Eur J Clin Pharmacol (1995) 48 : 489–494

PHARMACOKINETICS AND DISPOSITION

O. J. Degrossi · M. Ortiz · E. B. Degrossi
H. García del Río · J. C. Barreira · D. Messina
E. Kerzberg · E. J. A. Roldán · E. Montuori · A. Pérez Lloret

Serum kinetics, bioavailability and bone scanning of ^{99m}Tc-labelled sodium olpadronate in patients with different rates of bone turnover

Received: 30 June 1994/Accepted in revised form: 29 March 1995

Abstract The activity of olpadronate labelled with technetium-99m(^{99m}Tc) was monitored in plasma and urine samples after single oral (925 MBq ^{99m}Tc/10 mg, coadministered with 50 mg cold drug) and intravenous (925 MBq ^{99m}Tc/5 mg) administrations to two groups of patients with different rates of bone turnover. The first group comprised high bone turnover (HBTO) patients suffering from Paget's bone disease; the second group comprised patients with normal to low bone turnover (NBTO) having the diagnosis of rheumatoid arthritis and secondary osteoporosis. Kinetic variables were correlated with anthropomorphometric variables, biological markers of bone metabolism and plasma proteins. Data were also obtained after repeatedly dosing the HBTO patients. Additionally, Paget's bone and healthy bone (PB/HB) uptake before and after low-dose oral treatment were assessed by means of scintigraphy. Results showed that most of the kinetic variables did not differ between the two groups of patients, except for a greater V_{ss} and smaller blood area under the curve AUC in the patients with HBTO. After a repeated-dose administration period, the blood AUC activity and Whole Body Retention (WBR) of the HBTO patients tended to be similar to those of the NBTO patients. In both groups, after oral dosing, the C_{max} was 20 times lower than the $C_{0.5}$ after i.v. injection, and the oral bioavailability ranged from 3% to 4%. Finally, the plasma $t_{½}ß$ ranged from 9 to 14 h. Correlation coefficients were obtained from multiple regression analysis; kinetic variables showed very low correlations with anthropomorphometric measurements. In contrast the V_{ss} and WBR were significantly correlated with serum alkaline phosphatase levels and the V_{ss} also with urine hydroxyproline levels. Plasma protein concentration was also correlated with excretion parameters such as CL_P and plasma $t_{½}ß$ after an oral dose. Scintigraphic studies in the HBTO group allowed bone selectivity to be seen through skeletal drug uptake. The 15 Pagetic lesions analysed in the HBTO group showed a decrease in PB/HB ratio from 3.8 in the basal study to 2.7 after olpadronate administration for 30 days at the rate of 50 mg/day. In conclusion, the kinetic profile of ^{99m}Tc-labelled olpadronate, mainly AUC and WBR, showed a dependence upon bone metabolism and seemed unrelated to body size variables. HBTO patients showed a lower blood AUC but a higher V_{ss}. Both variables may have been reflecting the fact that the drug binds selectively with calcified tissues and, in turn,with the target compartment. Scintigraphy confirmed the labelled-compound bone selectivity as a desirable feature for a bone-scanning agent.

Key words Paget's bone disease, Osteoporosis, Olpadronate; bisphosphonates

O. J. Degrossi · M. Ortiz · E. B. Degrossi · H. García del Río
Nuclear Medicine Center, German Hospital, Buenos Aires, Argentina

J. C. Barreira · D. Messina
Department of Rheumatology, C. Argerich Hospital, Buenos Aires, Argentina

E. Kerzberg
Department of Rheumatology, JM Ramos Mejia Hospital, Buenos Aires, Argentina

E. J. A. Roldan (✉) · E. Montuori · A. Pérez Lloret
Department of Clinical Pharmacology, Gador SA, Darwin 429

Nitrogen-containing bisphosphonates (NCBs) seem to have a double-action mechanism depending on the dosage. At high dose rates, they are potent inhibitors of bone resorption, and at lower dose rates, they act as modulators of the bone-remodelling processes, increasing skeletal mass [1–4]. The latter mechanism seems to be advantageous when bisphosphonates are employed in long-term treatments because it has no adverse consequences upon bone metabolism [4,5]. The

