Leaching of tobramycin from PMMA bone cement beads

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The in vitro leaching characteristics of tobramycin from acrylic resin (PMMA) bone cement beads have been determined by a radioimmune assay. Tobramycin was incorporated at two concentrations into bone cement beads fabricated from three commercial brands of acrylic resin. Antibiotic leaching followed a curvilinear relationship of the form $X \cdot Y = A \cdot X + B \cdot Y$. All beads showed similar tobramycin leaching rates over time but the initial amount of leached material differed with the amount of tobramycin incorporated in the bead and the source of the PMMA bone cement. The data indicate that tobramycin-impregnated PMMA beads permit antibiotic leaching at a controlled rate compatible with possible clinical application.

INTRODUCTION

Implantation of acrylic resin (PMMA) bone cement beads impregnated with an antibiotic, such as gentamycin or tobramycin, has been suggested as a local method of preventing and treating bone and soft-tissue infections.[1,2] The advantage of this approach to drug delivery is that very high local concentrations of an antibiotic can be obtained with minimal systemic levels.[3–6] The drug carrier system must be stable, nontoxic, easily fabricated, and of sufficient strength to permit easy insertion and removal from the surgical site. When fabricated in bead form and strung on a fine stainless-steel wire, acrylic resin bone cement is a suitable carrier. Furthermore, the antibiotic powder can be admixed with the resin powder before adding the liquid monomer for making the cement. Antibiotics selected for this purpose must have bacteriostatic or bactericidal activity toward the target organisms and must also have sufficient thermal stability to prevent their degradation during the curing reaction of the cement. Liquid antibiotics may also be used provided they are miscible with the methylmethacrylate monomer.

The aminoglycoside tobramycin possesses broad-spectrum activity against gram-negative and some gram-positive organisms and has good thermal stability. This study was undertaken to determine the in vitro rate of release of tobramycin from PMMA bone cement beads.

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MATERIALS AND METHODS

Using the manufacturers' recommended powder/monomer ratio of 40 g/20 ml, three brands of PMMA bone cement were mixed with two levels of tobramycin, a low level (LL) of 1.2 g and a high level (HL) of 2.4 g/40 g of cement powder. The cements used in this study are detailed in Table I. After thorough mixing of the tobramycin and cement powders, the monomer was added and the dough packed into a Teflon-coated bullet mold around 1.2 mm diameter stainless-steel wire. This produced strings of 6 mm diameter PMMA beads containing 1.2 mg (LL) and 2.4 mg (HL) tobramycin per bead.

The beads were immersed continuously in 2.0 ml aliquots of distilled water in tubes over 24 h for periods of up to 12 days. Every 24 h, the solution was removed from the tube and replaced by fresh distilled water. Each 2-ml aliquot was assayed for its tobramycin content using a commercial radioimmunoassay procedure (American Diagnostics, Ames Laboratories). All studies were performed in triplicate for the three types of bone cement at the two antibiotic levels.

RESULTS

Radioimmunoassay measurements of the tobramycin leached from the PMMA bone cement beads gave the solution levels summarized in Table II. The recorded levels were within 10% of each other for all cement beads; consequently only the mean values are presented here to simplify the tabulated data. It was found that the amounts of tobramycin leached from the six bead systems was in the order: cement 1 (HL) > cement 3 (HL) > cement 2 (HL) > cement 1 (LL) > cement 3 (LL) > cement 2 (LL).

Examination of the elution-time behavior using classic curve-fitting techniques, namely log-log plots, did not indicate adherence to a standard mathematical relationship but rather to a curvilinear relationship of the type:[7]

$$X \cdot Y = A \cdot X + B \cdot Y \quad \text{or} \quad Y = A + B(Y/X) \tag{1}$$

where X is time in days and Y is eluted tobramycin, A and B being constants.

TABLE I
Polymethylmethacrylate Resin Bone Cements

Cement	Manufacturer	Composition of powder *
1	E. Merck, Darmstadt, and Kulzer GmbH, Werheim	Methylmethacrylate–methacrylate copolymer + zirconium oxide
2	Howmedica Inc., Rutherford, NJ	Polymethylmethacrylate, methylmethacrylate–styrene copolymer mixture + barium sulfate
3	Zimmer Company, Warsaw, IN	Polymethylmethacrylate + barium sulfate.

* All cement powders mixed with methylmethacrylate monomer.

