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Generic Tobramycin Elutes From Bone Cement Faster Than Proprietary Tobramycin

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Abstract Elution of antibiotics from antibiotic-loaded polymethylmethacrylate (AL-PMMA) increases when soluble particulate filler is added to increase the permeability of the PMMA. Antibiotic powder is in itself soluble particulate filler. For greater volume fractions of filler, greater elution occurs. The volume of generic tobramycin powder is more than 3.5 times the volume of proprietary tobramycin powder for a 1.2 g dose leading to the question: Does generic tobramycin elute from AL-PMMA faster than proprietary tobramycin? We performed elution studies on AL-PMMA beads made with 1.2 g of either generic tobramycin or proprietary tobramycin per batch of PMMA. Generic tobramycin eluted more than two times faster than proprietary tobramycin. The release mechanism started as dissolution-driven zero-order release for the generic bead set but for the proprietary bead set the released mechanism started as anomalous diffusion. The release mechanism progressed to diffusion-driven first-order release in both. The increased volume of the generic tobramycin caused more tobramycin to be available for release. The increased elution of tobramycin associated with the greater volume of generic tobramycin powder could lead to clinically higher levels of tobramycin in wound fluid and local tissues; however, the higher volume of powder could potentially cause greater mechanical compromise of the PMMA.

Introduction

Elution of antibiotics from antibiotic-loaded polymethylmethacrylate (AL-PMMA) is enhanced by adding soluble particulate filler [3–7]. The antibiotic powder used to make AL-PMMA is in itself soluble filler. The permeability of the AL-PMMA will increase as the volume of antibiotic powder relative to the volume of PMMA polymer powder (volume fraction) increases [6, 7].

Several premixed AL-PMMA products including one containing 1 g tobramycin (Simplex P with tobramycin; Stryker Orthopaedics, Mahwah, NJ) have been approved by the FDA for use in revision arthroplasty fixation. The volume fraction of tobramycin in Simplex P with tobramycin is not disclosed. During physician-directed manufacture of AL-PMMA beads using proprietary and generic tobramycin, we observed (ACM) that 1.2 g of generic tobramycin powder has considerably greater volume for the same 1.2 g dose of proprietary tobramycin. The greater volume of powder per dose observed for the current generic brand of tobramycin compared with the volume per dose of proprietary tobramycin raised the question: Does generic tobramycin elute from AL-PMMA faster than proprietary tobramycin? This is important for both laboratory studies and for clinical performance.

We hypothesized that tobramycin elution from AL-PMMA made with 1.2 g of generic tobramycin is greater than tobramycin elution from AL-PMMA made with 1.2 g of proprietary tobramycin.

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Materials and Methods

We measured tobramycin eluted from AL-PMMA beads made with one of two tobramycin powders, either proprietary (Nebcin®; Lilly, Indianapolis, IN) or generic (Pharma-Tek, Huntington, NY) mixed in Palacos® PMMA (Biomet Inc, Warsaw, IN), 1.2 g per 40 g of polymer powder and 20 mL of monomer (1.2/61.2 = 1.96% w/w). The noncompressed volume of the antibiotic powders was measured in a graduated cylinder. The 1.2-g dose of proprietary tobramycin was approximately 3.5 cc. The 1.2-g dose of generic tobramycin powder was approximately 12.5 cc, 3.57 times (12.5/3.5) greater than the volume of the proprietary tobramycin (Fig. 1).

We mixed the tobramycin powder and the PMMA polymer homogeneously before adding the monomer in a bowl at atmospheric pressure. We made 7-mm diameter beads using a silicone mold with the AL-PMMA in the dough phase. We placed three groups of five AL-PMMA beads for both generic and proprietary tobramycin in 20 mL of deionized water. The total tobramycin load for the 15-bead set made with proprietary tobramycin was 75.1 mg and for the generic 15-bead set was 74.5 mg (calculated using the bead weight × weight fraction of tobramycin). We partially exchanged the fluid (5 of 20 mL) on Days 1–28, then on Days 30, 32, 34, 36, 42, 60, 90, 120, and 180. We assayed tobramycin concentration using ultraviolet spectrophotometry at $\lambda = 269$ ηm and calculated and plotted released tobramycin versus time. Total available tobramycin, the mass of drug released if elution was carried out until infinity (M_{inf}), was tallied and diffusion coefficients were calculated for each bead set at multiple timeframes.

