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At the time of publication, author Anh D. Le was affiliated with Ostrow School of Dentistry, University of Southern California. Currently, (s)he is a faculty member at the School of Dental Medicine at the University of Pennsylvania.

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Abstract

Objective: We hypothesized that patients with bisphosphonate (BP)-related osteonecrosis of the jaw (BRONJ) accumulate higher levels of BP in bone than those without BRONJ. Study Design: Using the Pmetrics package and published data, we designed a population pharmacokinetic model of pamidronate concentration in plasma and bone and derived a toxic bone BP threshold of 0.2 mmol/L. With the model, and using patient individual BP duration and bone mineral content estimated from lean body weight, we calculated bone BP levels in 153 subjects. Results: Mean bone BP in 69 BRONJ cases was higher than in 84 controls (0.20 vs 0.10 mmol/L, $P < 0.001$), consistent with the toxic bone threshold of 0.2 mmol/L. BRONJ was also associated with longer duration BP therapy (5.3 vs 2.7 years, $P < 0.001$), older age (76 vs 70 years, $P < 0.001$), and Asian race (49% vs 14%, $P < 0.001$). Conclusions: Our model accurately discriminated BRONJ cases from controls among patients on BP therapy. © 2013 Elsevier Inc.

Keywords

MeSH Aged, Aged, 80 and over, Bisphosphonate-Associated Osteonecrosis of the Jaw, Bone and Bones, Bone Density Conservation Agents, Case-Control Studies, Diphosphonates, Female, Humans, Jaw Diseases, Male, Middle Aged, Regression Analysis, Risk Assessment EMTREE drug terms bisphosphonic acid derivative, bone density conservation agent, pamidronic acid EMTREE medical terms aged, article, bone, case control study, chemically induced disorder, female, human, jaw disease, jaw osteonecrosis, male, metabolism, middle aged, regression analysis, risk assessment, very elderly

Disciplines

Dentistry | Oral Biology and Oral Pathology | Periodontics and Periodontology

Comments

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Population pharmacokinetic and pharmacodynamic modeling for assessing risk of bisphosphonate-related osteonecrosis of the jaw

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Objective. We hypothesized that patients with bisphosphonate (BP)-related osteonecrosis of the jaw (BRONJ) accumulate higher levels of BP in bone than those without BRONJ.
Study Design. Using the Pmetrics package and published data, we designed a population pharmacokinetic model of pamidronate concentration in plasma and bone and derived a toxic bone BP threshold of 0.2 mmol/L. With the model, and using patient individual BP duration and bone mineral content estimated from lean body weight, we calculated bone BP levels in 153 subjects.
Results. Mean bone BP in 69 BRONJ cases was higher than in 84 controls (0.20 vs 0.10 mmol/L, $P < 0.001$), consistent with the toxic bone threshold of 0.2 mmol/L. BRONJ was also associated with longer duration BP therapy (5.3 vs 2.7 years, $P < 0.001$), older age (76 vs 70 years, $P < 0.001$), and Asian race (49% vs 14%, $P < 0.001$).
Conclusions. Our model accurately discriminated BRONJ cases from controls among patients on BP therapy. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:224-232)

Millions of Americans receive antiresorptive drugs to treat common bone disorders such as osteoporosis and skeletal complications associated with osseous metastasis and multiple myeloma.[1] Of the antiresorptive drugs, nitrogen-containing bisphosphonates (BP), with their high affinity for bone and long safety record, constitute the largest class. They can be given orally or intravenously and are widely used because they are relatively inexpensive and effective across a broad spectrum of cancer and osteoporosis types.[2] However, a serious complication and adverse effect of BP therapy is bisphosphonate-related osteonecrosis of the jaw (BRONJ). This condition has been reported with both oral and intravenous BP therapy and is characterized by painful and exposed nonvital jawbone (sequestrum) in the oral cavity.[3] Severe BRONJ cases can interfere with oncological or rheumatologic care of patients. Importantly, there are no universally accepted protocols for treatment of BRONJ and there is no known cure. Accordingly, some patients never experience disease resolution and the negative impact on affected individuals and the health-care system is significant.

