BoneKEy-Osteovision. 2007 September;4(9):236-251
http://www.bonekey-ibms.org/cgi/content/full/ibmske;4/9/236
DOI: 10.1138/20070271

# *PERSPECTIVES*

# Bisphosphonate Treatment and Fracture Repair

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**Abstract**

Bisphosphonates are widely used in patients who sustain fractures. Despite much research in the area, it is still unclear whether bisphosphonates in the current regimens used have a positive or negative effect on bone repair. Most evidence suggests that bisphosphonates have little effect on the progression of endochondral ossification. However, as suppressors of bone resorption, they clearly affect callus remodeling. Many studies have been performed utilizing continuous daily dosing of bisphosphonates. While it is not proven that dosing frequency is critical in clinical practice, the recently introduced intermittent dosing regimens may have less of an effect on callus remodeling. Lastly, protocols may be able to be modified to have a desirable impact on initial callus accumulation at the fracture site while still allowing remodeling to proceed. *BoneKEy-Osteovision*. 2007 September;4(9):236-251.


## Introduction

Nitrogen-containing bisphosphonates (N-BPs) are pharmaceutical agents commonly used for the treatment of a number of metabolic bone disorders, including osteoporosis and Paget's disease, as well as metastatic bone disease (1-3). The treatment of osteoporosis with N-BPs has proven extremely effective, resulting in increased net bone mass and reduced bone turnover, and thus leading to a reduction in fracture incidence (4). The efficacy of N-BPs in metabolic bone disease has been attributed to their capacity for prolonged, high affinity binding to bone surfaces, as well as their potent anti-osteoclastic activity. Because of a long-term suppression of bone catabolism (resorption), patients receiving bisphosphonates show a steady enhancement of mineralized bone tissue. It was initially perceived that bisphosphonates (BPs) prevented resorption of existing bone tissue, thus preserving the bone architecture. However, subsequently it has been revealed that BPs also allow for enhanced or prolonged secondary mineralization (5;6).

There are three main clinical questions that might affect patients with regards to bisphosphonate treatment and bone repair:
First, can BP naive patients presenting with a fracture be recruited to BP treatment programs without interfering with repair of the sentinel fracture? This has obvious implications for the clinical management of new patients presenting with their first osteoporotic fracture.

Second, can a BP be successfully applied as an adjunctive agent to improve outcomes in bone repair in certain circumstances? The concept of using BPs as a tool for modulating the catabolic response in bone healing is a recent development, but one that has potentially wide applications for orthopedic medicine.

Third, are patients on chronic BP therapy at risk of adverse outcomes after fracture or surgical manipulation of bone tissue? As the number of osteoporotic patients on chronic BP therapy increases, so does interest about the possible negative effects BPs may have on the skeleton that could affect bone repair (7-9). Of particular concern is the potential for chronic BP dosing to inhibit bone anabolism; the potential for BPs to suppress the early

stages of endochondral fracture repair; disruption by BPs of hard callus remodeling; and the potential risks associated with osteonecrosis of the jaw (ONJ). This review focuses on fracture and bone repair outside the jaw, as ONJ has been reviewed extensively in the recent literature (10;11).

This article reviews the current pre-clinical information on the action of BPs on bone healing, as well as the limited clinical information available. While it is not possible to make strong recommendations on the use of BPs at the time of bone healing, we present at the conclusion of this review what we believe to be a logical rationale based on current information.

## Bisphosphonates: Mechanism of Action

BPs are synthetic analogues of pyrophosphate possessing a non-hydrolyzable P–C–P backbone with two covalently bonded side chains ($R^1$ and $R^2$). The bisphosphonate structure has an intrinsic *bone hook* that enables it to rapidly and strongly bind to bone surfaces (12). More recently it has become apparent that the side chain also contributes to hydroxyapatite (HA) binding, with differences in binding between clinically used BPs (13). Unlike the simple, non-nitrogen containing BPs that work via their metabolic conversion into toxic ATP analogues, the N-BPs bind and inhibit the enzyme farnesyl diphosphate synthase (FPPS) (14;15). FPPS repression interferes with the mevalonate pathway, which in turn disrupts the post-translational lipid modification of cellular proteins. The anti-resorptive potency of N-BPs correlates with their binding affinity to FPPS, suggesting that this is the principal mechanism underlying N-BP action (15).