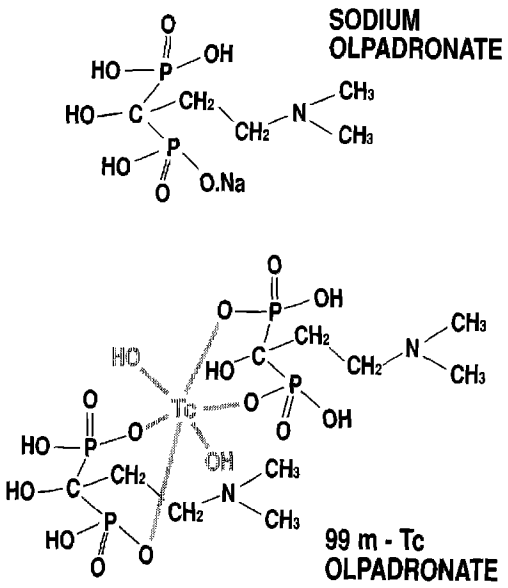

Fig. 1 A perspective view of anhydrous salt of sodium olpadronate and the technetium atom coordinated to two molecules of the protonated form of olpadronate

different bone compartments. Bisphosphonate tolerance and acceptance thereof is related to extraskeletal kinetic properties. Generally speaking, these are compounds showing low bioavailability, high osteotropism, long half-life in the skeleton and short half-life in plasma, they are not metabolized and most of them simply disappear by glomerular filtration [6,7]. The kinetic characteristics, namely disappearance, osteotropism and rapid excretion rate, account likewise for the low degree of exposure of extraskeletal tissues to bisphosphonates and, consequently, for the absence of systemic toxic effects. Bisphosphonate salt low bioavailability and solubility are related to digestive system irritation, which is evidenced by symptoms ranging from simple dyspepsia to vomiting or gastritis. Thus, kinetic properties are of interest from different points of view. Olpadronate (WHO, proposed INN List 71, previously named dimethyl APD) is a new NCB (Fig. 1), which differs from disodium pamidronate, the standard NCB, in that it is 50 times more soluble in water at pH 7.0, 5 times more potent as an inhibitor of bone resorption [3] and may cause less disturbances in the multicellular bone unit functioning (osteoclast-osteoblast interactions), a characteristic associated with bone biomechanical yielding [8]. The toxicological tests show a similar profile to that of disodium pamidronate [9] but tolerance data in humans are still very scarce, though necessary, to describe the kinetic plasma profile and bone uptake of this new NCB.

Because adequate methods for the direct assessment of olpadronate in biological fluids are still under development, this first study was intended as an indirect approach to describe the kinetics of olpadronate in humans. The activity observed in plasma and urine after oral and intravenous administration on an HBTO group and another NBTO group of patients is reported here. Kinetic variables were correlated with anthropomorphometric measurements, bone metabolism tracers and the plasma proteins. Data were also obtained after repeatedly dosing the HBTO patients. As a secondary aim, healthy bone and Paget's bone captation before and after low-dose treatment was assessed in the HBTO group, by means of scintigraphy, in order to describe ^{99m}Tc-labelled olpadronate use as a bone-scanning agent within the same protocol.

Material and methods

Subjects

Since NCBs are potent inhibitors of bone resorption, tending to accumulate on the skeleton, and the research protocol required the use of repeated doses, an agreement was reached with the Research and Ethics Committees of the Buenos Aires German, Argerich and Ramos Mejia Hospitals to the effect that only patients suffering from bone metabolism disturbances, for whom the use of the said compounds could be beneficial, were admitted and experimentation with healthy volunteers was avoided. The final protocol was approved by the Ministry of Health and Social Welfare. Two different groups of patients were selected. The first one included elderly male HBTO subjects in whom Paget's disease of bone had been diagnosed, according to clinical, biochemical and radiological criteria. The second group included adult NBTO women, with osteoporosis secondary to rheumatoid arthritis and previous corticoid exposure. Diagnosis was based on the radiological finding of at least one non-traumatically flattened vertebra and current serum alkaline phosphatase and urinary hydroxyproline levels under the upper normal value (Table I). As there were no healthy volunteers in this group, the term "normal" relates only to the current level of biological markers of bone metabolism and does not necessarily exclude qualitative abnormalities provoked by the disease itself or previous treatments. Calcaemia, the plasma electrophoretic proteinogram and creatininaemia were also assessed in all patients and mid-molecule Parathyroid Hormone (PTH) fragments in the HBTO group. The main anthropomorphometric characteristics were assessed, and laboratory tests were performed during the month prior to the active trial phase.

