

POTENTIAL AND LIMITATIONS OF BONE ANABOLIC THERAPY WITH PARATHYROID HORMONE.

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INTRODUCTION: Therapy of osteopenic states consists mainly of treatment with anti-resorptive agents, such as hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), various calcitonins and bisphosphonates (BPs). While anti-resorptive agents are powerful tools for preventing or retarding bone loss, their impact in patients with established osteoporosis is less impressive. Owing to our difficulties to identify patients at risk at an early stage, osteopenia remains often undetected until substantial amounts of bone have been lost or even until fractures occur. Anabolic drugs like PTH might be of particular value for treating the large group of osteopenic patients detected at a late stage and should show significant advantages over anti-resorptive agents with regard to the reduction of fracture rates. This abstract addresses the potential and limitations of bone anabolic therapy with PTH.

METHODS & RESULTS: PTH can exert both anabolic and catabolic effects on bone depending on the pattern of exposure to the hormone [1]. The optimal duration of the PTH pulses in rats to create the pulsatile pattern was investigated by Dobnig and Turner [2]. Results demonstrate that the exposure of bones to supraphysiological levels of hPTH exposure should not exceed 6 to 7 hours in total. Similarly, in osteoblast-like cells isolated from newborn rat calvaria [3], intermittent exposure to PTH for the first 6h of each 48h cycle stimulated osteoblast differentiation, while continuous exposure to PTH during the 48h incubation-cycle strongly inhibited osteoblast differentiation. Both, cAMP/PKA and Ca²⁺/PKC signaling pathways, appear to be involved independently in the bone response to PTH but activation of the former is mandatory for the bone anabolic effect.

Initially, PTH-induced bone gain appears to result from direct activation of bone lining cells on virtually all cancellous and cortical surfaces

(activation of modeling drifts) [4;8]. Bone apposition on cancellous surfaces leads to trabecular thickening (*Fig 1*) a decrease in trabecular separation [5;6] with their number remaining unchanged. Endocortical and periosteal bone apposition are also observed.

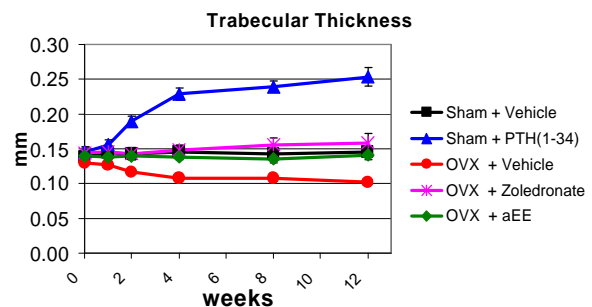


Fig 1: Trabecular thickness measured in the proxim. tibia metaphysis in OVX-rats by microCT.

The anabolic action of PTH and presumably most other bone forming agents is critically dependent on the existing template [7; 8]. Severely osteopenic bones with a poor template will show less dramatic bone gains when therapy is initiated, and *de novo* formation of trabecular bone has not been observed following the administration of therapeutically relevant doses of PTH.

PTH is anabolic for bone when administered less than daily, an important finding when considering that parenteral (s.c.) administration is required for at least 18 months to achieve the desired therapeutic results. Several studies [8;9] demonstrated the anabolic action of PTH in rats and primates [5] even when administered every 3 or 4 days only.

Bone gain is not infinite and indeed is limited by a feed-back mechanism (mechanical sensor?) and the bone mass strength achieved in the plateau is dependent on the PTH-dose (*Fig 2*).

ovx
Daily PTH s.c.

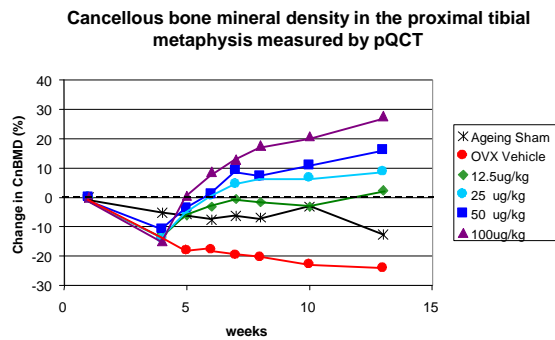


Fig. 2: PTH: Dose dependent increase in cancellous BMD measured by pQCT in the prox. tibia metaphysis in rats. OVX-intervention study.