Evidence from *in vitro* models suggests that N-BPs at the bone surface are taken up specifically by resorbing osteoclasts (16;17). Other cells are exposed to BPs while they are in solution, but only osteoclasts seem to take up large amounts of bound BP from the bone. This uptake causes a significant and specific reduction in osteoclast function, which leads to a decrease in bone catabolism (18;19). While bone formation in the remodeling space continues for a short while, after a few months bone formation is also reduced as the activation frequency drops, reducing the number of remodeling sites. There is to date no evidence for prolonged uncoupling of bone formation and resorption with BP treatment.

Bisphosphonates have beneficial effects in the treatment of osteoporosis by preventing the premature removal of primary mineralized tissue and by increasing secondary mineralization. Primary mineral deposition refers to mineralization at the calcification front, while secondary mineralization describes the slower progressive increase in deposition that occurs subsequently. In a study where post-menopausal osteoporotic women were treated with alendronate (ALN) therapy, the mean degree of mineralization of bone was increased up to 11.4%, compared to untreated controls. These results translate to significant increases in BMD at the sites measured and significant increases in bone strength (20).

## Bisphosphonates and Fracture Reduction in Osteoporosis

Osteoporosis is a major cause of community concern and underlies a high fracture risk in the elderly population, particularly post-menopausal women. Recent public health strategies to reduce the burden of osteoporosis have focused on identifying at-risk individuals and applying appropriate screening and intervention programs (21). Numerous studies illustrate that N-BP treatment can result in extensive increases in bone mineral density (BMD) and a subsequent reduction in fracture incidence.

For over a decade, oral ALN has been widely used to treat osteoporosis. ALN has been shown to reduce the incidence of vertebral fracture by 44% in osteoporotic women with reduced BMD (22). A trial in a cohort of 2027 women with osteoporosis and at least one vertebral fracture showed even more significant effects with ALN treatment. Fifteen percent of control patients sustained new vertebral fractures, whereas only eight percent of women receiving ALN sustained fractures (23). Daily risedronate (RIS) has also been shown to reduce fracture incidence, with the cumulative incidence of new vertebral fractures reduced by 41% over a 3-year

period in post-menopausal osteoporotic women (24).

The current trend in osteoporosis management is to allow for dosing regimens with reduced frequency in order to improve patient compliance (25). ALN and RIS are now offered as weekly formulations for osteoporosis (26;27). Ibandronate (IBAN) trials have examined monthly and three monthly dosing (28), and newly published clinical trial results giving a once-yearly infusion of 5mg of zoledronic acid (ZA) in postmenopausal women demonstrated a 70% decrease in the occurrence of vertebral fractures and a 40% decrease in hip fractures (1). Thus, as a class of drugs, bisphosphonates can be highly effective in the prevention of osteoporotic fractures and have the potential to significantly reduce the burden of this disease on society.

**Effects of Bisphosphonates on Fracture Repair**

Fracture healing is a complex process that encompasses numerous stages of tissue modeling. The initial response to injury involves an inflammatory reaction that stimulates the localized invasion of immune cells and mesenchymal progenitors. The mesenchymal cells differentiate and produce a stabilizing central cartilage or fibrocartilage plug, known as a soft callus, which is flanked by intramembranous vascularized bone or hard callus. The cartilage is subsequently mineralized and replaced with primary woven bone through endochondral ossification until the fracture site is bridged. Re-vascularization is part of the endochondral ossification process. Once the fracture is bridged, the primary hard callus is remodeled into mature lamellar bone until a structure similar to that prior to injury is achieved (29). While the stages of fracture healing are best understood by this sequential description, it should be appreciated that some of the events are occurring simultaneously. For instance, the peripheral hard callus is being remodeled into lamellar bone while centrally cartilage mineralization, vascular invasion and woven bone formation are still taking place.

Both bone anabolism and catabolism are key determinants to how successfully a fracture will heal; the size of the net callus formed is dependent on the interplay of these opposing responses (30). While the moment of inertia is the principal geometric element in resistance to load, remodeling of the woven bone callus into lamellar bone provides further modulation of the material properties, which also affects the actual resistance to re-fracture. As the initial anabolic response to fracture is not resorption-dependent, BP treatment leads to an increase in callus size through callus retention, with a concomitant reduction in remodeling into lamellar bone. An increase in bone size will usually lead to an increase in strength unless the material properties are adversely affected in a gross manner.

