Orthopaedic bone cement

DO WE KNOW WHAT WE ARE USING?

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Bone cements produced by different manufacturers vary in their mechanical properties and antibiotic elution characteristics. Small changes in the formulation of a bone cement, which may not be apparent to surgeons, can also affect these properties. The supplier of Palacos bone cement with added gentamicin changed in 2005. We carried out a study to examine the mechanical characteristics and antibiotic elution of Schering-Plough Palacos, Heraeus Palacos and Depuy CMW Smartset bone cements.

Both Heraeus Palacos and Smartset bone cements performed significantly better than Schering-Plough Palacos in terms of mechanical characteristics, with and without additional vancomycin (p < 0.001). All cements show a deterioration in flexural strength with increasing addition of vancomycin, albeit staying above ISO minimum levels. Both Heraeus Palacos and Smartset elute significantly more gentamicin cumulatively than Schering-Plough Palacos. Smartset elutes significantly more vancomycin cumulatively than Heraeus Palacos.

The improved antibiotic elution characteristics of Smartset and Heraeus Palacos are not associated with a deterioration in mechanical properties. Although marketed as the ‘original’ Palacos, Heraeus Palacos has significantly altered mechanical and antibiotic elution characteristics compared with the most commonly-used previous version.

Palacos R40G (Schering Plough, Welwyn Garden City, United Kingdom) was the most commonly recorded brand of polymethylmethacrylate (PMMA) bone cement used during arthroplasty in England and Wales in 2005.1 Palacos R40G (hereafter referred to as Schering-Plough Palacos) had a market share of 62%, compared with the next most commonly-used types; CMW Antibiotic Loaded Cement (14%) (Depuy CMW, Blackpool, United Kingdom) and Biomet Palacos (Biomet UK Ltd, Bridgend, United Kingdom) (13%).1 In 2005 Palacos PMMA sold by Biomet and Schering-Plough was removed from the market and replaced by Palacos R + G produced by Heraeus Medical (Newbury, United Kingdom) (hereafter referred to as Heraeus Palacos). All these brands contain gentamicin.

The use of antibiotic-loaded bone cement in primary hip arthroplasty lowers the risk of subsequent revision.2,3 In revision hip and knee replacement surgery additional antibiotics are commonly added to PMMA, either as a depot of antibiotic in the form of a spacer or beads, or when cementing the definitive prosthesis.4,5 Gentamicin is the most commonly-added antibiotic, as it has a broad antibacterial spectrum relevant to joint replacement and elutes from PMMA.6 However, not all organisms associated with prosthetic infection will be gentamicin sensitive, and some strains of methicillin-resistant Staphylococcus aureus (MRSA) are also gentamicin resistant. Vancomycin can be used in these circumstances.

Systemic vancomycin therapy has a narrow therapeutic range and potential toxicity. The addition of vancomycin to PMMA may avoid the need for prolonged systemic therapy and has been shown to be efficacious.7,8 The volume of additional antibiotics needs to be carefully assessed, as too much may significantly reduce the mechanical properties of the cement.9,10 Smartset GHV, PMMA (Depuy CMW) has been available since August 2003. It contains twice as much pre-mixed gentamicin (1 g) in situ as either Schering-Plough Palacos (0.5 g) or Heraeus Palacos (0.5 g) per 40 g mix. It is also claimed by the manufacturers to have improved handling characteristics. We felt that it might be advantageous in revision surgery in view of its anticipated higher elution of gentamicin. We initially intended to compare the antibiotic elution and mechanical characteristics of Schering-Plough Palacos and Depuy CMW Smartset
Elution testing. Vancomycin was chosen as it is used frequently in our revision arthroplasty practice. Prior to adding the monomer, 40 g mix of vancomycin and 2 g vancomycin. The vancomycin (Alpharma Ltd, Barnstaple, United Kingdom) was mixed into the cement body environment with constant humidity of 53% and temperature of 21°C. The PMMA was mixed using a Depuy CEMVAC vacuum mixing device (Depuy, Leeds, United Kingdom), as is standard practice in our unit. The cement was extruded into the syringe nozzle and allowed to set. Lengths of 4 cm were then cut from the nozzle, producing three samples per mix. Two samples were then chosen for analysis on the basis of lack of any obvious defects. For each cement type and antibiotic combination two mixes were prepared to provide a total of four samples. Each sample was placed into a separate glass bottle containing 100 ml phosphate-buffered saline (PBS), which was then incubated aerobically at 37°C. At specified time intervals, as shown in Figure 1, 1 ml of the PBS solution was removed from each container and placed into a plastic Sarstedt vial (Sarstedt Ltd, Leicester, United Kingdom). These were immediately frozen at -20°C. The cement pellets were washed in fresh PBS, blotted dry, and placed into clean universal containers containing 20 ml PBS. These were then re-incubated until the next specified time interval, when the procedure was repeated. At the end of the testing period, all samples were removed from the freezer and allowed to reach room temperature. Each sample was then tested to measure the concentration of vancomycin (and gentamicin if appropriate) using Fluorescence Polarisation Immunoassay (Bio-stat Healthcare Group, Stockport, United Kingdom). This is a competitive immunoassay, based on test samples competing with fluorescein-labelled antibiotic (in the reagent pack) for the limited number of antibody sites. The greater the final fluorescence, the more labelled antibiotic has attached, indicating a lower concentration of the antibiotic under investigation in the test sample. Standardised internal controls were run as test samples to confirm the accuracy of each batch of samples tested.