In general, all patients taking a given BP drug are dosed similarly, largely ignoring weight, age, or other anthropometric and interindividual pharmacokinetic (PK) differences. In September 2011 an advisory panel to the U.S. Food and Drug Administration voted 17 to 6 to recommend that labeling for BP drugs for treatment of osteoporosis should include specific information regarding duration of therapy based on an individual's risk of adverse events associated with longer-term use.[4] These risks include atypical subtrochanteric and femoral fractures, atrial fibrillation, esophageal cancer, and BRONJ. To fulfill this Food and Drug Administration recommendation, population PK and pharmacodynamic (PD) studies are a necessary first step to predict the distribution of BP-associated risk among all patients and the probability of an adverse effect in a single

Statement of Clinical Relevance

There is a significant need to understand the population pharmacokinetics and pharmacodynamics associated with bisphosphonate therapy to inform clinical decision making and therapeutics and also to reduce the serious adverse effects associated with longer-term therapy.

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patient for a given BP exposure. Currently available evidence and pharmacologic research remain inadequate to make quantitative decisions to optimize BP dosing and duration of therapy.

Therefore, the purposes of this pilot study were (1) to create a predictive model linking BP bone accumulation to BRONJ and (2) to identify patient characteristics that may be associated with an increased risk for BRONJ in patients taking BP drugs. Our hypothesis was that patients with BRONJ accumulate higher concentrations of BP in bone versus those without BRONJ and that a BP PK–PD model could help clinicians assess or predict risk for BRONJ.

MATERIAL AND METHODS

BP PK modeling

We first designed a population PK model of BP in plasma and bone, using data from 9 patients enrolled in a previously published study.[5] The authors of the study kindly provided us with BP doses and times, as well as urine and plasma concentrations and sample times. Data from that study were limited to the BP pamidronate, and because of this our model is predicated on pamidronate data. The subjects received 15 mg pamidronate intravenously daily, with intensive blood and urine sampling and monitoring over the first 5 days of therapy. We fitted the data to structural PK models using the Non-Parametric Adaptive Grid algorithm within the Pmetrics package (available from http://www.lapk.org) for R 2.14.1 (available from http://www.cran.r-project.org).

We tested 2 different structural PK models. The first model did not have a rapidly equilibrating tissue compartment and the second model did. Both models had a central compartment that represented plasma and a peripheral bone compartment with 1-way drug input from the central compartment and no elimination. Like other drugs in the BP class, pamidronate is not metabolized, is eliminated exclusively as unchanged drug in the urine, and nearly irreversibly accumulates in bone. Thus, we assumed that the cumulative amount of drug in bone at the end of each 24-hour period was equal to the total dose given minus the total amount excreted in urine.[5,6]

Intercompartmental transfer rates were all parameterized as constants, as was elimination from the central compartment. There were no covariates in the original dataset available to us, so we were unable to test the influence of factors such as weight, renal function, or food intake on pamidronate PK parameters in our model. All model parameters were transformed to their natural logarithms to avoid simulating negative values in the second step, described in the following paragraph. We chose the final model on the basis of the Akaike Information Criterion (AIC) and visual inspection of observed versus predicted plots.

BP PK–PD simulation

We derived a toxic threshold BP concentration of 0.2 mmol/L in bone by the following approach. Using in vitro cellular assays, Landesberg et al. found extracellular BP concentrations of >0.1 mmol/L to be toxic.[7] BP bound to bone is liberated into solution by osteoclastic resorption and secretion.[8] At physiological pH, the equilibrium concentration ratio of solution:bone is approximately 1:2. To achieve 0.1 mmol/L in solution, the concentration of BP in bone therefore must be approximately 0.2 mmol/L.

The concentration of BP in bone will depend upon the amount of BP distributed to bone and the volume of bone to which it is bound. We modeled bone volume as the product of the total bone mineral content (BMC) and the density of bone. Bone density ranges from 1.0 to 1.1 kg/L in osteoporotic patients, and they have a total BMC of 1.4 to 2.8 kg (3.1-6.2 lbs).[9] Although bone density is not uniform throughout the skeleton, for the purposes of this model, we assumed it to be. Because most patients with osteoporosis are given oral, rather than intravenous BP, for our simulations we fixed oral BP bioavailability at 0.7%[10] and assumed that the PK between oral and intravenous BP was otherwise the same. Selecting the extremes of the BMC ranges for osteoporotic patients,[9] we chose a reference BMC of 1.5 kg to represent a smaller or lighter person and a BMC of 3.0 kg for a larger or heavier person. Bone density was assumed to be 1.0 kg/L.[9]