Multiple studies have been performed in various animal models to imitate the scenario of fractures occurring in patients on BP treatment. Most have demonstrated extensive increases in fracture callus size and some have shown improvements in mechanical properties with BP treatment (31-46).

Experiments have been performed on fracture healing using the non-nitrogen containing BP clodronate (CLOD). In a bilateral tibial fracture model, rats receiving CLOD 50 mg/kg/week regained tensile load capacity equivalent to that of the un-fractured bone (32). Remodeling into lamellar bone was observed over 8 weeks at this dose, but the mineral content was noted to be higher. In a later study in a segmental tibial osteotomy model, rats receiving 10 mg/kg/day showed no delay in bone union, but treatment did affect spatial orientation with retention of primitive chondral remnants (33). CLOD dosing in a plated-fracture model in rabbits resulted in a reduction in osteopenia and an increase in the net callus under the plate (34).

Lenehan *et al*. (31) studied the effects of etidronate (ETID), another non-N-BP, administered subcutaneously to mature beagle dogs at dose levels of 0.1, 0.5, and 5.0 mg/kg/day for a 20 week period, to determine the drug's effects on fracture healing. At a dose of 0.1 mg/kg/day, ultimate load at failure and flexural rigidity of the fractured limbs equaled or exceeded that of saline control animals, and radiographic healing was normal. At a dose of 0.5 mg/kg/day, ultimate load at

failure and flexural rigidity of the fractured limbs proved inferior to saline control values, and radiographic healing appeared delayed. At a dosage of 5.0 mg/kg/day, there was obvious radiographic non-union, and the callus of fractured radii had little inherent flexural rigidity or strength. Mineralization appeared totally disrupted at the higher dosage level. Clearly, ETID has a negative effect on bone repair. In fact, ETID has been used to prevent heterotopic ossification (47).

As the more potent N-BPs do not interfere with mineralization, these drugs have less potential to impede fracture repair than CLOD or ETID. In another fracture study in beagles, dogs were dosed with daily ALN with the aim of determining any detrimental effects. A dose of 2 mg/kg/day, substantially higher than the recommended human dose for treating osteoporosis, was given for 9 weeks preceding fracture, 16 weeks after fracture, or both before and after fracture (25 weeks). Despite the high doses for extended duration, normal bone healing was observed at the fracture site in all dogs. When ALN treatment was given only during the fracture healing period, this led to a 2-3 fold increase in callus size at 16 weeks, compared to those receiving a placebo (35).

Li and colleagues performed a study where rats were pre-dosed with 0.01 or 0.1 mg/kg of incadronate (INCAD) prior to creating a femoral osteotomy (37). Pre-dosing with INCAD was sufficient to increase callus formation, indicating that bound bisphosphonate could recirculate enough to affect osteoclasts at the fracture callus, or had other systemic effects such as decreasing osteoclastogenesis. Continuation of INCAD treatment (3 doses per week for 16 weeks post-fracture) increased callus formation even further, however, the hard callus again failed to remodel. Notably, in terms of mechanical properties, the delay, in remodeling in the continual does group, was offset by the increased amount of callus; INCAD still produced an overall improvement in bone strength.

More recently the same investigators studied the effects of the same doses of INCAD on the early stages of fracture healing at two and four weeks (38). By measuring the concentration of the BP in the fracture callus at these time points, the authors provide important information on the accumulation of BP in the fracture callus during the healing process. In those animals only pre-dosed with the drug, INCAD concentration in the callus was less than in intact bone, while in continuous pre- and post-dosed groups the INCAD concentration in the callus was around 2-fold higher than in the intact bone. Callus area was significantly enhanced in the continuous high dose group, compared with controls at four weeks. At the two-week time point, however, no statistically significant difference was seen in callus area, although a visual difference could be observed. Li and colleagues concluded from their work that there would likely be no clinical benefit in using bisphosphonates to increase callus formation.

The effect of pamidronate (PAM) on fracture repair was investigated in sheep as a large animal model. The aim of this study was to assess the potential effects of BPs on fractures around cancer metastases in patients already treated with BPs (41). A dose of 0.5 mg/kg/week was given for 4 weeks pre-operatively and 12 weeks post-operatively, resulting in an increase in mineralization of the woven bone callus. Torsional strength was also increased in the treated group, but specimens did display a considerable delay in remodeling.

