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USE OF PAMIDRONATE IN CHRONIC AND ACUTE BONE LOSS CONDITIONS

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Summary Involutional osteoporosis (OP), Osteogenesis imperfecta (OI) and Reflex sympathetic dystrophy syndrome (RSDS) are conditions in which an increase in bone resorption has been described. It therefore seems logical to prescribe a potent inhibitor of bone resorption like pamidronate (APD) in a patient suffering from any of these conditions. In our experience, oral as well as intravenous APD therapy was able to increase significantly bone mineral density (BMD) in patients with OP. This increase was more marked at the lumbar spine than at the proximal femur. With cyclical intermittent APD therapy, a plateauing effect in the BMD results during the third year appeared. After weaning from APD therapy, a remanent effect was observed: no loss of bone apparently occurred for at least two years, but the biological remodeling parameters re-increased earlier. The protective action on OP fractures has still to be clearly demonstrated, however. In children with OI, oral APD therapy has produced a dramatic increase in bone mass, without adversely interfering with the growth spur. The effect on fracture rate is still debatable in such a protean condition. Intravenous APD administered daily for twelve days has provoked a dramatic improvement in patients with long lasting RSDS which had resisted to various well-accepted therapies. However, this was an open trial, and these favorable preliminary results should be confirmed in a double-blind study.

Key words: osteoporosis, osteogenesis imperfecta, pamidronate

Involutional osteoporosis is the consequence of an increase of both bone resorption and bone formation, with the latter unable to cope with the former. The net result, therefore, will be a negative bone balance with loss of bone mineral. Whether one stimulates bone formation without affecting bone resorption, as with sodium fluoride plus calcium therapy, or inhibits bone resorption without affecting bone formation, as with antiresorbers like estrogens, calcitonin or bisphosphonates, the net result will be similar: a positive bone mass may be achieved. Whether the gain in bone mass with antiresorbers will remain unabated as long as they are administered, like with the positive bone forming agent fluoride, is still unsettled.

We report our experience with therapy of involutional osteoporosis and secondary forms of osteoporosis like glucocorticoid-induced osteoporosis, osteogenesis imperfecta as well as in local osteoporosis like regional sympathetic dystrophy syndrome (RSDS).

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Involutional Osteoporosis.

Oral therapy: We started trials with (3-amino-1-hydroxypropylidene)1,1-bisphosphonate (disodium pamidronate or APD) after the experience acquired in therapy of Paget's disease of bone. Giving 600 mg disodium pamidronate per day orally to 14 patients (5 males, 9 females) suffering from Paget's disease of bone for an average period of 15.3 (2.2) months [mean (SEM)], we found a statistically significant gain in bone mineral content (BMC) amounting to 0.5% per month at midshaft radius not affected by this condition, as measured by single photon absortiometry (SPA) of the forearm (Norland-Cameron Bone Mineral Analyzer). At distal radius, a similar increase in BMC was observed, but it did not quite

reach statistical significance[1]. In a preliminary trial comprising 12 patients (4 Males, 8 Females) of average age 56.3 (3.5), disodium pamidronate was given orally at a dose of 100 mg 30 minutes before meals t.i.d. (Aminomux®, Gador SA, Buenos Aires)[2]. The treatment was discontinued every 2 months for a free period of 2 months. After a follow-up of 8.2 (1.2) months (range:2-14 months), an increase in BMC of 5.8 (1.1) % was observed at the lumbar spine (L), as measured by dual photon absortiometry (DPA) (Novo Lab-22 A). This increase was statistically significant ($p<0.001$) and corresponded to a BMC gain of 0.67% per month. Midshaft radius BMC, as measured by SPA (Norland-Cameron Bone Mineral Analyzer) also increased, but this increase did not reach statistical significance.