Table 1 Main characteristics of selected patients in the normal to low bone turnover (NBTO) group and high bone turnover (HBTO) group. Means (SE). Urinary HOP upper normal value= 77 mg/24 h; serum alkaline phosphatase upper normal value=130 UI·l^{-1}

Group (n)	NBTO (6)	HBTO (5)	HBTO/NBTO (%)
Urinary hydroxyproline HOP (mg/24 h)	54.0 (4.3)	89.0 (14.8)	+ 65.0
Serum alkaline phosphatase (UI·l^{-1})	119.2 (7.2)	287.8 (130.2)	+ 140.0
Age (years)	35.3 (2.2)	67.6 (2.7)	+ 91.0
Body weight (kg)	64.4 (6.7)	75.1 (4.6)	+ 16.6
Relative body weight (% ideal)	+ 8.8 (3.9)	+ 11.6 (5.2)	+ 31.8
Body surface area (m^2)	1.64 (0.8)	1.83 (0.1)	+ 11.6

Once the patients had been selected, their written consent was obtained for their stay in the German Hospital, under the auspices of the Nuclear Medicine Center, and for the performance and monitoring of the kinetic tests. During their hospital stay, the patients were maintained under similar dietary conditions and the active trial phase was begun under fasting conditions.

Tracer, drug administration and protocol

Each patient was dosed intravenously with ^{99m}Tc-labelled olpadronate (925 Mbq ^{99m}Tc/5 mg olpadronate). Labelling of the radiopharmaceutical compound was done by means of a method based on the electrolytic generation of Sn^{2+} (Centellokit, Gador SA, Buenos Aires) [10, 11]. Radiopharmaceutical controls performed by the chromatographic method [11] allowed the lots containing more than 1% free technetium or colloids to be discarded. In addition, scintigraphy provided evidence for the lack of a liver image (caused by colloids) or of thyroid or gastric mucosa concentrations (caused by the presence of free technetium).

After intravenous injection, blood samples were obtained at intervals of 0.5, 1, 2, 4, 6, 8, 12 and 24 h after the injection. Radioactivity was assessed in plasma aliquots by means of a "well counter" type scintillation detector with a spectrometer. Seven days after the first trial, patients were confined again in order to repeat the trial—this time upon the administration of an oral dose of 925 MBq ^{99m}Tc/10 mg of olpadronate solution associated with 50 mg (one enteric-coated tablet) cold drug. HBTO patients underwent a 30-day treatment on a 50-mg/day oral dose, at the end of which the kinetic test was repeated for the third time, after a new intravenous administration of 925 MBq-^{99m}Tc/5 mg olpadronate.

Mathematical model for statistical calculation

Blood assessments were obtained as percentage per litre in relation to the total dosage of the labelled compound. In urine, radioactivity was expressed as a percentage of the dose. On the basis of these relations, quantities are presented as mass units ($mg \cdot ml^{-1}$) per milligram administered dose. Time units are expressed in hours and decimal fractions. To perform the kinetic variable calculation, a computer program for an IBM PC was used. The area under the curve (AUC) was taken between the first (extrapolated at 0 h) and the last blood concentration measurements. Truncated areas were calculated according to the trapezoidal method. Plasma disappearance mean rate was calculated using linear regression. A new redistribution phase up to 1–5 h and a β-disappearance phase from the 6th h after administration were specifically measured. Blood clearance was calculated according to the following formula: CL = dose/total AUC. A volume of distribution, as estimated in the stationary state of blood concentrations (V_{ss}), and a volume of distribution up to a theoretical zero concentration (V_z), were assessed. Bioavailability (f) was determined by means of the formula $f = (Ae \text{ p.o.}/Ae \text{ i.v.}) \times (D \text{ i.v.}/D \text{ p.o.}) \times 100$, where Ae is the amount of activity excreted through the urine during 24 h and D is the total administered dose.

Scintigrams

In all the kinetic tests performed intravenously, bone scintigrams were taken at 3-, 4- and 6- h intervals, using a gamma camera and an MDS A2/A3 computer system, analog and digital images being obtained. Due to the characteristic kinetics of olpadronate, the best images were recorded from 4 to 6 h after administration.