The above experiments were performed on normal bone in various species. Surprisingly few experiments have been performed in models such as the ovariectomized (OVX) rat. As well as being a cause of fracture, osteoporosis itself can lead to a delay in fracture repair (48). Age also plays a role, with further delays in healing noted in older animals. Meyer *et al*. showed that at 32 weeks of age, sham-operated rats took 12 weeks to restore normal strength to their fractures, while OVX rats remained significantly lower (49). At 50 weeks of age, neither sham nor OVX rats completely restored the full strength of their fractured femora. The gain in mineral density normally seen on the fractured side was diminished by OVX.

In a rat model of osteoporotic fracture, female OVX rats were fractured and treated with or without 0.01mg/kg/day of ALN (36). Rats receiving ALN at 6 weeks generated calluses of a similar size, but higher mineral

content. Continued BP dosing until 16 weeks led to a delay in the removal of the woven bone callus and its replacement with lamellar bone; this indicates a key role for osteoclasts in hard callus remodeling. It remains to be seen if an altered regimen could provide desirable gains in mineralization and callus volume yet permit adequate remodeling.

In summary, BP treatment during fracture healing has been explored using a variety of BPs, dosing regimes, and orthopedic animal models. These studies have found that a decrease in catabolism is sufficient to increase callus size and strength in a variety of closed and open fracture models in animals. It is also clear from these reports that continuous BP dosing can delay or preclude hard callus remodeling, leaving an irregular, albeit mechanically sound, woven bone callus, rather than establishing a more ordered lamellar bone callus.

## Bisphosphonate Therapy for the Enhancement of Bone Repair

### *BPs and fracture repair*

The experiments discussed above were designed to model patients on BPs who sustain fractures or those who sustain a fracture and then start BPs. More recently, investigations have been performed to examine which regimens, if any, could improve callus size and strength in bone repair while minimizing negative effects on remodeling. Studies have also been performed to look into possible roles for BPs in other bone repair situations such as total joint arthroplasty.

In an open rat osteotomy model, PAM was able to generate significant increases in callus bone mineral content (BMC) and callus volume, and up to a 60% increase in fracture callus strength, compared to saline controls, by 6 week post-fracture (50). Likewise, a rat closed fracture model treated with ZA showed significant increases in mineralized callus size and strength of up to 50%, compared to saline controls (51). In these experiments, a variety of different BP dosing regimens were tested, including giving a single bolus systemic dose. Similar positive mechanical outcomes could be obtained using single bolus BP treatment as by giving the same overall BP dose as divided weekly doses, although hard callus remodeling was superior in the bolus group (52). Moreover, timing of the bolus treatment was also important, with BP dosing two weeks after fracture producing a larger callus volume than dosing at the time of fracture (51). Timing also had an effect on BP accumulation in the callus. ZA dosing at the time of fracture (T0) led to very little distribution of ZA to the callus, as there was no callus to bind to at the time of the dose. In contrast, dosing at 1 and 2 weeks (T1 and T2) led to a similar 2-fold increase in N-BP in the fractured bone to that found by Li *et al*. (38). Very little ZA was seen to recirculate in the callus over the six week time course when C14 autoradiography experiments were performed.

In a rabbit model of distraction osteogenesis (DO), an orthopedic procedure with a capacity to produce large amounts of new bone, ZA was found to enhance the net amount of regenerate produced over six weeks and thus lead to increased bone strength (53;54). These results have also been achieved with IBAN (55) and systemic and local ALN in a similar rabbit model (56). Although DO is analogous to fracture repair, it is nevertheless a highly anabolic process where catabolic inhibition may give a superior outcome compared to a fracture.

### *BPs and anabolic-deficient bone healing*

Since the outcome of fracture repair is dependent on the combination of anabolic and catabolic responses, BPs should only be able to enhance healing when the endogenous anabolic response is sufficient. Certain bone repair situations feature an anabolic deficiency, either due to extensive physical trauma, and/or to an associated deficit in growth factors, osteogenic factors or bone-forming cells. For example, high-energy open fractures have a poor prognosis and can develop delayed union or non-union due to anabolic deficiency. In these cases, the simple application of a BP to reduce catabolism may be insufficient to facilitate healing.