According to the encouraging results of this preliminary trial, 23 patients (13 males, 10 females of average age 58.9 (2.6) were given 250-300 mg of disodium pamidronate orally 30 minutes before the meal(s), either in one 250 mg capsule or in three 100 mg capsules (Aminomux®, Gador SA, Buenos Aires)[3]. The treatment was administered cyclically and intermittently 2 months on and 2 months off, with 500 mg elemental calcium as supplement on retiring. The patients were followed for an average period of 20.2 (2.4) months, corresponding to a treatment duration amounting to 38.7 patient-years. L-BMC, measured by DPA, significantly increased from 2.9 (0.11) to 3.14 (0.11) g/cm ($p<0.001$), varying greatly from patient to patient, but corresponding on average to an increase of 6.3 (1.0)%/year. Midforearm BMC, measured by SPA, increased on average by 2.5%/year. This study was further prolonged[4], and a control group (n=56) aged 56.7 (0.7) on calcium alone was followed simultaneously. The lumbar bone mineral density (L-BMD) measured by DPA increased significantly by 2.4 (1.0)% in the first year ($p<0.05$), and by 2.5 (0.9) % in the second year ($p<0.01$) of therapy. No significant change in L-BMD was observed either during the third year [n=18;+0.1(1.5)%], in the fourth year [n=11;+0.4(1.7)%], or in the fifth year [n=7;0.1(1.5)%] (Fig 1). The control group loss in L-BMD amounted to 2.4 (0.6)%. In the appendicular skeleton, there was a non significant but potentially clinically relevant increase of BMC at midshaft forearm, as measured by rectilinear SPA (Molsgaard Nuclear Data type 1100), during

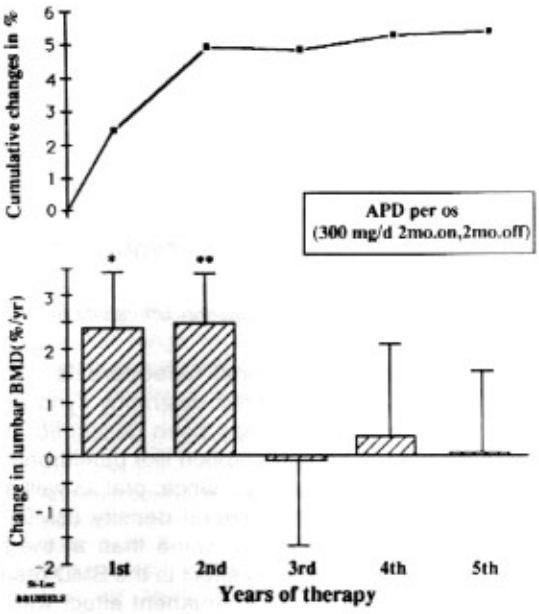

Fig. 1.- Annual changes (in per cent per year) in lumbar bone mineral density (BMD) (lower part of the figure) and cumulative changes (in percent of initial values) during therapy with cyclical intermittent pamidronate (APD), administered orally 300 mg per day 2 months on, 2 months off, measured by dual energy X-ray absorptiometry (DXA).

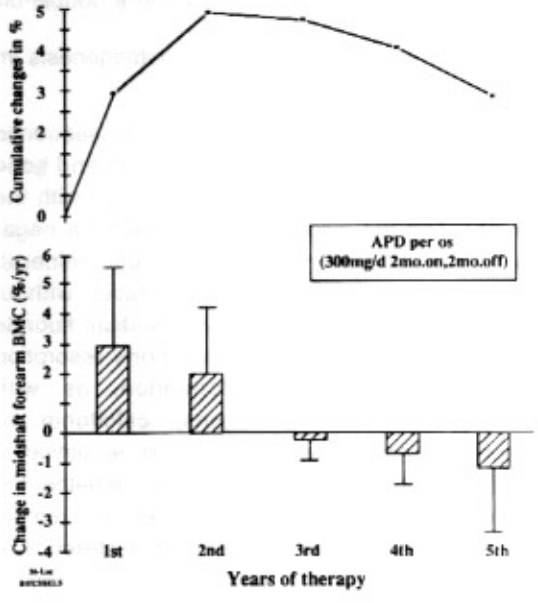

Fig. 2.- Annual changes (in per cent per year) in midshaft forearm bone mineral content (BMC) (lower part of the figure) and cumulative changes (in percent of initial values), during therapy with cyclical intermittent pamidronate (APD), administered orally 300 mg per day 2 months on, 2 months off, measured by single photon absorptiometry (SPA).