In all HBTO patients, scintigraphic images were obtained in the basal study performed intravenously and again after the 30-day oral

against digital images, of regions of interest (ROIs) over the lesions, normal bone and soft tissue background with the same number of pixels [10], and calculation of the ratio of lesions to normal bone. The second method was used on analog images, following the method described by Patel et al [12], as employed by Ryan et al [13]. Scans were scored using a semiquantitative scale: 0 = no apparent lesions; 1 = just detectable increased activity; 2 = easily detectable increased activity without loss of definition of adjacent bone; 3 = easily detectable increased activity but with loss of definition of adjacent bone and 4 = easily detectable activity from lesion with none visualized from adjacent normal bone. The studies were assessed under blinded conditions, withno knowledge of whether they were pre or post-treatment. For each patient a mean score was obtained by adding the individual lesion score and dividing by the number of lesions.

Data analysis

The curves shown in the figures appear as mean values (SEM) unless (SD) is indicated. Students t-test was used for similar samples while comparing the data obtained through one or the other routes of administration and the t-test was used for independent data while comparing the HBTO and NBTO groups. Bone scan scores were compared using the dependency test. Kinetic variables were correlated with biochemical and anthropomorphometric variables by the multiple linear regression test. Body surface area was calculated by means of a nomogram. The ideal weight was assessed according to the method of the Society of Actuaries (Diem K, 1965). A TADPOLE III program, in its IBM PC version, was used, with a two-tail, $P < 0.05$ value being deemed as significant.

Results

No serious or unexpected events were recorded during the study. In addition to the biochemical data shown in Table I, the following values were obtained for the patients: mid-molecule PTH fragment 70.6 (11.9) $pg^{-1}ml$, calcaemia 9.4 (0.2) mg% and creatininaemia 0.95 (0.07 $mg \cdot dl^{-1}$).

Kinetics and bioavailability

Table 2 shows the kinetic variables calculated after oral and intravenous administration in the HBTO or NBTO patient groups (see complete curves in Fig. 2). After oral dosing, the C_{max} values were 20 times lower than the $C_{0.5}$ values after intravenous injection. Average bioavailability of the oral solution was 3.4 (1.9)% in the HBTO group, 3.6(1.2)% in the NBTO group and 3.6(0.4)% in the HBTO group after repeated oral doses. The V_{ss} in orally treated NBTO patients was 2.8 times lower than in HBTO patients and 3.6 times lower than in the same group when treated intravenously. Fig. 3 shows the AUC in each of the patients studied. AUCs were smaller in the HBTO group after oral and intravenous administrations. No other meaningful differences between the two groups were detected. According to urinary activity, whole body retention was estimated at 34.6% after the first intravenous dose in HBTO and decreased to 28.9% after 30 days oral

Table 2 Mean kinetic variables from blood samples of normal to low bone turnover (NBTO) patients or high bone turnover (HBTO) patients treated either with single intravenous or oral ^{99m}Tc-labelled olpadronate. *Last column* shows HBTO patients treated repeatedly with oral cold olpadronate and then assessed after intravenous ^{99m}Tc-labelled olpadronate

	After single doses				After repeated oral doses
Group	NBTO p.o.	NBTO i.v.	HBTO p.o.	HBTO i.v.	HBTO i.v.
n	6	6	5	5	4
Mean C_{max} ($ng \cdot ml^{-1}$)	2.85	–	2.08	–	–
Mean t_{max}(h)	2.79	–	2.05	–	–
Mean C 24 h ($ng \cdot ml^{-1}$)	0.67	2.07	0.53	1.67	1.90
AUC 0–24 h ($ng \cdot h \cdot ml^{-1}$)	32.63	186.15	27.78	145.23	158.28
AUC t_{max} p.o.	7.34[c]	86.16[a,c]	1.97	39.19[a]	–
V_{ss}(l)	13.90	50.44	38.29	67.08	64.64
V_z(l)	–	62.76	–	87.01	84.93
CL_p($ml \cdot min^{-1}$)	15.34	85.13	36.21	104.65	91.03
$t_{½}ß$ (h)[b]	13.8[d]	9.55	12.01	9.86	10.80
MRT (h)	11.16[d]	10.43	14.31	11.19	11.98

