Elution profiles of a synthetic $CaSO_4$ pellet loaded with vancomycin and tobramycin

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Abstract

Local antibiotic delivery vehicles have long been popularized for the management of biofilm related infections. The rationale of such vehicles is to provide high concentrations of local antibiotics while simultaneously avoiding renal toxicity. Presented is a 100% pure synthetic calcium sulfate hemi-hydrate precipitate, Stimulan (Biocomposites, Keele Science Park, Staffordshire, United Kingdom), impregnated with 240 mg tobramycin and 500 mg vancomycin per 10 g mixture. This vehicle is bioabsorbable, promotes bone growth, has a physiologic pH, and is hydrophilic. We assayed the elution of antibiotic levels obtained from serum and davol drains among 50 patients in the 5 postoperative days. The elution of vancomycin and tobramycin was greatest on day 1 than that demonstrated on days 2, 3, 4, and 5; serum levels were largely undetectable. Our findings demonstrate that this calcium sulfate preparation provides adequate therapeutic delivery of vancomycin and tobramycin while avoiding dangerous serum levels.

Introduction

Chronic infection is the bane of all orthopedic surgeons. To combat such a complication, antibiotic carriers have been used as an adjunct in surgical protocols. The object of such local delivery mechanisms is to provide for the elution of antibiotics exceeding the minimum inhibitory concentrations (MIC) of the most notorious infecting pathogens. Currently, antibiotic-impregnated polymethylmethacrylate (PMMA) is the “gold standard” of therapy in two-stage surgical management of infected total joints. Unfortunately PMMA is not bioabsorbable. PMMA necessitates additional surgery for removal, thus rendering it inadequate as a physiologic construct in one-stage treatment of osteomyelitis while also potentiating bacterial surface adhesion and possible secondary infection. Additionally, PMMA has been associated with sustained antibiotic serum levels resulting in allergic reactions. As an alternative, gypsum-mined calcium sulfate pellets have gained popularity as a reabsorbing carrier capable of providing potent dosages of antibiotics without the need for further surgical intervention. The problem with these calcium sulfate preparations, however, stems from their naturally acidic pH, toxic impurities, and hydrophobicity; three characteristics shown to result in persistent postoperative wound drainage.

This study examines elution profiles of a unique calcium sulfate preparation with physical properties in contrast to the less pure aforementioned modality: a 100% pure synthetic calcium sulfate hemi-hydrate precipitate impregnated with 500 mg vancomycin and 240 mg tobramycin per 10 g mixture. The Stimulan pellet distinguishes itself through its higher purity, physiologic pH, and hydrophilic properties.

This crystal becomes soft after hydration, does not scratch periprosthetic components, and has shown complete dissolution within 2-3 weeks as demonstrated by radiographic lucency. Tobramycin and vancomcyin were selected for incorporation into this pellet based on their gram-negative and gram-positive microbial coverage. The concentrations chosen were based on optimal hardening of the calcium sulfate.

Materials & Methods

Stimulan was combined with vancomycin and tobramycin intraoperatively. Upon completion of surgical debridement and implantation of periprosthetic components, the calcium sulfate pellets were applied to the wound so as to provide filling of the void. In the five postoperative days, serum and Davol drain samples were assayed to evaluate the eluting properties of the Stimulan carrier impregnated with vancomycin and tobramycin. …….

Results

50 patients undergoing revision arthroplasty for infected total joints or major multiple revisions were analyzed. Cases include 33 knees (1 bilateral), 15 hips, 1 elbow, and 1 shoulder. Average patient age was 61 years composed of 22 females and 28 males.

Mean Local Antibiotic Levels		
Postoperative Day	Vancomycin (µg/mL)	Tobramycin (µg/mL)
1	265	31
2	172	9.4
3	146	6.4
4	146	5.3
5	104	4.6

Table 1. *Assayable* antibiotic levels obtained from Davol drains in postoperative days 1-5.

The average antibiotic levels obtained from Davol drains represent only those instances where antibiotic concentrations were assayable. In majority of cases on days 1 and 2, vancomycin and tobramycin concentrations exceeded the maximum assayable limit of 400 µg/mL and 20 µg/mL, respectively. As a result, the mean concentrations are lower than actual. However, the values listed are still representative of high initial concentrations with subsequent tapering off in the following days. Serum levels of vancomycin and tobramycin demonstrated concentrations below the minimum assayable values of 2.0 µg/mL and 0.5 µg/mL, respectively. This held true for all but 6 patients. In each case, the serum concentrations were low enough and for short enough duration that the consequence of systemic toxicity was not a concern.

Table 2. Serum levels of vancomycin and tobramycin in postoperative days 1-5.

Serum Antibiotic Levels (µg/mL)										
Pt. ID #	**DAY 1**		**DAY 2**		**DAY 3**		**DAY 4**		**DAY 5**	
	VANC	**TOBRA**	**VANC**	**TOBRA**	**VANC**	**TOBRA**	**VANC**	**TOBRA**	**VANC**	**TOBRA**
01	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
02	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
03	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
04	2.4	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
05	<2.0	0.7	<2.0	0.7	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
06	2.5	0.7	2.4	<0.5	2.0	<0.5	<2.0	<0.5	<2.0	<0.5
07	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
08	2.6	1.8	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
09	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
10	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
11	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
12	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
13	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
14	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
15	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
16	3.1	1.1	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
17	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
18	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
19	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
20	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
21	2.2	0.9	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
22	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
23	3.7	4.1	3.3	1.5	3.0	<0.5	2.5	<0.5	<2.0	<0.5
24	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
25	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
26	<2.0	0.6	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
27	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
28	<2.0	2.1	<2.0	0.8	<2.0	0.6	<2.0	<0.5	<2.0	<0.5
29	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
30	<2.0	0.7	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
31	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
32	<2.0	1.7	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
33	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
34	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
35	<2.0	1.7	<2.0	0.7	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
36	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
37	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
38	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
39	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
40	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
41	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
42	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
43	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
44	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
45	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
46	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
47	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
48	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
49	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
50	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5

Conclusion

The ability to adequately combat chronic infection is enhanced when proper surgical debridement and exchange of periprosthetic components is combined with a local antibiotic delivery vehicle capable of eluting potent concentrations of antibiotics. Due to the tenacity of sessile biofilm matrices, able to elude destruction of parenterally administered antibiotics, a cocktail of tobramycin and vancomycin is indicated to account for eradication of heterogenous colonies. Based on our results and clinical experience, the Stimulan pellet proves to be a high-quality platform for the local delivery of antibiotics as well as a stable vehicle for incorporation of both vancomycin and tobramycin.