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Annotation

Parathyroid hormone and fracture healing

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This annotation describes some early rat studies which conclude that parathyroid hormone (PTH) has more dramatic stimulatory effects on bone repair than on untraumatized bone. It also suggests, based on the effects of PTH on osteoblasts, that it is more likely to accelerate normal fracture healing than to prevent non-union. The only 2 controlled clinical trials that have been published are critically discussed. Although both are encouraging and appear to show acceleration of normal fracture healing, they have methodological shortcomings that preclude definitive conclusions. ■

Intermittent PTH treatment increases the number of osteoblasts

A stimulatory effect of parathyroid extracts on bone formation was described already in 1932 (Selye 1932), but this finding was more or less forgotten, since continuous overproduction of parathyroid hormone (PTH) was found to cause bone loss. When it was later discovered (or rediscovered) that intermittent dosing of PTH has anabolic effects on bone, PTH became a hormone of interest for treatment of osteoporosis. Then suddenly, at least one drug company cancelled its attempts to develop PTH into an osteoporosis drug when it was found that it can cause osteosarcoma in rats (Vahle et al. 2002). However, it turned out that this phenomenon was specific for a certain strain of rat, and only with lifelong treatment at extreme doses, starting at birth (Vahle et al. 2004). For humans, the risk is minimal.

Now, there are two PTH-related drugs on the market for treatment of osteoporosis, a segment of the protein (1–34) or the full length protein (1–84). These drugs increase the cancellous bone mass and reduce the risk of vertebral and non-vertebral fractures (Neer et al. 2001). The mechanism of action is complicated and not fully understood. It interacts with several signaling pathways, and is related to mechanical loading. One important result of these processes is that it increases osteoblast recruitment and survival, leading to an increased number of these bone-making cells (Jilka 2007).

PTH is a potent stimulator of bone formation, especially at sites of regeneration

Troels Andreassen in Århus, Denmark, was the first to show accelerated fracture repair with PTH (Andreassen et al. 1999). His group studied the healing of tibial shaft fractures in rats, and noted increased strength and improved histological maturity, using very high doses of PTH (1–34). He then persuaded me to study the effects of PTH in bone chambers (Skripitz et al. 2000a). This enabled us to compare the effects on regenerating bone with those on bone undergoing normal baseline remodeling. The bone chambers are empty compartments inside titanium implants. After insertion, they will be filled with newly-formed bone. The amount of bone inside the chamber becomes a measure of the bone-forming capacity of the animal. 6 weeks after implantation, the chamber contained mainly bone marrow with few trabeculae. With a high dose of PTH, the chamber instead contained almost compact bone (Skripitz et al. 2000a). The difference was even apparent with the naked eye. In contrast to these striking effects, we could see only a minimal—or no—effect on the cancellous bone of a vertebra or the distal femur (Skripitz 2000b). This encouraged us to study the effect in a model for cancellous bone healing. At that time there were no such models, but we realized that drilling a hole into cancellous bone would cause a healing response. If a screw were to be placed in the hole, this response would form new bone tissue, grasping the threads and holding the screw in place. By measuring the force needed to pull the screw out, we could get a measurement of the strength of the bone formed as a result of the cancellous healing response. In this model, we were able to triple the pull-out force by 6 weeks of PTH treatment (Skripitz and Aspenberg 2001a, b). A long series of other animal experiments have then confirmed the positive effects of PTH on fracture healing in different species, locations, and under various pathological conditions (for a review, see Skripitz and Aspenberg 2004).

From rats to humans

The rat experiments used huge doses, and although we tried

to reduce them, we did not know how to translate dosing from rats to humans. Only recently have we been able to repeat the screw pull-out experiment using a dose of PTH (1–34) that is nowadays considered to be clinically relevant (Vahle 2004), and we have still found a dramatic response (submitted manuscript). Moreover, even with correct dosing, in those days it was far from certain that our findings would be relevant to humans anyway—considering other species differences, not least the difference in size.

PTH acts mainly by increasing the longevity of osteoblasts. It is not a differentiation factor like the Bone Morphogenetic Proteins (BMPs). Thus, if fracture healing in a patient has never started properly (e.g. due to NSAIDs, extensive soft tissue damage, or infection), it is unlikely that PTH treatment can help. In the case of normal healing, however, there will be lots of osteoblasts in place in the fracture callus. If PTH can make these cells work harder and longer, more patients might reach functional restoration at an early time point.

A failed wrist fracture study with interesting findings

In the year 2000, I was invited to the drug Company Eli Lilly to talk about our experiments. They were developing PTH (1–34) into an osteoporosis drug. I had with me a suggestion for a small single-center trial on unoperated distal radial fractures, with evaluation of local bone density at a single time point as the suggested primary outcome variable. This led to years of discussion, and for a long time it was uncertain whether there would ever be any study. Finally, however, in 2004 a randomized, double-blind, multicenter trial was launched. The primary outcome variable was the time to radiographic healing, defined as restored cortical continuity in 3 out of 4 visible bone contours.

The patients were randomized in 3 groups: placebo, ordinary osteoporosis dose (20 µg), or double dose (40 µg). Radiographs were obtained every second week from 5 weeks onward, and the hypothesis was that the double dose would shorten the time to cortical continuity in comparison to the placebo group. We found no such difference (Aspenberg et al. 2010).