the first year [+3.4(2.6)%], as well as the second year, with a trend to some loss of effect thereafter (Fig.2)[+1.8(2.2)%]. No significant changes were observed both at distal and proximal forearm. The control group lost bone significantly, -2.4 (0.4),-1.8(0.3), -1.6(0.3)% per year, at distal, proximal and mid-forearm, respectively. The alkaline phosphatase activity dropped significantly ($p<0.05$) after 12 months of therapy, from 43.3 (3.2) to 35.5 (2.7) IU/l (NV 10-60 IU/l), with no further decrease at 24 and 36 months. The same trend of changes was observed for the fasting urinary hydroxyproline/creatinine ratio. No untoward effects have been observed with these small intermittent cyclical doses of APD, except for some mild gastrointestinal upsets in a few cases, not necessitating withdrawal from therapy.

Intravenous therapy: In order to circumvent this plateauing effect observed with the oral route of cyclical administration, we undertook a study with intravenous pamidronate (60 mg intravenously every 3 months) in 14 patients suffering from involutional osteoporosis [Age 62.1(2.1) years, initial L-BMD (QDR-1000, Hologic Inc) 0.762 (0.035) g/cm^2; initial proximal femur (PF) (total hip region)-BMD 0.703 (0.030)g/cm^2]. They were compared with a control group on calcium alone (500 mg of elemental calcium)(n=23;L-BMD 0.701(0.027) g/cm^2; PF-BMD [0.698(0.027)g/cm^2]. During follow-up in the control group, there was no significant change neither in L-BMD (+1.1(0.9) and + 0.9(0.9)%) nor in PF-BMD (-0.14(0.84), and -1.1(0.7)% during the first and second year, respectively. In the treated group, however, a significant increase in L-BMD was observed during both the first (+3.8(0.8)%) and the second year (+2.6(1.4)%), versus non significant change in PF-BMD in either year (-0.13(1.0)% and -0.2(1.3)%, respectively in the first and the second year. A trend to a plateauing effect was, therefore, again observed at the lumbar spine during the second year. In order to try to circumvent this plateauing effect also observed with the intravenous administration of pamidronate, we undertook a study with larger doses of intravenous pamidronate (30 mg daily for 5 consecutive days repeated every 2 months)[5]. Twenty-three patients suffering from involutional osteoporosis were randomly allocated to pamidronate I-V or to the same APD regimen with, in addition, 75 mg/day of enteric-coated sodium fluoride plus 1.5 g/day of elemental calcium for 2 years. L-BMD and PF-BMD were measured by DXA. The first year, L-BMD increased significantly in both groups ($p<0.001$), amounting to 4.1 (1.6)% and 6.4 (1.8)% in the I-V APD alone and the combined therapy group, respectively. In the second year, however, the increase in L-BMD remained only significant in the combined therapy group (+6.2 (1.8)%). PF-BMD did not change significantly in the combined therapy group during the first year, but increased dramatically in the single therapy group. During the 2nd year, the changes in PF-BMD were no longer significantly different in any group (Table 1). During each cycle of IV-APD, a sharp but short-lived increase in iPTH, similar in both groups was observed all along the 2 years. Serum osteocalcin expressed as yearly mean values was higher in the combined therapy group than in the APD alone group, underlying the promoting effect of NaF on bone formation. The same trend was observed for alkaline phosphatase activity. Urinary desoxypyridinoline over creatinine ratio remained more elevated in the combined therapy group, but was significantly decreased in the APD alone group (Table 1).

Remanent effect of pamidronate: It is also interesting to examine what happens to bone

Table 1: Yearly mean values of bone remodeling parameters and percentage change in proximal femur BMD in the group treated with pamidronate + NaF (A) compared with the pamidronate alone group (B)

Parameter	Group A	Group B	p
1st year			
OC (ng/ml)	4.1 (1.3)	4.0(1.2)	NS
AP (U/l)	12.2 (1.5)	9.0(0.7)	<0.05
DP/C (molar ratio)	28.3 (2.3)	16.9(1.0)	<0.01
PF-BMD (%)	-0.4 (0.7)	+2.7(0.7)	<0.05
2nd year			
OC (ng/ml)	3.1 (0.7)	1.5(0.5)	0.09
AP (U/l)	13.9(2.2)	12.7(2.6)	NS
DP/C (molar ratio)	30.5(3.4)	19.3(3.0)	<0.05
PF-BMD (%)	+1.7(1.7)	+0.9(2.1)	NS