We determined whether the cumulative recovered tobramycin elution from AL-PMMA made with 1.2 g of generic tobramycin was greater than tobramycin elution from AL-PMMA made with 1.2 g of proprietary tobramycin using repeated-measures analysis of variance (ANOVA); we confirmed the data was normally distributed using the Kolmogorov-Smirnov test. The level of significance was set at 0.05.

Fig. 1 A comparison of Nebcin (Lilly, Indianapolis, IN) on the left and generic tobramycin on the right illustrates the difference in volume for the same 1.2 g dose. The generic tobramycin volume is approximately 3.5 times greater than the volume of the proprietary tobramycin.

Results

Generic tobramycin eluted from AL-PMMA faster ($p < 0.000006$) than proprietary tobramycin by two times or more at all time periods (Fig. 2). The cumulative mass of released tobramycin released by time t (M_t) was 0.35 mg at 1 day, 1.83 mg at 5 days, and 3.21 mg at 10 days for proprietary tobramycin; and 0.70 mg at 1 day, 3.98 mg at 5 days, and 7.05 mg at 10 days for generic tobramycin. Between 90 and 120 days, progressively less was released until all of the available tobramycin was released. No measurable elution occurred after 120 days. For the bead set made with generic tobramycin, M_{inf} was 15.14 mg representing 20.33% (15.14/74.5) of the total tobramycin contained in the PMMA. For the bead set made with proprietary tobramycin, M_{inf} was 6.35 mg, representing 8.46% (6.35/75.1) of the total tobramycin contained in the PMMA. The ratio of released tobramycin (M_t) to available tobramycin (M_{inf}) as a function of time was similar for both bead sets (Fig. 3). The coefficient of diffusion (n) derived from $M_t = k\, t_n$ is the slope of the log-log plot of M_t/M_{inf} as a function of time (t) (Fig. 4). Initially, the coefficient of diffusion was near 1 for the generic bead set consistent with dissolution dominating the release process (Fig. 5).

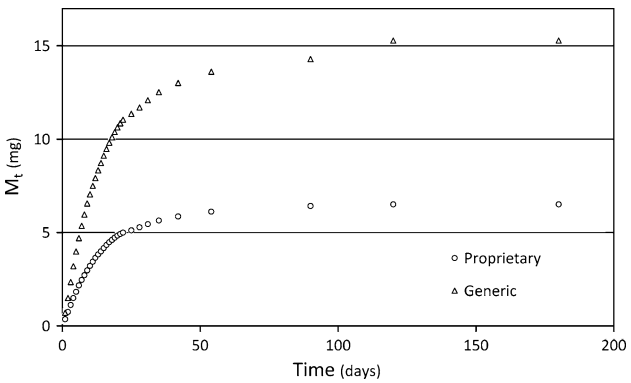

Fig. 2 Cumulative tobramycin release as a function of time showing the release pattern of tobramycin from antibiotic-loaded polymethylmethacrylate. Beads made with generic tobramycin elute more than twice as fast as beads made with proprietary tobramycin.

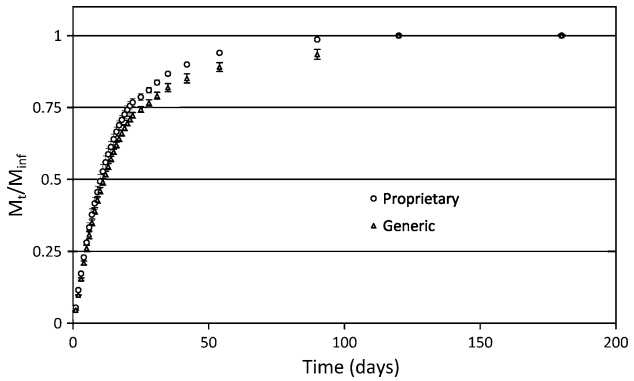

Fig. 3 Tobramycin release ratio showing the ratio of released tobramycin mass (M_t) at time (t) over the total tobramycin available for release (M_{inf}) as a function of time. The ratio for the generic bead set is similar to the proprietary bread set suggesting the mechanisms of release are similar for both.