[a] At 0.5 h
[b] From 6 to 24 h
[c] $n = 4$
[d] $n = 5$

noted in the NBTO group. The $t_{½}ß$ values ranged from 9 to 14 h, and mean retention time values between 10 and 14 h. A significant ($P < 0.05$) correlation was found between serum alkaline phosphatase and V_{ss}($r = 0.68$) and WBR ($r = 0.81$); V_{ss} also correlated with urinary hydroxyproline ($r = 0.74$) after oral administration; CL_p correlated with albumin ($r = 0.82$) and $t_{½}ß$ with the β^- protein fraction ($r = 0.96$) after oral administration. Very low correlations were found between kinetic variables and anthropomorphometric measurements (r between 0.56 and -0.40). There was a high positive correlation between circulating PTH levels and C_{24}($r = 0.80$), AUC ($r = 0.82$) and C_{max}($r = 0.81$) and a negative correlation between these levels and CL_p ($r = -0.83$); however, since they were analysed for only five individuals, they were not statistically significant. Post-intravenous kinetic variables were not correlated with post-oral variables and showed a different behaviour pattern, which perhaps depended on the concentration.

Scintigrams

Scintigraphic studies carried out on HBTO patients (Fig. 4) allowed selectivity to be seen through skeletal uptake and the rapid alterations in the pathological

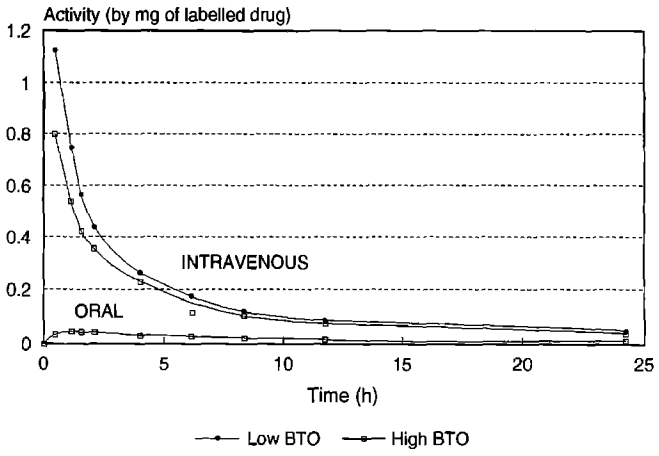

Fig. 2 Plasma activity of ^{99m}Tc-labelled olpadronate in patients with normal to low or high bone turnover (BTO) after oral and

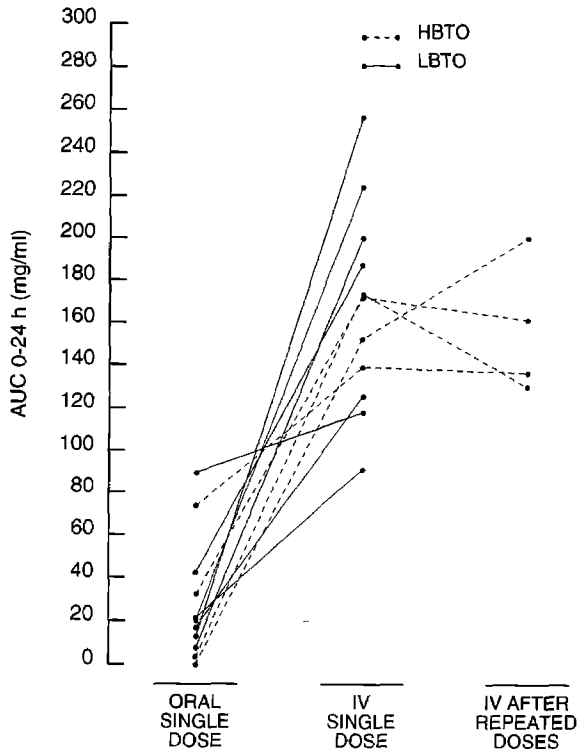

Fig. 3 AUC of ^{99m}Tc-labelled olpadronate plasma levels in patients with high (HBTO) or normal to low (NBTO) bone turnover after a

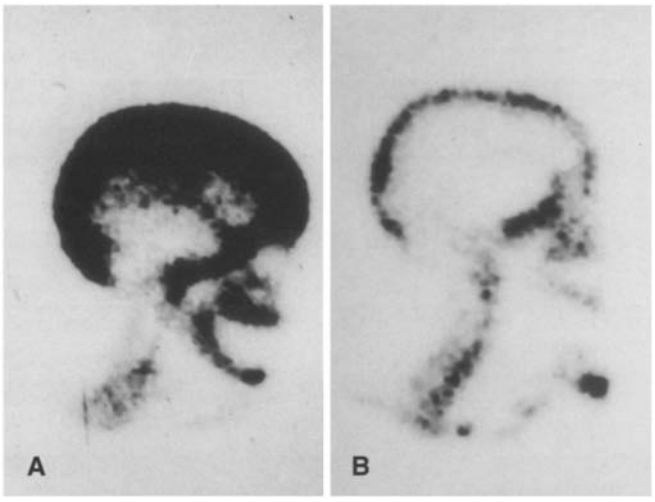

Fig. 4 A,B Effects of oral sodium olpadronate daily administration (50 mg per day, 30 days) in a patient with Paget's disease. Scan images performed with ^{99m}Tc-labelled olpadronate (**A**) before and (**B**) after treatment