Upon cessation of treatment, bone mass and strength must be maintained either through antiresorptive therapy (SERM, HRT, BP, CT) or continuous anabolic treatment with PTH or else the bone will be lost again [10]. Continuous PTH for maintenance may not be a good choice since it would keep bone in a state of high turnover.

One of the greatest concerns with PTH is indeed the potent activation of Haversian and cancellous bone remodeling seen in primates (11), dogs and rats (Fig 3) [12], which is also evident in clinical trials, especially in the ultradistal radius [13]. The good

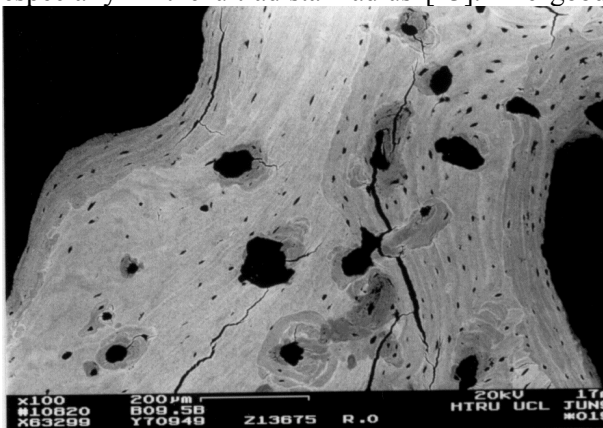


Fig 3: BSE-image of rat vertebra showing strong bone remodeling after long-term treatment with PTH(1-34).

news about the Haversian remodeling is, that this bone loss appears to represent a transient phenomenon and that the remodeling space will fill in after cessation of anabolic treatment [14]. Clinical data also suggests that co-treatment with antiresorptive agents may prevent some of the remodeling associated with PTH-therapy [15].

By the time PTH will become widely available to patients as a bone anabolic agent, a considerable number of them will have been exposed to

bisphosphonates. BPs are rapidly integrated into the superficial layers of the mineralized matrix and thus it was important to study possible interactions of such a pretreatment on the response to PTH. Pretreatment of old rats with a low dose of 28µg/kg of alendronate (s.c., 2 inj/week) blunted the anabolic response to the PTH-analog SDZ PTS-893 administered at 100µg/kg (s.c. daily) as measured by DEXA and pQCT [16]. In agreement with bone mass data, biomechanical tests showed reduced gain in bone strength after treatment of rats with the analog in BP pretreated animals. Serial pQCT measurements indicated that the PTS-893 induced activation of bone formation was delayed by roughly two weeks and that in addition, pretreated rats failed to achieve the same bone gain in the plateau as their placebo pretreated controls. The blunting of the anabolic response may result from a physicochemical interaction of the matrix embedded BP with the first responding cell i.e. the bone lining cell. However, the benefit of adding an anti-remodeling agent to PTH-treatment, especially with regard to the reduction in Haversian remodeling, may outweigh the worries about the blunted anabolic response.

DISCUSSION & CONCLUSIONS: At this time, PTH is the only approved bone anabolic treatment for postmenopausal osteoporosis. PTH activates bone lining cells into bone forming osteoblasts within 6 hours after transient exposure. The peptide increases trabecular thickness but is unable to generate a new bony template in severely depleted areas. Endocortical and periosteal bone formation is also induced by PTH. Upon cessation of treatment, bone will be lost unless it is protected by antiresorptive therapy. Co-treatment regimens (PTH + antiresorptive agent) appear to offer some protection against PTH-induced Haversian and cancellous bone remodeling. However, some data indicate, that BPs can blunt the initial response of the bone lining cells to PTH, possibly through some physicochemical interaction. Despite of some limitations, PTH is a promising novel therapy for the treatment of OP.

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