OC=osteocalcin; AP=alkaline phosphatase; DP/C=fasting urinary deoxypyridoline over creatinine ratio; PF-BMD=proximal femur bone mineral density.

mass and remodeling after withdrawal from pamidronate therapy. In that aim, we followed 19 patients, previously treated for 4.3 (0.5) years with cyclical intermittent pamidronate, during 30.3 (2.2) months after weaning from therapy[6]. L-BMD, measured by DXA, did not change significantly in the first two years, but decreased on average 1.8% in the third year ($p<0.001$) from the last year on therapy) PF-BMD did not change significantly for three years (Fig. 3). The biological parameters of bone remodeling increased progressively with elapsing time (Table 2), underlying probably a loss of pamidronate activity. Several transiliac bone biopsies were performed in patients undergoing vertebral or peripheric fractures for histomorphometric purposes. No apparent impairment of the dynamic parameters of bone formation was observed.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a condition in which bones are abnormally brittle. Owing to the described increase of osteoclastic bone resorption and of the osteoclast count in this condition[7], we have treated several children with cyclical intermittent pamidronate[8-10]. A positive effect on both the bone mineral content and density was observed. Opaque metaphyseal bands corresponding to the periods of therapy were observed on the X-ray films taken twice yearly in the still growing children (Fig. 4). The April-June bands appear denser than the October-December bands, underlying a seasonal variation in bone remodeling. Another finding on the X-rays was that the oldest parallel radio-opaque bands had faded away. This was already visible after 6 months in the "Fall" bands, leading to the complete disappearance of the oldest first bands at some of the metaphyses. Thus the dense bone apparently undergoes complete

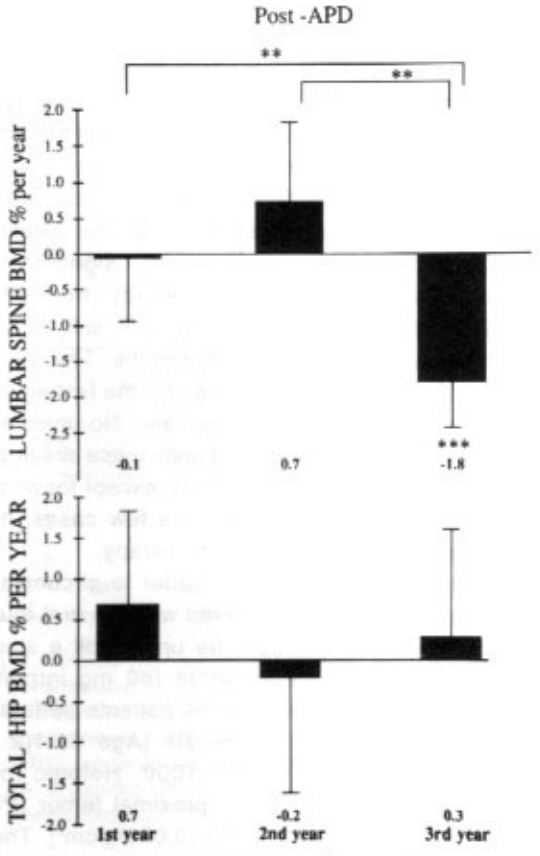

Fig. 3.- Annual changes (in per cent per year), as compared to the las year when still on pamidronate therapy, of the bone mineral density (BMD) of the lumbar spine (upper panel) and of the upper extremity of the femur (total hip), after weaning from therapy.

Table 2: Mean annual values of biological parameters of bone remodeling versus time after stopping pamidronate therapy

Follow-up (years)	Last year still on therapy	After stopping pamidronate First year	Second year	Third year
Alk P'se (IU/l)	41.9 (6.0)	45.1 (3.8)¶	49.7 (4.8)*	50.5 (4.3)¶
FU Ca creat (µg/mg)	0.152 (0.044)	0.140 (0.025)	0.160(0.032)	0.182 (0.043)
FU Hypro/creat (µg/mg)	31.8(10.9)	29.2 (7.0)	40.0 (4.4)¶	41.9(9.6)¶

¶$p<0.05$; *$p<0.01$ as compared to the last year still on therapy; Alk, P'se= alkaline phosphatase activity; FU Ca/creat = fasting urinary calcium/creatinine ratio; FU Hypro/creat = fasting urinary hydroxyproline/creatinine ratio.