TABLE II
Observed and Estimated Tobramycin Leaching Levels (μg/ml)

	Cement 1				Cement 2				Cement 3			
	Low level		High level		Low level		High level		Low level		High level	
Day	Obs.	Est.	Obs.	Est.	Obs.	Est.	Obs.	Est.	Obs.	Est.	Obs.	Est.
1	133	140	424	439	79.4	78.3	240	249	118	129	214	232
2	11.8	13.4	62	49.7	11.5	6.0	30	19.1	6.2	7.5	14	34.5
3	10.8	10.3	50	38.4	6.8	4.6	23.2	14.6	5.6	5.7	38	26.8
4	6.6	9.2	44	34.4	6.2	4.1	21.0	13.1	4.0	5.1	34.6	24.2
5	11.0	8.7	46	32.5	4.6	3.9	12.0	12.3	5.0	4.8	48	22.8
6	12.6	8.3	44	31.2	3.6	3.7	13.0	11.8	4.4	4.6	25.0	22.0
7	12.0	8.0	44	30.4	3.7	3.6	10.2	11.5	9.0	4.5	16.0	21.4
8	7.4	8.0	25.4	29.9	2.6	3.6	9.3	11.3	4.4	4.4	18.6	21.0
9	5.4	7.8	25	29.4	3.1	3.5	8.5	11.1	3.0	4.3	14.8	20.7
10	4.8	7.8	16	29.1	2.2	3.5	6.5	11.0	6.0	4.3	14.8	20.5
11	5.8	7.7	14.4	28.8	1.5	3.4	7.3	10.9	2.0	4.3	12.2	20.3
12	7.4	7.6	12.8	28.6	1.2	3.4	5.4	10.8	3.2	4.2	13.0	20.2

Accordingly, a plot of leached tobramycin against (leached tobramycin)/(time in days) gives a straight line of slope equal to constant B and an intercept on the Y-axis equal to constant A. The derived values of A and B are given in Table III.

Equation (1) can be rewritten in the form:

$$Y = (A \cdot X)/(X - B)$$

or

$$\text{Leached tobramycin} = [A(\text{time in days})]/[(\text{time in days}) - B] \quad (2)$$

Values of the leached tobramycin calculated using Eq. (2) are given in Table II. Comparison of the observed and estimated levels of leached tobramycin, Table IV, using the Chi-square test showed no statistically significant difference ($p > 0.05$) between these totals.

DISCUSSION

The data presented here indicate that the value of constant B is virtually identical for the three PMMA beads at both tobramycin levels, Table III. This suggests from Eq. (2) that the rate of tobramycin leaching was similar for all three bead systems over the test period of 22 days. It also follows that the amount of tobramycin leached from the beads upon initial immersion is large since the denominator in Eq. (2) is close to zero at time values of <1 day. This suggests that constant B is determined by the solubility of the leached entity, tobramycin.

TABLE III
Values of Constants A and B in Leached Tobramycin = (A [time])/([time] − B)

Cement	Tobramycin addition	Constant A	Constant B
1	Low level	7.02	0.95
	High level	26.35	0.94
2	Low level	3.13	0.96
	High level	9.94	0.96
3	Low level	3.88	0.97
	High level	18.61	0.92

TABLE IV
Estimated and Observed Total Leached Tobramycin

	Cement 1		Cement 2		Cement 3	
Addition level	Low	High	Low	High	Low	High
Estimated	236.8	801.4	121.6	386.1	178.5	486.4
Observed	228.6	807.6	126.3	386.5	170.8	468.0
Difference*	8.2	−6.2	−4.7	−0.4	7.7	18.4

* Difference is nonsignificant using the Chi-squared test.

The six systems studied here differ in the value of the constant A and this suggests that this constant is determined by the characteristics of the PMMA used to fabricate the beads and the level of tobramycin incorporation within the beads.

Elution of the gentamycin from PMMA beads in vitro has been previously reported,[3,8,10–12] leaching occurring at a diffusion-controlled rate with the rate being dependent on the type of acrylic resin used, the level of antibiotic incorporation, and the bead surface area.[8] The detailed kinetics, however, were not reported.

CONCLUSIONS

The values of constant A and B in Eq. (2) have clinical significance, constant B is time related while constant A is dependent on the amount of leachable tobramycin and the permeability characteristics of the bead. The near-uniform value of constant B for all beads indicates that the leach rate of antibiotic is virtually the same for all beads. This would be anticipated from the fact that the rate-limiting factor in leaching is the solubility of tobramycin.

The value of constant A is determined by leachability of tobramycin from the beads, this being a function of the level of tobramycin incorporation and its accessibility within the beads. The drug accessibility is determined by the bead porosity and the surface rugosity, greater porosity and roughness permitting more effective inward diffusion of the eluent water. The greater the value of constant A, the more tobramycin is leached from the bead.

There is mounting experimental evidence[11,12] and clinical experience[13,14] that locally placed antibiotics are effective in preventing and curing bone and soft-tissue infection. Understanding the pharmacology of these new drug delivery vehicles is important in improving their effectiveness.

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