With the final pamidronate PK model mean parameter values and full covariance matrix in the Pmetrics package, we simulated 1000 sets of PK parameters and corresponding plasma BP concentrations and bone BP amounts from a dosing regimen of 70 mg administered orally once weekly, the most common alendronate regimen, for example. We then calculated the weekly bone BP concentrations for 10 years of therapy, based on a BMC of 1.5 kg, and again for 3.0 kg, as references. Additionally, we calculated the bone BP concentrations for each subject in the model validation study population, described next, based on their individual estimated BMC and treatment duration. To estimate each subject's BMC, we used a linear regression equation derived from the relationship between lean body weight and BMC.[11]

Model validation and identification of additional factors associated with BRONJ

To validate the usefulness of our model, we compared predictions made by the model to observations from an ongoing natural history case–control study at our institution. Appropriate institutional review board approval

was obtained for this human subject research (USC-IRB approval HS-09-00307). Male and female adult dental patients from a 5-year span (2007-2011) at the Ostrow School of Dentistry of the University of Southern California with a history of compliant oral or intravenous BP therapy for 3 months or greater were included in the study. The electronic medical record system of our dental hospital was queried for potential study candidates. From the natural history study, we included 100 randomly selected patients with BRONJ and 100 randomly selected patients without BRONJ, all of whom were receiving BP therapy for either rheumatologic or oncological care. We used a simple randomization protocol with a random number generator scheme using Microsoft Excel.

From the study of 200 patients, for the present report we selected a subset of patients based on meeting the following ascertainment criteria. For study inclusion, all disease group cases required a diagnosis of a stage 0 to 3 BRONJ lesion, established by standard clinical and radiographic protocol as per the American Association of Oral and Maxillofacial Surgeons diagnostic criteria.[12] To minimize confounding variables or effect modifiers, patients were excluded from the study if they (1) had a history of head and neck radiation or osteoradionecrosis; (2) had concomitant steroid therapy with BP therapy, because steroids are thought to be a compounding risk factor for BRONJ; (3) had renal or hepatic disease or failure, which can effect BP PK; and (4) had a history of both oral and intravenous BP therapy, which confounded accurate cumulative and adjusted dose calculations. There were 84 controls and 69 BRONJ cases included for final analysis after applying all aforementioned ascertainment criteria.

Standardized documentation of medical and dental history and therapy records were available for all patients in addition to BP medication history, including type, route of administration, dose, duration, and underlying reason for taking BP. For each patient, we calculated the cumulative BP dose by multiplying the dose, dose frequency, and duration of therapy. We multiplied all oral doses by 0.007 prior to calculating the cumulative dose based on the bioavailability (0.7%) of oral BP drugs used by patients in our study to enable comparisons with patients who received intravenous therapy.

A head and neck exam with radiographic imaging had also been performed and documented for all patients as part of the routine clinical protocol. All BRONJ patients in the study were diagnosed by one of the study investigators (PPS) according to American Association of Oral and Maxillofacial Surgeons guidelines and using clinical criteria and radiographic imaging for every patient and histopathology when necessary. For BRONJ patients, osteonecrosis treatment history and lesion parameters such as stage, size, location, morphology, and duration were collected.

Statistics

An Excel spreadsheet was created to include all aforementioned data. R 2.14.1 (available from http://www.cran.r-project.org), including the Pmetrics nonparametric and parametric population modeling and simulation package (available from http://www.lapk.org), and SPSS (SAS/PASW) statistical software version 20.0 (IBM, Armonk, NY) were used for modeling, simulation, and covariate analysis. Prior to analysis, all data columns or variables were first assigned to categories of nominal, ordinal, interval, or ratio. Frequency tables were generated where appropriate and distribution was assessed. Means, standard deviations, and standard error of the means were calculated for applicable parametric data, and analysis of variance was used for assessment of statistical significance between groups and among groups for certain normally distributed data involving nominal and interval or ratio values. Covariates were selected on the basis of their known, potential, or theoretic relationships with BP risk and pharmacokinetics. For categorical variables, frequency and relative percentages were calculated and the univariate association with each variable and BRONJ disease was determined using Wald's test of association. For continuous variables, the mean and standard deviation was calculated and the association with each variable and BRONJ was determined using Wald's test. Logistic regression was used to evaluate the risk of BRONJ. Variables with a univariate P value of 0.20 or less were considered potential candidates to be included in a multivariate logistic model and interaction terms were evaluated using Wald's test.

