC) of each antibiotic was evaluated against Escherichia coli (American Type Culture Collection 25922, Microbiologics Inc.) using a microbroth dilution assay in quadruplicate. MICs of temperature-exposed antibiotics were compared to those of stock solutions of antibiotics that had not undergone heating or incubation.

Results: The thermal conditions of the 1-cm bead and tibial spacer models did not alter the MICs for any antibiotics. Tobramycin and amikacin also showed minimal change in MIC over time when subjected to prolonged incubation at body temperature. The MIC of meropenem increased four-fold after 7 days of incubation and rose exponentially over the next 21 days. The antimicrobial activity of minocycline declined at 24 hours and by 7 days was higher than the testable range for the assay used.

Conclusion: Having appropriate options available for local therapy in the face of infection is of paramount importance. Amikacin retained antimicrobial activity over time when subjected to the thermal conditions of PMMA in the tested 1-cm bead and tibial spacer models. Amikacin (and perhaps meropenem) may be acceptable alternative antibiotics for local delivery in PMMA for the treatment of severe infections, especially gram-negative infections, that are resistant to currently used antibiotics. Further studies on the elution characteristics of these antibiotics from various PMMA models are also warranted.