Mechanical testing. Each cement was mechanically tested according to ISO 5833:200211 to examine the compressive strength, elastic strength and elastic modulus. An Instron 5366 machine (Instron, High Wycombe, United Kingdom) was used and tests were carried out at 23°C according to ISO standards. A total of 18 samples which were separately obtained were tested for each combination of cement and antibiotic, equating to three runs of the standard ISO tests (six samples per run).

Statistical analysis. The data were normally distributed and parametric tests were used. For the elution data the total antibiotic release (the area under the curve) was compared using a two-tailed t-test. Univariate analysis (one-way analysis of variance (ANOVA)) was used to compare the mechanical data, to see whether there were any significant differences in mechanical properties, due either to the type of cement or the quantity of antibiotic added. Post hoc individual comparisons between two cements were made with a two-tailed t-test. Significance was assumed at a level of p < 0.05. Statistical analysis was undertaken according to the advice from the University of Sheffield Statistical Services Unit.

Results

Elution. Both Smartset and Heraeus Palacos eluted significantly more gentamicin in total than did Schering-Plough Palacos. For Smartset this was statistically significant in the native form (t-test, p = 0.009) and with 2 g added vancomycin (t-test, p = 0.02) and for Heraeus Palacos in the native form (t-test, p = 0.006) and with 1 g (t-test, p = 0.008) and 2 g added vancomycin (t-test, p = 0.0003) (Table I). All the cements showed a synergistic effect of increased gentamicin elution with increasing vancomycin addition. Smartset eluted significantly more total vancomycin than Heraeus Palacos with the addition of 1 g (t-test,
p = 0.02) and 2 g vancomycin (t-test, p = 0.02) (Table II). Figures 1 and 2 illustrate the mean rate of gentamicin and vancomycin elution from each cement combination. For clarity, not all cement and antibiotic combinations have been included and the x axis (time) has been logarithmically transformed. It can be seen with all cements that there is an initial rapid release of antibiotic, followed by a rapid decrease within the first hour.

**Mechanical properties.** All the cements remained above the ISO minimum standards for compressive strength, flexural strength and flexural modulus with the addition of either 1 g or 2 g of vancomycin. For all mechanical properties tested there were significant differences depending on cement type and quantity of antibiotic added (ANOVA, p < 0.001).

**Compressive strength.** As shown in Table III, both Smartset and Heraeus Palacos performed significantly better than Schering-Plough Palacos with all levels of antibiotic addition (all t-test, p < 0.01).

**Flexural strength.** All cements showed a deterioration in flexural strength with increasing quantity of vancomycin added (Table IV) (ANOVA, p < 0.01). Smartset has a significantly higher flexural strength than the other two cements with no additional antibiotics and the addition of 1 g vancomycin (p t-test, < 0.01). There is no difference with the addition of 2 g vancomycin.

**Flexural modulus.** Smartset and Heraeus Palacos performed significantly better than Schering-Plough Palacos with all levels of antibiotic addition (Table V) (ANOVA, p < 0.01). All cements showed a deterioration in flexural modulus with increasing addition of vancomycin (ANOVA, p < 0.01). Smartset had a significantly higher flexural modulus than Heraeus Palacos with the addition of no additional antibiotics and 1 g vancomycin (ANOVA, p < 0.01).

**Discussion**

Our study has shown that Smartset elutes more gentamicin and vancomycin than the two forms of Palacos tested. The increased gentamicin elution reflects the higher content of gentamicin in the product at manufacture. This increase in pre-mixed gentamicin concentration is not associated with a deterioration in its mechanical properties compared with the two other cements tested. With the addition of 2 g vancomycin the mechanical properties of all the cements still exceeded minimum ISO standards.