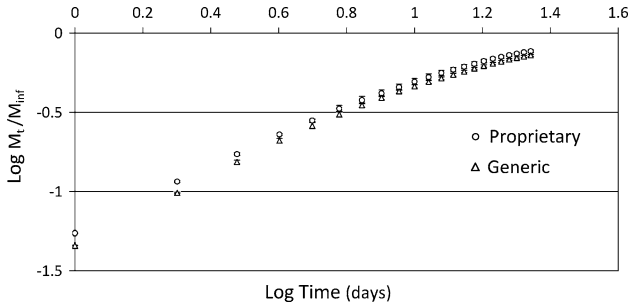

Fig. 4 Log of tobramycin release ratio as a function of the log of time. The slope of this log-log plot is the coefficient of diffusion (n) used in Fig. 5. The slope is similar for the two bead sets and it decreases with time.

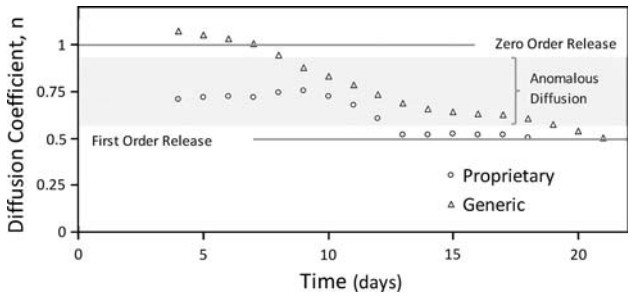

Fig. 5 The coefficient of diffusion (n) from $M_t = kt_n$ as a function of time. The coefficient of diffusion (n) indicates the dominant release mechanism. The plotted values are a 5-day moving average not including Day 1 [2]. When $n = 1$, release is dominated by dissolution of the particulate tobramycin directly into the eluent (zero-order release, constant rate). When $n = 0.5$, release is dominated by diffusion of tobramycin from deep in the pore system (first-order release, rate is dependent on the amount of remaining tobramycin). Between 0.5 and 1, the release mechanism is termed anomalous diffusion, a combination of dissolution and diffusion. During the first 9 days, dissolution appeared more dominant in the generic bead set than the proprietary bead set. Subsequently, the release mechanisms appear similar as anomalous diffusion transitions to diffusion in both.

The proprietary bead set started with a coefficient of diffusion less than one but greater than 0.5, consistent with combined dissolution and diffusion (anomalous diffusion). Diffusion became more important as more tobramycin was released over time until it dominated the release mechanism with a diffusion coefficient near 0.5 by 13 days for the proprietary bead set and by 20 days for the generic bead set.

Discussion

The amount of antibiotic in AL-PMMA is traditionally measured by weight, but volume fraction is the determinant for permeability [5]. The observation that 1.2 g of tobramycin by different manufacturers has markedly different volume raised the question: Is there a difference in the elution of tobramycin from AL-PMMA beads made from two tobramycin powders of the same weight but of differing volume? The orthopaedic literature does not document elution variance dependent on manufacturer of the antibiotic or volume of the antibiotic.

There are several weaknesses of this study. We assumed homogeneity of the tobramycin in the AL-PMMA beads. Previous permeability studies suggest the homogeneity of particulate filler mixed in PMMA polymer using this mixing protocol is good, even for 1 g of filler [7]. Both the generic bead set and the proprietary bead set had three five-bead groups leading to release data that were an average of the five beads in the eluent, thereby minimizing any effect from lack of homogeneity. The two doses of tobramycin used in this study are only single data points for the volume of a 1.2 g dose of tobramycin by each manufacturer. Although there may be variance in the volume of drug per 1.2 g dose by each manufacturer, the appearance was typical by experience (ACM) and the conclusions would not change if these data were at either extreme of the possible volume variance. Ultraviolet spectrophotometry is a very efficient way to assay tobramycin with a clear absorption spike at 269 ηm. Elution of substances other than tobramycin from the AL-PMMA beads causes background noise, limiting the sensitivity for very low concentrations (< 0.01 μg/mL). To accommodate this potential error, the duration of elution between assays was increased until the concentration was above measurement sensitivity. Eventually the concentration of tobramycin in the eluent cannot increase above the sensitivity level, as in the last 60-day interval for this study. The resulting unmeasured mass of available tobramycin leads to an insignificant underestimation of M_{inf}, even considering it is well known that aminoglycoside elution from PMMA is detectable at low levels for years [8]. This very long-term drug release is probably diffusing through the PMMA