Our group explored this paradigm by utilizing a critical-sized defect model in a rat femur (57). This model fails to unite in 100% of animals due to an inadequate anabolic response. Addition of a single dose of 0.1mg/kg of ZA in this model failed to produce any callus, confirming that in the

absence of endogenous bone formation, an anti-catabolic agent cannot enhance bone healing sufficiently to generate union.

When an anabolic stimulus, bone morphogenetic protein-7 (BMP-7/OP-1), was delivered locally at a dose of 50µg into the fracture gap, the site bridged completely with bony callus by 8 weeks. The addition of a single dose of ZA further enhanced callus formation, producing an 87% increase in callus volume, correlating to a 107% increase in callus strength, when compared to OP-1 alone. Thus, if an exogenous anabolic stimulus such as OP-1 is required, BPs can be used synergistically to enhance the response to such agents. In a study using a bone chamber model in rats, the anabolic response generated by bone graft was maximized by systemic dosing with ZA (58).

In an alternative report, Toro *et al*. used an open fracture model in OVX rats, which showed a 59% non-union rate at 6 weeks post-fracture (59). While this model may have had an anabolic deficiency that impeded healing, treatment with ALN pre- and post-fracture was able to significantly increase the union rate over controls. Hence, even in an environment where the anabolic response is reduced, antagonizing catabolism using BPs may be beneficial, but only if some endogenous anabolism remains.

## Potential Complications of Bisphosphonate Therapy during Facture Healing

### *Disruption of bone anabolism*

Bisphosphonate administration results in temporary uncoupling of anabolism and catabolism, resulting in decreased bone catabolism without a corresponding decrease in anabolism. However, chronic BP dosing or more limited high-dose BP can lead to suppression of bone anabolism. Although numerous *in vitro* studies have shown mild positive effects of BPs on the proliferation and differentiation of osteoblast cells (60), this finding is in conflict with many animal and clinical studies that suggest BP treatment can in fact reduce bone formation (8;9;61-64).

In a recent attempt to better understand the *in vivo* effects of BPs on bone anabolism, rats were treated daily for over five months with RIS (0.1, 1.0 or 10 µg/kg), ALN (0.05, 0.5 or 5.0 µg/kg), or saline. Periosteal mineral apposition rate (MAR) in the femora and tibiae was significantly reduced in all groups (26–36% for ALN, 22–29% for RIS) (9). These data suggest a potential for chronic BP treatment to significantly depress bone anabolism, although the precise mechanism for this remains unclear. In a recent human biopsy study, yearly ZA treatment for osteoporosis decreased activation frequency while MAR was maintained (65).

In a case study of 9 patients receiving long-term ALN treatment for osteoporosis (10 mg/day or 70 mg/week), delayed fracture healing was noted in 6 cases ranging from 3 months to 2 years post-fracture (8). Bone biopsies from all patients revealed a complete absence of the double labels present in normal aged matched control bone and bone formation rates were reduced up to 100-fold in these patients. Four of these patients still exhibited delayed or non-unions after ALN therapy was terminated. These authors suggest that the substantial reduction in bone turnover in these chronically treated patients was manifested as a reduced anabolic response that delayed fracture healing. However, it cannot be confirmed that ALN therapy in these patients was the only determinant of reduced bone turnover.

In contrast, a study of children with osteogenesis imperfecta (OI) who had been treated chronically with high doses of PAM showed no delay in the healing of closed fractures (66). Surgical osteotomies, on the other hand, showed significant delays in healing when influenced by PAM treatment. The difference in healing response could be attributable to mechanical stimuli through weight bearing or to reduced anabolic response after the soft tissue damage of open surgery. It is possible that this effect may be attributable to the disease itself, as recent studies show differences in osteoblastic responses to ALN in cells from OI patients versus controls (67). A more recent study of similar patients with OI confirmed that PAM exhibited no effect on the process of closed fracture healing (68).

The most recent and possibly most relevant clinical evidence comes from a trial of ZA in patients presenting with hip fractures (69). In this study, 1065 patients with hip fractures were randomized to receive ZA within 90 days of fracture and 1062 to receive placebo. Subsequent infusions were given yearly. The study showed significantly decreased rates of subsequent clinical fractures and improvements in mortality. Importantly for this discussion, there was no difference in the rate of clinical delayed union of the qualifying hip fracture between the ZA (3.2%) and placebo (2.7%) (P=0.61). It is important to note that in the study design only symptomatic hip pain was followed up such that patients were not systematically radiographed to look for delayed union. However, the absence of a striking increase in clinical delayed unions provides some reassurance that such intervention can reduce subsequent fracture rates without interfering with union of the initial fracture.