As noted by other authors, there is a synergistic effect with the addition of vancomycin, leading to increased gentamicin elution in all cements.12,13

As far as we are aware, there are no published clinical studies on Smartset bone cement but there are other studies examining its properties in vitro. Simpson et al12 have compared the in vitro antibiotic elution and mechanical properties of Smartset and Refobacin Palacos (also known as Biomet Palacos) both without pre-mixed gentamicin. In
their study they added gentamicin and vancomycin to the cements and looked at antibiotic elution and mechanical properties. They concluded that Refobacin Palacos demonstrated better gentamicin elution characteristics. They also found some advantage to Refobacin Palacos in terms of mechanical properties, but only with certain antibiotic combinations. A direct comparison with our results cannot be made, as we used PMMA with pre-mixed gentamicin. As this is the form used by most surgeons, we feel the results of our study may be more applicable to clinical practice.\textsuperscript{1,14}

We have also shown that the properties of Heraeus Palacos compared with Schering-Plough Palacos are different, with superior elution of antibiotics and mechanical characteristics shown by Heraeus Palacos.

Palacos bone cement has always been produced by Heraeus Kulzer Medical GmbH, Hanau, Germany. It was previously licensed for sale to both Schering-Plough and Biomet (whose product was called Refobacin Palacos). The two products were sold in a formulation with additional antibiotics, but Schering-Plough added these themselves after the initial manufacture of the PMMA cement, whereas for the Biomet product Heraeus added the antibiotics as part of the initial manufacture. It has been confirmed by Heraeus Kulzer that the product now sold as Heraeus Palacos, and tested in this study, is exactly the same as that produced by Schering-Plough.

### Table III. Compressive strength – mean values in MPa with 95% confidence intervals

<table>
<thead>
<tr>
<th>Cement type</th>
<th>Additional antibiotic</th>
<th>1 g vancomycin</th>
<th>2 g vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schering-Plough Palacos</td>
<td>88.8 (85.9 to 91.7)</td>
<td>89.1 (85.6 to 92.6)</td>
<td>90.5 (88.2 to 92.8)</td>
</tr>
<tr>
<td>Heraeus Palacos</td>
<td>108.1 (106.2 to 110)</td>
<td>105.7 (103.1 to 108.8)</td>
<td>100.4 (97.9 to 102.9)</td>
</tr>
<tr>
<td>Smartset</td>
<td>104.1 (102.2 to 106)</td>
<td>107.1 (103.4 to 110.8)</td>
<td>98.4 (96.5 to 100.3)</td>
</tr>
</tbody>
</table>

### Table IV. Flexural strength – mean values in MPa with 95% confidence intervals

<table>
<thead>
<tr>
<th>Cement type</th>
<th>Additional antibiotic</th>
<th>1 g vancomycin</th>
<th>2 g vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schering-Plough Palacos</td>
<td>66.5 (65 to 68)</td>
<td>64.1 (61.9 to 66.3)</td>
<td>55.6 (53.3 to 57.9)</td>
</tr>
<tr>
<td>Heraeus Palacos</td>
<td>73.2 (71.5 to 74.9)</td>
<td>65.9 (63.9 to 68.5)</td>
<td>63.2 (60.8 to 65.6)</td>
</tr>
<tr>
<td>Smartset</td>
<td>79.7 (76.6 to 82.8)</td>
<td>71.4 (68.1 to 74.7)</td>
<td>63.1 (61 to 65.2)</td>
</tr>
</tbody>
</table>

### Table V. Flexural modulus – mean values in MPa with 95% confidence intervals

<table>
<thead>
<tr>
<th>Cement type</th>
<th>Additional antibiotic</th>
<th>1 g vancomycin</th>
<th>2 g vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schering-Plough Palacos</td>
<td>2194 (2079 to 2309)</td>
<td>2320 (2227 to 2413)</td>
<td>2239 (2086 to 2392)</td>
</tr>
<tr>
<td>Heraeus Palacos</td>
<td>3302 (3191 to 3413)</td>
<td>3414 (3288 to 3540)</td>
<td>3264 (3163 to 3365)</td>
</tr>
<tr>
<td>Smartset</td>
<td>3639 (3542 to 3736)</td>
<td>3674 (3603 to 3745)</td>
<td>3321 (3181 to 3461)</td>
</tr>
</tbody>
</table>

### Table VI. Official statement from Heraeus Kulzer representative

The manufacturer of the bone cement products and brand owner of PALACOS with and without Gentamicin and in all variations has always been and still is Heraeus Kulzer. Heraeus Kulzer supplied Merck and later its successor Biomet with Refobacin PALACOS R in Germany and Austria, while Schering-Plough was Heraeus Kulzer’s distribution partner in the other European countries. Heraeus Kulzer’s bone cement product appeared in the variation of “PALACOS with Gentamicin” in the distribution via Schering Plough and in the variation of “Refobacin PALACOS R” for distribution via Merck, later Biomet. For PALACOS with Gentamicin (distributed by Schering-Plough) the — pharmacopoeia-conforming active-agent — Gentamicin was supplied by Schering-Plough.