matrix rather than from the pores of the beads. Although the release of tobramycin from the beads made with generic tobramycin is more than twice as fast as from beads made with proprietary tobramycin (Fig. 2), the underlying mechanisms lead to similar ratios of released tobramycin to available tobramycin, M_t/M_{inf} (Fig. 3). The apparent release pattern seen in this investigation (Fig. 2) is similar to that seen in all AL-PMMA elution studies consistent with first-order release (rate dependent on the amount of drug available for release); however, determination of the coefficient of diffusion (n) reveals there are two mechanisms at play with a smooth transition from one to the other that is not obvious from the raw data. Initially, for the generic bead set, the diffusion coefficient (n) is approximately 1. $n = 1$ is associated with a constant rate of release dominated by dissolution (zero-order release) (Fig. 5). This occurs when there is sufficient particulate tobramycin available for dissolution to maintain a saturated solution throughout the pores of the PMMA. Tobramycin is released from the pores into the eluent at a constant rate. As the particulate tobramycin dissolves, the site of dissolution becomes progressively deeper into the pores. The solution in the pores remains saturated and the release of tobramycin from the pores remains constant until the amount of particulate tobramycin decreases to the point that there is not enough left to maintain a saturated solution throughout the pores. Tobramycin concentration in the pores decreases proportionally to the amount of available drug remaining controlled by diffusion of tobramycin through the pores (first-order release, $n = 0.5$) (Fig. 5). When the diffusion coefficient (n) is between 1 and 0.5, the release mechanism is driven by both dissolution and diffusion (anomalous diffusion) [2]. The beads made from generic tobramycin initially had enough tobramycin available for dissolution to dominate release into the eluent (Fig. 5). By Day 9, as progressively more tobramycin was released, the mechanism became anomalous diffusion. The beads made from proprietary tobramycin did not have enough particulate tobramycin or the dissolution rate of the denser antibiotic particles caused the diffusion process to occur on the same time scale as the dissolution processes leading to anomalous release rather than constant zero-order release. Release of tobramycin continued by anomalous diffusion for several days until release of tobramycin from both bead sets became first-order release, essentially all by diffusion, after particulates were fully dissolved and release was driven purely by diffusion.

Both bead sets had the same drug load and both bead sets had the same fundamental release mechanics, ie, dissolution when there is drug available for direct dissolution into the surrounding eluent, progressing continuously to a combination of dissolution and diffusion, ultimately to release completely by diffusion when the available drug for release is deep in the pore system. The faster release of tobramycin from the generic bead set measured in our study is most likely the result of more of the tobramycin being available for release through a more effective pore system, greater permeability, and faster diffusion. The proprietary tobramycin is made up of smaller, more compact particles, leading to smaller pores with less interconnections and more PMMA between closed pores. More tobramycin is isolated deep in the substance of the PMMA and unavailable for dissolution and diffusion. The generic tobramycin is made up of less compact particles leading to more pore interconnections, greater permeability, and more drug available to the surrounding eluent, thereby causing greater release. The higher surface area of the less compact particles also leads to faster dissolution of the generic drug compared with the proprietary drug. The higher volume per 1.2 g of generic tobramycin compared with the volume of 1.2 g of proprietary tobramycin does lead to a greater elution of tobramycin from AL-PMMA, consistent with the expected permeability increase [6]. Increased elution of the contained antibiotic is desirable clinically to control local bacteria, but that comes at the cost of potentially greater degradation of material properties associated with increased porosity.

Structural properties of the beads were not tested. The relative degradation in mechanical performance is important because this dose of antibiotic is only reasonable for use as prophylaxis in fixation of implants. This dose is never sufficient to use as a depot in the treatment phase for orthopaedic infections, in which mechanical properties are less important. Data on material properties of AL-PMMA using the same generic tobramycin have been reported showing a 36% decrease in strength [1]. That degradation in strength was attributed to hand mixing failing to take into consideration the relative volume of the antibiotic powders [1]. The dose of tobramycin we used is slightly (but we believe unimportantly) greater than the dose approved by the FDA for revision arthroplasty. The volume variance in the tobramycin powders used in this study has the potential to effect structural performance of the AL-PMMA, dependent on brand or volume of tobramycin used for physician-directed applications.

Generic tobramycin sulfate elutes from AL-PMMA more than two times faster than proprietary tobramycin.

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