RESULTS

Model selection

The model with a fast-equilibrating peripheral tissue compartment in addition to the plasma and bone compartments had an AIC of 1008 compared with 1165 for the model without the nonbone tissue compartment ($P < 0.0001$), where a lower AIC for nested models is superior. Additionally, the root mean square error of individual Bayesian posterior plasma pamidronate predictions versus observations was better for the 3-compartment model (6.72) than for the 2-compartment model (11.76) and also for bone (66.28 vs 92.67). The observed versus predicted plot for the 3-compartment model is shown in Figure 1. The linear regressions for plasma and bone both had a slope near 1, intercept near 0, and $R^2 > 0.90$, indicating an excellent fit of the data.

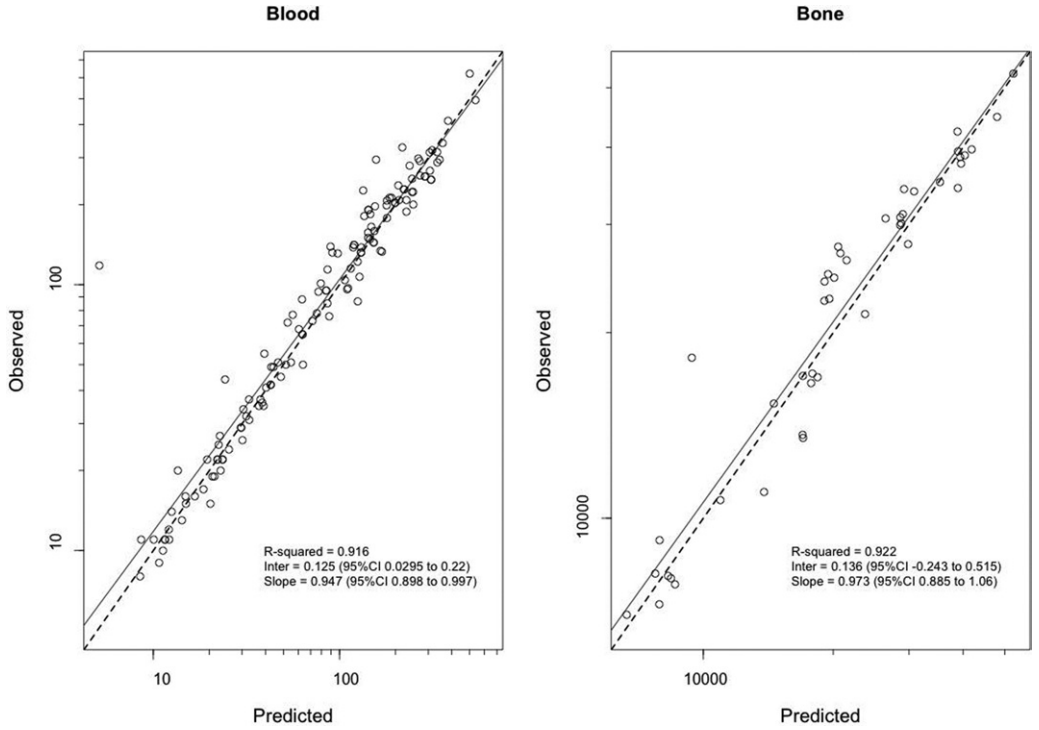

Fig. 1. Observed versus predicted pamidronate concentration (ng/mL) in blood (left) and amount (ng) in bone (right) using the final 3-compartment pharmacokinetic model. Predictions are based on the median of each subject's Bayesian posterior pharmacokinetic parameter distribution. Statistics are shown for the regression line (dashed) and compared with a reference line (solid) of slope 1, which represents the ideal.

Therefore, we chose the 3-compartment model as the final model.

Study population and model validation

Table I summarizes the clinicopathologic, pharmacotherapeutic, and demographic characteristics of the study population. There were 84 controls and 69 BRONJ cases included for final analysis after applying all aforementioned ascertainment criteria. Of the 69 BRONJ cases, 61% were stage 0 and stage 1 asymptomatic lesions, whereas 31% were stage 2 and stage 3 symptomatic lesions. Symptoms included pain, paresthesia, or dysethesia. All BRONJ cases showed panoramic radiographic evidence of an ill-defined radiolucent lesion of affected bone, with radiopaque sequestrum formation evident within the lesion in 29 (42%) of these cases. Histopathology was available for 41 cases (59%) because not all cases required surgical biopsy for diagnosis or treatment. Histopathologic features comprised inflamed and nonvital bone or a diagnosis consistent with acute or chronic osteomyelitis.