*Delayed endochondral union*

Until recently, osteoclasts were considered to be the primary cell type responsible for the removal of cartilage during endochondral fracture repair. This has led to concern as to whether BPs would interfere with the replacement of the soft cartilaginous callus with woven bone, leading to prolonged mechanical instability and delayed union. Under such circumstances, it would be advisable to discontinue BP treatment in osteoporotic patients receiving BPs who sustain a fracture (7). However, there is emerging evidence from laboratory and clinical studies that this is not the case.

By specifically targeting osteoclastic resorption with bisphosphonates, it has been shown that osteoclasts are not essential for the early stages of soft callus replacement. No delays occurred in the union of the bone segment by new bone with CLOD administration in rat tibial fractures (32;33). In rat femoral fractures treated pre- and post- fracture with ICAN, no adverse effects on the initial healing process were noted (38;44) and radiological healing was normal (37). In rat femoral fracture models treated with PAM (open fractures) and ZA (closed fractures), radiological fracture healing was not attenuated with BP treatment (50;51). Finally, as an alternative model to BP-induced osteoclast dysfunction, endochondral fracture repair was examined in an osteopetrotic rat, the incisor absent (*ia/ia*) rat, whose osteoclasts are non-functional. As in BP-treated animals, the initial stages of fracture repair proceeded normally in the *ia/ia* rat (McDonald and Little, unpublished data).

These data imply that the functional activity of osteoclasts may be redundant for the generalized process of endochondral ossification. Certainly, inhibition of osteoclast function had no adverse effects on the growth plates of long bones of mice (70). These authors eliminated osteoclast function from the process of endochondral ossification at this site both using CLOD and two mutant mouse models that lack osteoclasts completely, the colony *c-fos* knockout mouse and the osteopetrotic (*op/op*) mouse. Based on these findings, it is reasonable to suggest that the cells compensating for osteoclasts to remove cartilage at the growth plate may also be compensating in the early stages of endochondral fracture repair (71;72).

However, complete inhibition of bone repair in a rabbit calvarial defect model was seen with high local doses of PAM (73). Either 2 mg or 3 mg PAM was delivered in a poly L-lactide-co-glycolide (PLGA) carrier. These doses of PAM led to substantially decreased bone formation at 2 weeks and apparent avascular necrosis at later time points. Notably, as a calvarial bone healing model, this system does not reflect normal endochondral processes that occur in long bones. It is therefore unlikely that a lack of cartilage removal underlies the deficient healing caused by PAM. Instead, a combination of anti-angiogenic, anti-matrix metalloprotease (MMP), and local cellular cytotoxic effects caused by continual release of PAM is likely. As opposed to clinical dosing where the BP rapidly binds to mineral and is only in the tissue fluids for a few hours, this polymer dosing method would allow concentrations of PAM to be continually in solution and thus affect cells other than resorbing osteoclasts. In a rabbit distraction osteogenesis study where lower doses produced benefit, a high dose of

ALN, 75μg/kg weekly, inhibited bone repair (56).

It seems feasible from these results that while transient retention of early bone scaffold via BP action may generate possible advantages, very high doses can in fact impede the anabolic response, and should be avoided.

*Delayed hard callus remodeling*

Remodeling of the hard callus formed through endochondral processes comprises the final stage of fracture healing. Through the resorption of primary woven bone callus and its replacement with the more mature lamellar bone, the callus volume is reduced and the fracture site returns to its original structural form. Osteoclastic resorption is undoubtedly essential to this process, and numerous studies document delays in hard callus remodeling with BP treatment (36;40;64;74). Up until the stage of union, the preservation of a substantial woven bone callus is beneficial, as it improves the mechanical strength of the callus and thus its resistance to re-fracture. After union, however, retention of primary callus may be detrimental, due to its inferior material properties when compared to the lamellar bone that ultimately replaces it (75).