Since Heraeus decided in 2005 to self-distribute its products in all territories, Refobacin PALACOS R was re-labelled into PALACOS R+G and, further, PALACOS R+G was introduced also in the territories formerly distributed via Schering Plough with PALACOS with Gentamicin. PALACOS R+G contains Gentamicin that is sourced by Heraeus Kulzer. It is the same Gentamicin (e.g. pharmacopoeia-conforming, grain size, release behaviour etc.) already used for the Refobacin PALACOS R. Hence, improvement in the release behaviour with regard to the antibiotic agent may, since the bone cement components as such are identical for all variations, be a result of the use of the Gentamicin prepared and supplied by Heraeus Kulzer (as opposed to the Gentamicin supplied by Schering-Plough for PALACOS with Gentamicin).
viously sold as Biomet Refobacin Palacos (Table VI). Any differences in the characteristics of the versions of Palacos are thought by Heraeus Kulzer to be due to the difference in grain size of the added gentamicin. The issue of differences between ‘old’ and ‘new’ versions of Palacos has also been addressed by Dall, Simpson and Breusch.15 Their comparison of Heraeus Palacos (‘new’) and Biomet Refobacin Palacos (‘old’) found differences between these cements, primarily in handling characteristics but also in mechanical properties. This is not what would be expected, given the statement that Heraeus Palacos and Refobacin Palacos are the same product. Dall et al16 carefully controlled for extrinsic factors in their study, but could not control for intrinsic factors that might produce variability between cement batches, such as bead sizes and concentrations of initiator and accelerator compounds.

Historical promotional material from Schering-Plough and current material from Heraeus refer to the Swedish Hip Registry.14,17 According to this source, between 1992 and 2000 Refobacin Palacos was only used in one case, compared with 64 508 cases using Schering-Plough Palacos R+G. In the period 2000 to 2005 Refobacin Palacos was used in 12.6% of cases, compared with 65.2% for Schering-Plough Palacos. Given the information that Heraeus Palacos is exactly the same product as Refobacin Palacos, long-term registry data from this source may not apply to this product. The confusion is compounded in a paper by Hallan et al.18 They reported a radiostereometric study comparing Palamed G (Biomet) and Palacos R with gentamicin (Schering-Plough). In a footnote they state that Palacos R with gentamicin and Palacos R+G have the same properties (based on information from Heraeus Kulzer GmbH). This is not supported by our study. There are a number of potential weaknesses in our study. On a number of measures Smartset performed better than the two other cements. It is not possible to say whether this was due to inherent properties of this brand of cement or to the increased quantity of pre-mixed gentamicin. The results of Simpson et al12 suggest that the latter may be the case. The wider confidence intervals of Smartset on elution testing may imply greater variability of elution, but we feel are more likely to be related to the fact that testing was carried out in two batches for this cement, with greater inter-batch than intra-batch differences. These differences may therefore have been related to the elution testing method rather than the cement.

Prior to mechanical testing we discarded any samples with obvious voids. This may have biased our results, although the same protocol was followed for all cement types. The mechanical testing carried out examined only the ISO standards. It is not known whether performance on these tests has any correlation with long-term clinical performance. These properties were chosen for their ease of testing, and the fact that standards do exist with which manufacturers must comply. When bone cements are released or reformulated by their manufacturers it is important that orthopaedic surgeons are aware of their characteristics, in terms of both antibiotic elution and mechanical properties. We have shown that a new bone cement, Smartset, has at least equivalent (or better) properties than established brands on in vitro testing. We have also demonstrated differences in the properties of the currently available form of Palacos compared with the most frequently used previous version. Heraeus Palacos performed better than Schering-Plough Palacos on in vitro testing, but because its properties are different we feel it is misleading to advertise the product referencing historical clinical results derived mostly from Schering-Plough Palacos. Surgeons will naturally be cautious of products that have been more recently released and do not have established clinical results. It is important that they are aware that changes to established products may alter their in vitro properties, although it is not possible to know whether this will change their clinical performance.

The authors would like to thank Mr. J. Gray (Depuy) for his help in arranging resources to allow this study to be carried out. The cost of elution testing was met by Depuy CMW and mechanical testing carried out using facilities at Depuy CMW, Blackpool.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References