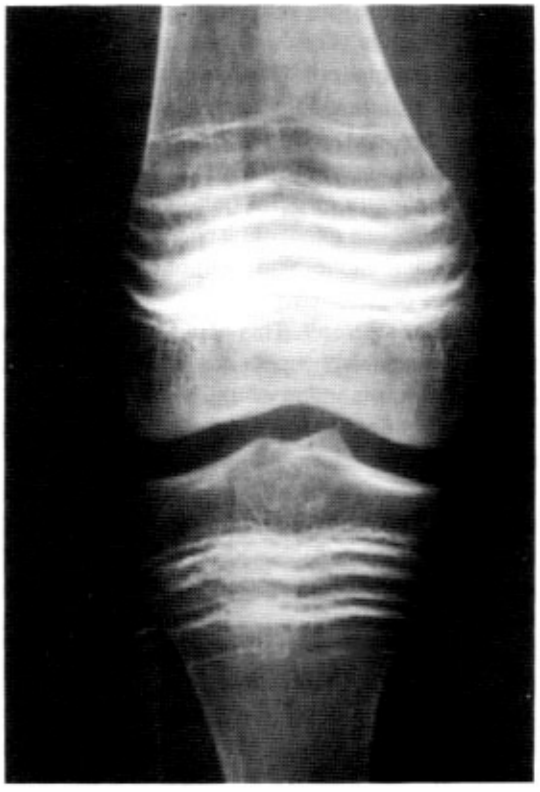

Fig. 4.- Opaque metaphyseal bands corresponding to the periods of cyclical intermittent pamidronate administered orally. See the text for details.

resorption with elapsing time. As far as the fracture rate is concerned, no definitive conclusion could be drawn in such a condition whose evolution may be variable in time. Moreover, no untoward effect on growth was observed. Bishop et al. have since dramatically amplified our preliminary experience with pamidronate therapy of O.I.[11].

Reflex Sympathetic Dystrophy Syndrome

Reflex sympathetic dystrophy syndrome (RSDS) is a condition with protean clinical manifestations. Numerous therapies have been advocated for this condition, e.g. analgesics, NSAID's glucocorticoids, beta-adrenergic blocking agents, calcitonin, with varying and inconstant therapeutic effects. Some cases, even if treated early, prove to be resistant to therapy; it is particularly true when patients are suffering from RSDS of the foot, whose evolution may last from months to years[12]. RSDS is characterized by demineralization as seen on X-rays and by an accelerated bone turnover with an increased number of osteoclasts in bone biopsies[13, 14]. Therefore, we administered pamidronate (15 mg in 500 ml saline over 4 hours), intravenously daily for 12 consecutive days in 24 patients (20 F, 4 M) aged 52.7 (2.1) year suffering from RSDS, according to the well-accepted diagnostic criteria[14, 15]. In 80% of cases, RSDS was post-traumatic. The joints involved by the pathological process were the foot in 21 cases, the shoulder in 9, the hand in 6, the knee in 4 and the hip in one case. The vast majority of the patients (n=22) had already received unsuccessful subcutaneous injections of calcitonin. Thirty-one patients (91 %) healed completely without any sequelae. Three patients improved only transiently and required a second course of therapy with a further improvement in all 3. According to the cause, post-traumatic RSDS healed in 24 of the 27 cases of that origin. Four out of the 5 neurological cases healed, as well as the phenobarbitone-induced one; the single case of the idiopathic form healed as well. I-V pamidronate was successful in 20 out of the 21 patients with RSDS of the foot, as in 8 of the 9 patients with shoulder involvement, and in 3 out of the 4 knees with RSDS. The time schedule of healing differed according to the joint involved. In the foot, weight bearing was restored after a mean of 9.8 days (range 3-15). An unaided walk was rendered possible after 25.8 days (range 5 days-3 months). In the shoulder, a full range of painless motion was again possible after 25.1 days (range 3 days 3 months). In the knees, pain significantly improved after 5 to 15 days in 3 patients, but only after 60 days in the other two. Pain in the hands diminished in 6.3 days (range 3-10), followed, after a few days, by an improvement in mobility. A transient elevation of the body temperature ranging from 37.2 to 38.4 degrees Celsius occurred from day 1 to day 4 in 7 patients. A significant drop in the leukocyte count from a mean of 6,824 (356) per ml at initiation of therapy to a nadir of 5,616 (249) per µl after 5 days, without any modification in the respective proportions of the CD3, CD4 and CD8 ratios during therapy. A drop in serum calcium was also observed, from 9.62 (0.06) mg/dl before therapy to a nadir of 8.74(0.10) mg/dl at the 5th day of the pamidronate infusions, with no further decrease throughout the treatment period. This was not simply due to hemodilution by the

