Reviewer’s report

Title: Systemic alendronate prevents resorption of necrotic bone during revascularization. A bone chamber study in rats.

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Reviewer: Prof K W Ng

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

This is an in-vivo study of the effects of Alendronate treatment on resorption of bone grafts. The authors used a previously described model consisting of a bone conduction chamber made from titanium that is screwed into bone. Necrotic bone grafts were placed in the interior of the chamber which has two openings located at the bone end to allow ingrowth of new bone. This well characterized model allows an estimation of the rate of tissue ingrowth, with the ability to obtain tissues for histomorphometric analysis.

The experiments were well designed, and considerable care was taken to ensure that measurements were accurate and reproducible.

The results should be viewed in two parts. In the first experiment, animals were treated with Alendronate at a dose of 205 mg/kg-1 x day-1. The results conclusively showed that resorption of necrotic bone in the chambers was significantly inhibited in animals treated with high dose Alendronate. Migration of osteoblasts was not prevented, so that new bone was layered onto the necrotic bone. In contrast, the marrow cavity was minimally developed. However the concentration of Alendronate would be well above that used in the therapy of osteoporosis in humans.

Discretionary revision:

Did the authors obtain an estimate of the number of multinucleated TRAP positive cells in the chamber in control versus treated animals?

In the second experiment, animals were treated with Alendronate at a dose of 4 mg/kg-1 x day-1, in order to simulate a concentration closer to that used in the treatment of osteoporosis. A qualitatively similar result was obtained.

Compulsory revision:

However, the authors had to use a different batch of animals from another breeder for the second set of
experiments. Consequently, the conclusion drawn from their experiments was diminished because the control groups from the two sets of experiments were not comparable aE” a point conceded by the authors. This difference between the control groups introduced a confounding factor into the interpretation of the results. What would have been a good result was now thrown in doubt because a question had arisen about the validity of the comparison. It certainly markedly lessened the impact of their findings. Once it became apparent that the two animal batches behaved differently, the authors should have made very effort to perform both sets of experiments with animals from one breeder. Although one can fully sympathise with the plight of the authors, it is not a substitute for scientific rigor.

**Competing interests:**

None declared.