Morphologically, sustained BP treatment can lead to a failure to form a new lamellar bone cortex or neo-cortex at the periphery of the callus and retention of primary woven bone tissue. INCAD treatment in rats at doses of 0.01 or 0.1 mg/kg thrice weekly for 2 weeks prior to fracture surgery and continuing until 16 weeks post-fracture produced extensive increases in callus size (44). Even out to this late time point, new bone had not remodeled to form a cortical shell, as was seen in the pre-treated only group. Other rat models of BP dosing and fracture repair have demonstrated comparable findings (36;42). In terms of overall mechanical strength, the larger callus volume in BP-treated animals can generally compensate for the deficiency in intrinsic material properties, yielding similar or increased resistance to re-fracture. However, normalizing for total callus volume (or moment of inertia) demonstrates that the woven bone callus has inferior material properties to remodeled lamellar bone (52). Thus a prolonged or indefinite delay in callus remodeling may be seen as an adverse outcome that could affect fatigue resistance or energy required to fracture.

Based on data showing that bolus BP dosing has the ability to yield an initially stronger woven bone callus with a capacity to remodel, it may be possible to reduce the dosing frequency of BPs to minimize their effects on hard callus remodeling (50-52). Further studies will be required to develop the optimal dosing regimes to apply these concepts to clinical use.

*Osteonecrosis of the jaw (ONJ)*

ONJ is a severe but rare complication that has been linked to the administration of BPs. Patients receiving cancer doses of BPs who simultaneously experience dental problems requiring surgery are at highest risk. Current evidence indicates that for patients receiving BPs for the management of osteoporosis, the benefits in terms of osteoporotic fracture prevention outweigh the small chance of developing ONJ (11). Nevertheless, recent recommendations for patients about to begin BP therapy include a dental examination prior to treatment so that potential dental problems can be addressed in the absence of BPs (10).

Reductions in dosing frequency have already been associated with a reduced incidence of ONJ (76). The aim of BP treatment to improve fracture repair also uses reduced frequency bolus dosing to allow remodeling (50-52). Thus it is unlikely that ONJ represents a significant risk under these conditions. However, BP therapy may be contraindicated for the management of mandibular fractures due to the sensitivity of this site. It should be noted that there is no specific evidence to suggest that ONJ could result from using a BP to treat a mandibular fracture. Mandibular distraction osteogenesis has been successfully completed experimentally under ZA treatment (77).

*Evidence-based evaluation of potential BP complication in fracture repair*

Osteoclasts play a key role in bone remodeling and homeostasis and thus concerns about the use of BPs in fracture repair are well-founded. However, the evidence would suggest that strategic

BoneKEy-Osteovision. 2007 September;4(9):236-251
http://www.bonekey-ibms.org/cgi/content/full/ibmske;4/9/236
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management of osteoclast activity can be neutral or even advantageous to the final bone healing outcome (Table 1).

Reports have shown that chronic dosing with bisphosphonates has the potential to gradually reduce bone formation; this decrease in anabolism may affect bone repair, particularly for more severe injuries where a sizeable anabolic response is required (66). Thus 'bisphosphonate holidays' to allow a recovery of the native endogenous anabolic response may provide benefits in patients undergoing long-term BP treatment for osteoporosis.

While osteoclasts have often been speculated to be essential for the early stages of endochondral fracture repair, numerous studies have demonstrated that BPs do not negatively affect this process. Moreover, by suppressing early bone catabolism, they can maximize the size and strength of the initial woven bone callus and prospectively reduce the possibility of re-fracture.

Finally, several studies have demonstrated that prolonged daily dosing with BPs has the potential to obstruct the remodeling of the woven bone callus into the normal lamellar bone. While this has been presented as a major difficulty (37), the large woven bone callus still exhibits considerable mechanical strength, and evidence is lacking that this in and of itself will necessarily cause significant clinical problems. However most believe remodeling would be advantageous and the majority of the early benefits of increased callus size can be obtained with bolus BP dosing, while retaining the capacity to remodel later (50-52).

Table 1. Potential complications associated with BPs in fracture repair.

| Potential Complication | A problem? | Evidence |
|---|---|---|
| Disruption of bone anabolism | Potentially for chronic dosing | 8, 9, 66 |
| Delayed endochondral union | No | 32, 33, 39, 45, 69 |
| Delayed hard callus remodelling | With continuous treatment | 37, 41, 52, 64, 74 |
| Osteonecrosis of the jaw | For mandibular fractures? | 10, 77 |

**Emerging Themes and Future Directions**

*Clinical decision making based on current data*

We believe the preceding discussion highlights that BP treatment in the BP-naive situation can enhance callus size and mineralization without delaying endochondral ossification. The few clinical articles detailing possible detrimental effects involve patients on chronic long-term therapy, and animal experiments using high-dose therapy.