saline infusion, since ionized calcium dropped significantly in parallel. No patient complained, however, from subjective nor objective symptoms of hypocalcemia. Following the drop in ionized calcium, iPTH levels increased significantly from the fourth day [23.8(2.2)pg/ml before treatment, to 54.4 (12.0) pg/ml at the tenth day]. 1,25-dixydroxyvitamin D increased in parallel, from a mean of 26.7 (2.2) pg/ml before therapy, to a high of 50.6 (4.8) pg/ml after 7 days. The fasting urinary hydroxyproline to creatinine ratio dropped significantly from 33.5 (2.8) to 26.2 (3.3) µg/mg ant the end of pamidronate infusions, demonstrating a progressive decrease in bone turnover.

Discussion

Pamidronate therapy has proven to be efficient as far as BMD was concerned in involutional OP[16,17] and in O.I.[8-11]. However, we have observed a plateauing effect of therapy after 2 years. Valkema et al.[16], who administered pamidronate at the same cumulative dose as we did, but given orally continuously at a dose of 150 mg/day, showed that there was a linear increase of 3.1 (1.0) % per year for up to 4 years. Papapoulos et al.[18], reanalyzing these data[16] "with stricter and more conservative statistical methods", showed that the net result on L-BMD was 2.4 % per year for 4 years. The difference in the results between our study and that of Valkema et al.[16] could be explained by a differing intestinal absorption of the drugs since we used different tablets. Valkema et al.[16] used enteric-coated tablets prepared by the hospital pharmacy while we used gastro-resistant soft capsules prepared by a drug company (Gador SA, Buenos Aires, Argentina). Reid et al., using the same capsule as we did, but continuously, has clearly shown a plateauing effect in the increase in BMD, both in glucocorticoid-induced OP and in OP[17, 19]. Moreover, even with cyclical intermittent intravenous pamidronate therapy, we have also observed such a plateauing in BMD from the second year, as measured by both DPA and DXA[5,20]. In our large experience in open trials with intravenous pamidronate, we have observed a positive correlation between the fasting urinary hydroxyproline/creatinine ratio before therapy and the increase in L-BMD during the first year (Fig. 5). This suggests that the observed increase in L-BMD might be due to the refilling of the remodeling spaces, which is commensurate to the initial rate of bone remodeling. The pamidronate-induced decrease in bone resorption is followed by a drop in bone formation, owing to the coupling of bone resorption and bone formation, and leading to the observed plateau in bone gain. Nevertheless, a potential anabolic effect of bisphosphonates could theoretically arise from an amount of bone deposited within erosion cavities which would exceed the depth of erosion[21]. This could be the case for the other aminobisphosphonate alendronate[22]. The alternative explanation could be an increase in mineralization at the level of the osteons, favored by the dramatic slowing down of bone turnover[23]. This alternative hypothesis should easily be dismissed of confirmed by performing studies using microradiography. It should be recalled that we have observed a plateauing effect on BMD, despite the fact that pamidronate infusions continued to induce the same acute significant rise in both iPTH and 1,25-$(OH)_2$vitamin D_3 levels, implying that this pulsed secretion either was not high enough to stimulate bone formation in our patients, or that the pamidronate precluded the activation of bone resorption, a prerequisite to obtain the full anabolic effect of PTH in vivo, as demonstrated in preclinical studies with ewes by Delmas et al. for tiludronate[24]. Whatever the mechanisms of action, promising data concerning the vertebral fracture rate or the rate of other osteoporotic fractures has been published[18, 20] but no definitive conclusion may be yet drawn[17]. Further data are urgently