However, in spite of the lack of an effect of 40 µg, a post hoc analysis showed that the 20 µg group had a shorter time to continuity than controls (7 vs. 9 weeks; $p = 0.003$), and an analysis of all 3 groups together showed a p -value of 0.01. So there is little doubt that PTH had somehow influenced fracture healing. We now know that PTH, especially at the 40 µg dose, increases cortical remodeling in the radius, leading to increased porosity. Perhaps the increased remodeling had also blurred the new-forming contours that defined healing.

The “potato-sorting method” showed a clearer result than time to cortical healing

The wrist fracture study became a severe challenge, because precisely at this time, most centers with an interest in radial fractures and research switched to operative treatment of

almost all fractures. It took 2.5 years and 14 centers in 7 countries to collect 105 fractures. A third of the patients were recruited in Linköping. This enabled us to study a variant of the outcome variable that I had originally suggested, namely the radiographic status at 5 weeks. This is the time point when we tell the patient that she can start using her hand to hold a coffee cup, to open doors, and to carry her handbag. We therefore considered the status at 5 weeks to be a more relevant variable than the time to cortical continuity, and evaluated it in Linköping outside of the official protocol.

We used the “potato-sorting method”. Everyone can tell a big potato from a small potato without size definitions. Similarly, we classified the appearance of the 5-week radiographs as poor, intermediate, or good, deliberately without defining what it meant. After unblinding, it turned out that our classification was spectacularly accurate, with a clear relationship to the PTH dose. Of 8 placebo patients, 7 were classified as poor. Of 10 patients given 40 µg, only 1 was classified as poor (Aspenberg and Johansson 2010).

Having seen this, we went back to the radiographs to see what we had really meant by poor etc. It turned out that the “poor” cases never showed any visible bone callus at all, whereas the “good” cases showed a distinct bony callus, and the intermediate cases at least showed a suspected callus.

Based on its effects on osteoblast formation and survival, it is reasonable to assume that PTH would mainly increase the formation of an early bony callus, whereas cortical continuity is the result of more complicated phenomena that are not necessarily stimulated by PTH. Thus, I think that early callus is a better radiographic outcome variable for this kind of study.

The wrist studies are encouraging, but not conclusive

How should we interpret the results of the 2 papers on the wrist study? It must be remembered that the primary hypothesis could not be confirmed. All positive outcomes are from post hoc analyses. Even though they appear compelling, they should not be taken as proof of accelerated healing. There is a need for a confirmatory study. Furthermore, the study was not designed to evaluate clinical benefit for the patient.

Osteoporotic pelvis fractures. A randomized trial?

There has only been one more controlled study of PTH and fracture healing. Peichl et al. (2011) studied pelvis ramus fractures in 65 osteoporotic women. 21 women received daily injections of PTH (1–84), and 44 did not receive any extra treatment. CT of the pelvis after 8 weeks showed that all PTH patients had healed, and that only 4 of the controls had healed. 14 control patients remained unhealed even after 12 weeks. VAS for pain at 8 weeks was considerably lower for the PTH patients. The PTH patients could rise from a chair, walk 3 meters, and sit down again in 23 seconds (the timed up-and-go, TUG, test), whereas the controls needed 54 s. This is a very impressive difference, but also confusing, considering that the

normal value for 80–90 year olds is 11 s (Bohannon 2006). Patients with pertrochanteric hip fractures at discharge from hospital, on average 10 days after surgery, have a TUG time of 29 s (Kristensen 2012). Patients scheduled for hip replacement, who are in need of a walker, have 20 s (Unnanuntana 2012). It seems that the patients in Peichls study were far from functionally rehabilitated.

When reading the article, one is struck by the confusing description of the patient allocation process. The study is presented as a randomized controlled trial, but there is no mention of ethical approval, patient consent, or study registration. After personal contact, the senior author has informed me that 2 hospitals were involved. In one of them, every second patient was given PTH. For each untreated patient at that hospital, another untreated patient was also included from the other hospital, where none of the patients were given PTH. This study therefore has more of the elements of a case-control study than of a randomized trial, although it takes some scrutiny to realize that. The study design opens for the possibility of both sampling bias and placebo effects, and details of the blinding of the reviewers of the radiographs, who were also treating physicians, are not given. In spite of these shortcomings, the treatment effects were so dramatic that it is difficult to believe something other than that they reflect a true treatment effect of PTH.

Case series may be misleading

I have refrained from discussion of case series, which mainly deal with treatment started late because of fear of non-union. This opens for a phenomenon related to regression to the mean (some cases were about to heal anyway, although slower than average). Like many other variables, the healing time is likely to be log-normally distributed, which means that the most common healing time is shorter than the mean healing time, and that a few patients—just by chance—will have a considerably longer healing time without necessarily being problematic.

Conclusion

In summary, there is robust evidence from animal experiments that PTH can improve normal fracture healing, but this has still not been demonstrated beyond reasonable doubt in humans. The wrist study was correctly performed to avoid bias and placebo effects, but the positive effects were only seen in secondary endpoints and in a subgroup analysis. The pelvic study had

serious design flaws. It is, however, a very good idea to study pelvic fractures and to use the timed up-and-go test. Let us hope that this trial can be successfully repeated!

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