Therefore, we propose that it is safe to treat with BPs post fracture in BP-naive patients in clinical dose ranges used for osteoporosis. In patients who have been treated with BPs for >3 years, it may be possible to cease BP treatment while a fracture is healing without detrimental effects on fracture risk. This prevents excessive dosing of the fracture callus and may result in less remodeling delay. While this is unlikely to change overall bone turnover, it may permit more normal bone turnover at the fracture site itself.

*Conceptualizing BPs as an orthopedic tool*

By applying an anabolic-catabolic paradigm (30), it becomes apparent that any benefits that BPs may have on orthopedic repair will be dependent on the intrinsic anabolic response. Studies using a variety of surgical models reinforce this concept (Fig. 1).

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DOI: 10.1138/20070271

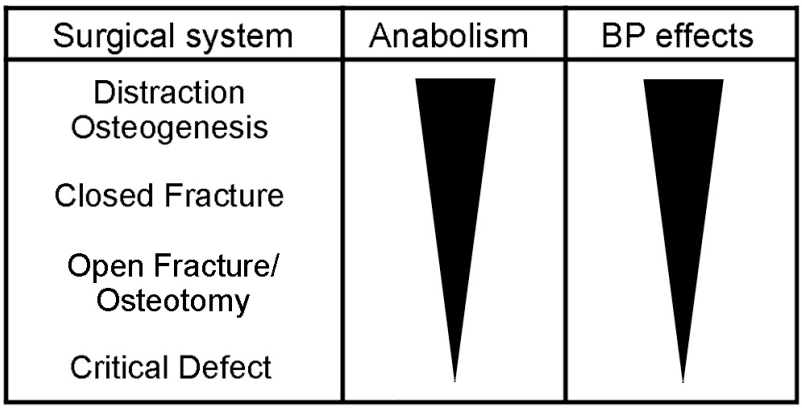


Fig. 1. The positive effects of BPs in fracture repair depend on the anabolism of the model system.

For example, distraction osteogenesis involves a strong anabolic response capable of generating large amounts of new bone. In a rabbit model and in a clinical case series, BP treatment was able to maximize the anabolic response leading to improved union (54;77). As previously discussed, early callus formation can be enhanced by strategic timing of BPs, again dependent on a sufficient anabolic response (50-52). In contrast, BP treatment alone was unable to rescue a critical defect model, although synergy was seen when a further anabolic stimulus was provided in the form of a bone morphogenetic protein (57). Improving our understanding of the anabolic and catabolic responses to different orthopedic injuries will allow the better application of BPs and anabolic therapies to improve clinical outcomes.

*Future Directions*

One key concept that has emerged from these studies is that normal osteoclast function may not be required for the early stages of endochondral fracture healing. This is not to say that BPs may not inhibit healing through some other mechanism. One possible avenue for further investigation revolves around the capacity of vascular endothelial cells to remove cartilage in the absence of osteoclasts via the secretion of matrix metalloproteases (70). High dose BP therapy can both inhibit MMP function and disrupt angiogenesis (79;80). MMP-9 and -13 knockouts have considerably delayed endochondral fracture repair (81;82).

There remain many unknowns in the clinical application of BPs for fracture treatment. We believe a number of specific issues still need to be addressed:

- Does intermittent IV dosing have less effect on bone turnover at the fracture site than weekly oral dosing?
- Does long-term exposure to high-dose BP treatment depress the anabolic bone response to fracture?
- Is this worsened or unaffected by continuation of therapy during bone repair? Can pharmaceutical anabolic treatments improve healing capacity in patients who have received long-term BP therapy and are slow to heal their fractures?
- Can BP regimens designed to reduce early catabolism but allow later remodeling be used to improve the outcome in bone repair?

These are fertile areas for worthwhile and clinically relevant research.

**Conflict of Interest:** Dr. Little reports that he receives consulting and licensing fees from Novartis Pharma, where he also serves on advisory boards. Dr. McDonald and Dr. Schindeler report that no conflicts of interest exist.

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