areas in three out of the four patients on whom post-treatment control could be performed. The 15 Pagetic lesions analysed before and after treatment, according to Roi's method, showed a decrease in PB/HB ratio from 3.8 (1.5) in the basal study to 2.7 (1.4) after olpadronate administration for 30 days at the rate of 50 mg per day ($P < 0.05$). The second method used for studying the evolution of the affected bone areas (semiquantitative) indicated similar variations. Table 3 shows the values obtained as average number of lesions per patient. The mean scores decreased from 2.40 to 1.60 ($P < 0.05$).

Discussion

The first issue to arise from these studies is related to the use of the tracer element associated with the bisphosphonate. Some authors find differences in the kinetic data when comparing, for instance, ^{14}C-labelled pamidronate with ^{99m}Tc-labelled pamidronate [14]. These differences seem to arise when the preparations have not been duly checked and there is consequently a greater colloid captation by the liver [15]. For this reason, chromatographic controls were carried out for the assessment of free technetium and labelled colloid particles, and the preparations which did not meet the selected specifications were rejected. The efficacy of this behaviour was subsequently corroborated by the absence of images in the liver and in those tissues (thyroid, gastric mucosa) which concentrate pertechnetate (free Tc). These precautions being taken, there is a surprising similarity between the ^{99m}Tc-labelled pamidronate [10] curves and those obtained by high-performance liquid chromatography (HPLC) [16] in spite of the different methodologies involved. Care must also be taken when interpreting the absorption curves since the Tc-labelled compound is a dimer (Fig. 1); in the case of olpadronate, however, the dimerization does not seem to affect its bioavailability. Olpadronate, like the other bisphosphonates, shows little absorption. The oral solution bioavailability is variable, its mean rate being 3–4%. Bioavailability has been estimated to be 1–4% for etidronate tablets [17]; 0.3% for pamidronate tablets [16]; 2–3% for tiludronate capsules [18] and 2% for clodronate capsules [19]. Although these calculations have been obtained by different methods, they all show considerable individual variability. Generally, the plasma kinetics of bisphosphonates has little to do with their bone activity. It may mostly depend on how much bisphosphonate is available in an active bone section such as the bone apposition surface compartment [20]. The fact that the V_{ss} is smaller and AUC is bigger in the NBTO group patients demonstrates the above-mentioned dependence. The current impossibility of estimating the kinetics of the assumed active bone compartment from the plasma activity levels causes posology schedules to be based on the dose-response curves obtained from bone metabolism tracers rather than on the peripheral kinetic variables [3]. As pamidronate was previously studied under an analogous protocol [10], some considerations can be made. Both compounds behave in a similar way to the plasma absorption and distribution curve profile and the bone uptake rate. Similarities have also been described in animal species when both compounds are dosed intravenously (Mondelo N. et al., unpublished communication). Olpadronate demonstrates, in HBTO or NBTO patients, a mean $t_{½}ß$ of 9–14 h and a higher WBR% than previously described in the pamidronate report [10], thereby leading us to assume that there may be the possibility of skeletal and extraskeletal accumulation upon repeated doses, which is not the case with pamidronate. A known fact is that bisphosphonate skeletal accumulation depends on dosage and on the BTO rate [20, 21]. In this trial, performed on HBTO and NBTO patients, there seem to be no major differences in many variables of the plasma olpadronate

Table 3 Means (SD) of semiquantitative bone scan scores on HBTO patients (Paget's disease) lesions, pre and post 30 days 50 mg oral olpadronate treatment

Patient	Number of lesions	Bone scan score	
		Pre-treatment	Post-treatment
1	3	3.0	2.7[a]
2	5	2.6	1.4[b]
3	1	2.0	
4	3	2.3	1.3[b]
5	3	1.7	1.0[b]
Total	15		
Mean	–	2.40 (0.54)	1.60 (0.75)

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.