Skeletal Distribution OF 14C-Labeled Bisphosphonate After Local Elution From Porous Implants

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Introduction: Zoledronic acid (ZA) is a 3rd generation, potent, long lasting bisphosphonate (BP) that is effective for increasing net bone formation within and around implants when administered systemically or when directly eluted from implants (1-3). Ideally the ZA eluted from an implant would remain mostly localized to the implant site so as not to needlessly affect skeletal bone remodeling at remote sites. The extent to which this occurs or whether ZA is more widely distributed through diffusion into the circulation is unknown. The purpose of this study was to utilize 14C-labeled ZA (Novartis) to quantify the localization and skeletal distribution of ZA in a canine intramedullary implant model.

Materials and Methods: Three implants 5 mm in diameter and 50 mm in length were manufactured of porous tantalum (Trabecular Metal™, Zimmer), a metallic biomaterial that is about 80% porous and has a mean pore size of about 450 μm. The implants were plasma spray coated with a 10-15 μm layer of hydroxyapatite (HA) of 98% purity, 99% density, 64% crystallinity and a calcium:phosphate ratio of 1.67. A solution of 1000 μg 14C-labeled ZA (specific activity=6.5 MBq/mg) in 500μl of distilled deionized water was evenly distributed onto each implant surface after which the implants were dried in an oven at 50°C overnight and sterilized using ethylene oxide. The ZA dosing procedure was identical to that used in prior studies (2). Each of the 3 implants was surgically inserted within the left femoral intramedullary canal of an adult mongrel dog (Fig 1) and left in situ for 6 weeks.

Results: The mean ZA values for 1-cm intervals along the 3 test femora and 9 other bones are listed in Table 1. Concentration of ZA (nanograms per g of dry bone)

| Bone/Sectin (cm) | 1  | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|------------------|----|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|
| Mean for 3 Test Femora | 2.5 | 0.5  | 0.9  | 1.2 | 2.3 | 1.5 | 0.8 | 0.6 | 0.4 | 0.3 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Mean for 9 Other Bones | 10 | 2  | 8  | 10 | 12 | 15 | 10 | 8  | 6  | 4  | 2  | 1  | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

* section adjacent to implant

The most striking observation was that very high amounts of ZA were present within the bone samples immediately adjacent to the implants – these values ranged from 243 ng to 1487 ng ZA/g of bone, with a mean of 800 ng ZA/g. As little as 1 cm proximal or distal to the implant location the values diminished markedly, by up to an order of magnitude. Excluding the 5cm region immediately adjacent to the implants, the mean ZA concentration for the 3 femora with implants was 73 ng ZA/g of bone (range= 4 ng to 375 ng ZA/g). All bone samples contained measurable amounts of 14C indicating diffusion of ZA into the circulation and a level of systemic distribution. This level was very low, however, with ZA levels in bones without the implant 1 to 3 orders of magnitude less those measured within the test femora directly exposed to ZA elution. Every bone sample from the metaphysis of the 9 bones without the implant (mean= 8.7 ng ZA/g bone) contained more ZA than bone samples from the diaphysis (mean= 2.2 ng ZA/g bone), a 4-fold mean difference that was significant at p<0.002. Absolute values in these 9 bones ranged from 0.8 ng to 22.6 ng ZA/g with a mean of 6.5 ng ZA/g, about 11-fold less in magnitude (p<0.001) than the mean concentration present in the bone samples proximal and distal to the implants and about 122-fold less in magnitude than the mean ZA concentration present in the 15 bone samples immediately adjacent to the 3 implants (p<0.0001). Taking into account bone loss during femur sectioning and manipulation it was calculated that a mean of about 15 μg ZA was present within a femur containing a ZA-dosed implant.

Discussion: This study provided valuable insight into how ZA that is locally eluted from an implant binds to adjacent bone and becomes distributed systemically. We knew from prior studies that about 50% of ZA injected intravenously is excreted within 24 h to 48 h (5). We now also know that ZA elution from an implant results in systemic distribution, presumably through diffusion from the implant site into the bloodstream. Ancillary elution studies using identical implants dosed with 14C-labelled ZA have shown that about 60% of the ZA is released within 6 weeks of hydration in aqueous solution, an amount equivalent to 60 μg ZA in this study. If half of this amount is excreted soon after surgery about 30 μg of ZA would be left, half (15 μg) of which was found in the femora with a ZA-dosed implant. The rest would be distributed throughout the skeleton, at levels that are evident from this study to be much less than the therapeutic dose required to appreciably affect bone remodeling. This is supported by the observation of ancillary studies that increases in net bone formation around ZA-dosed porous tantalum implants are very much confined to the immediate peri-implant space, where the ZA concentration was measured in this study to be two orders of magnitude greater than in remote sites of the skeleton. The extremely low levels of ZA that exist remote from the implant would mitigate against any risk of complications from ZA exposure, an added advantage of local elution directly from an implant. Further studies of this type should include sampling for ZA distribution at additional skeletal sites and at longer postoperative time periods.

References:

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