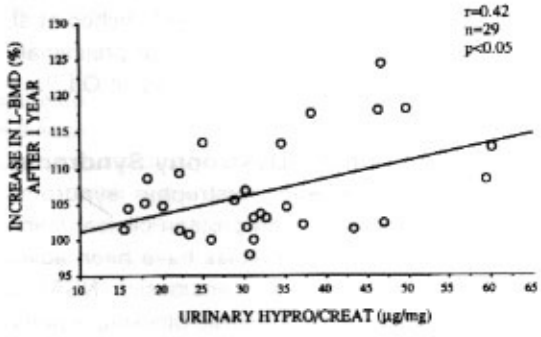

Fig. 5.- Correlation between fasting urinary hydroxyproline/creatinine ratio (Hypro/creat) prior to therapy and the increase in lumbar bone mineral density (L-BMD) after 1 year (in percent of initial values) on intravenous pamidronate therapy in 29 patients suffering from involutional osteoporosis.

needed as far as the preventive effect on fractures is concerned. The same is true for O.I. therapy. In RSDS, a potentially crippling condition, intravenous pamidronate has demonstrated some encouraging results, albeit this was not in a controlled trial[15], and it is therefore possible that the therapeutic results could be due, at least partly, to a placebo effect. However, it should be borne in mind that the success rate was high, that the patients had proven to be resistant to various other therapeutic regimens and did not show any spontaneous trend to heal. The mechanism of action of pamidronate in RSDS is unknown. Its antiosteoclastic activity, albeit very potent, cannot by itself explain such a dramatic positive effect. Some redistribution of blood flow in the diseased bones could supposedly be induced by decrease in bone turnover provoked by therapy alone, as shown in Paget's disease of bone. In our experience, no clinically significant side-effect has been observed with pamidronate therapy. Fever is a well-known self-limited complication of nitrogen-containing bisphosphonates, attributable to an acute phase reactant-like response possibly mediated by interleukin-6. No infection due to the transient leukopenia and no long-term toxicity were observed.

No freezing of bone occurred, and after stopping therapy, a progressive re-increase in the parameters of bone remodeling was observed after a few months, even after very large doses of pamidronate. Bone loss was not observed for at least 2 years, however, showing a long-lasting remanent protection of bone mass by the bisphosphonate. Therapy with pamidronate can, therefore, be considered to be a safe therapeutic agent in chronic as well as in acute bone loss conditions.

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Resumen.

Utilización del pamidronato en las enfermedades por pérdida crónica o aguda de hueso

La osteoporosis involutiva (OP), la osteogénesis imperfecta (OI) y el sindrome de distrofia simpática regional (RSDS) son condiciones en las que se describe un aumento de la resorción ósea. Por lo tanto parece lógico prescribir un potente inhibidor de la resorción ósea como el pamidronato (APD), en un paciente que sufre de alguna de estas condiciones.

En nuestra experiencia, tanto la terapia con APD oral como intravenoso es capaz de incrementar significativamente la densidad mineral ósea (BMD) en pacientes con OP. Este incremento fue más marcado en la columna lumbar que en el fémur proximal. Con la terapia cíclica intermitente de APD, resultó un efecto "meseta" en la BMD durante el tercer año. Después de suspender la terapia con APD fue observado un efecto persistente, aparentemente no ocurrió pérdida ósea por al menos dos años, pero los parámetros biológicos de remodelación volvieron a incrementarse más pronto. De todos modos, la acción protectiva sobre las fracturas en OP tiene todavía que ser claramente demostrada.

En niños con OI, la terapia con APD oral ha producido un drástico aumento en la masa ósea, sin interferir adversamente con el patrón de crecimiento. El efecto sobre la tasa de fractura tadavía es discutible en tal condición de cambio continuo. APD administrado diariamente por vía intravenosa durante veinte días provocó una drástica mejora en pacientes con RSDS de larga data que habían resistido a varias terapias bien aceptadas. Sin embargo, este fue un estudio abierto, y estos resultados favorables preliminares deberían ser confirmados en un estudio a doble ciego.

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