Figure 2 shows the median accumulation of bone BP over time with a dose of 70 mg weekly in 1000 smaller individuals (BMC 1.5 kg) simulated from the final model, 1000 larger individuals (BMC 3.0 kg), and 1000 individuals representing the mean of the study population (BMC 2.6 kg). With this dosing regimen, smaller individuals will reach the toxic threshold at a median of 3.3 years compared with 6.6 years for larger individuals. Included in Figure 2 is the mean of individually predicted BP bone concentrations (based on BP duration and estimated BMC) for BRONJ cases (0.20 mmol/L) versus the controls (0.10 mmol/L), which was statistically significant ($P < 0.0001$) and agreed remarkably well with our a priori calculation of a toxic bone BP concentration threshold based on in vitro data ($P = 0.55$ for difference from 0.2). The estimated BMC for cases was 2.59 and 2.61 for controls ($P = 0.57$).

Additional patient factors associated with BRONJ

Table I also shows the results of Wald's tests for univariate associations between patient factors and BRONJ. In the BRONJ group, 46 cases were related to oral BP use (38 alendronate, 3 ibandronate, 5 risedronate), 18 cases were related to intravenous BP use (14 zoledronate, 4 pamidronate), and 5 cases were related to combination therapy. Of the cases of BRONJ, 90% followed invasive dental procedures or oral trauma, which has already been established as a risk factor. A total of 41 percent of the BRONJ patients had a history of cancer as follows: multiple myeloma (n = 10),

Table 1. Summary of study population characteristics

Characteristic	*BRONJ patients (n = 69) (%)*	*Control patients (n = 84) (%)*	*Univariate P value (Wald's test)*
Age			<0.001
Mean	76	70	
Range	48–98	48–94	
Female	52 (75)	71 (85)	0.19
Race			
Caucasian	23 (33)	50 (60)	0.005
Hispanic	9 (13)	18 (21)	1.00
African American	3 (4)	4 (5)	0.61
Asian	34 (49)	12 (14)	<0.001
Height (cm)			0.65
Mean	161.0	161.8	
Range	137.1–185.4	147.3–190.5	
Weight (kg)			0.06
Mean	60.5	64.1	
Range	41.4–89.1	43.6–109.1	
BMI			0.13
Mean	23.4	24.5	
Range	16.6–35.8	15.7–39.0	
BP type*			
Alendronate†	38 (55)	60 (71)	0.02
Ibandronate‡	3 (4)	13 (16)	0.18
Risedronate§	5 (7)	0 (0)	0.02
Zoledronate¶	14 (20)	6 (7)	0.009
Pamidronate**	4 (7)	0 (0)	0.005
Combination	5 (7)	5 (6)	*
Oral route	49 (71)	73 (87)	<0.001
Adjusted dose (mg)			0.50
Mean	384.9	226.7	
Range	5.25–637.00	5.25–331.24	
BP duration (years)			<0.001
Mean	5.3	2.7	
Range	0.4–25.0	0.25–13.0	
Initial disease stage			–
0	11 (16)	Not applicable	
1	31 (45)		
2	22 (32)		
3	5 (7)		
Cancer history	28 (41)	Not consistently available	–
Osteoporosis	52 (75)	72 (86)	0.18

BMI, body mass index; *BP*, bisphosphonate; *BRONJ*, bisphosphonate-related osteonecrosis of the jaw.
*Not assessed because includes multiple differing BP drugs.
†Fosamax.
‡Boniva.
§Actonel.
¶Zometa.
**Aredia.

prostate (n = 7), breast (n = 4), colon (n = 3), lung (n = 1), and multiple primaries (n = 3).

By univariate analysis, BRONJ was significantly associated with a longer duration of BP therapy (5.3 vs 2.7 years, $P < 0.001$), older age (76 vs 70 years, $P < 0.001$), and race ($P < 0.001$). Asians comprised 49% of the BRONJ cases and only 14% of the controls ($P < 0.001$), whereas Caucasian race appeared to be protective (33% vs 60%, $P = 0.005$). Weight was marginally associated with BRONJ ($P = 0.06$), and Asians were significantly lower in weight than other races ($P < 0.001$). Sex, height, and body mass index were evaluated statistically and were not found to have any association with disease. Obesity, defined as body mass index ≥ 30, was also not statistically associated with disease. Some covariates such as cancer history, route of administration, patient comorbidities, or other medications were inconsistently present or not prevalent enough among patients or between groups to allow for statistical comparisons for association with disease. As an example, in the cancer group only a small number of patients had similar cancers, providing a lack of statis-

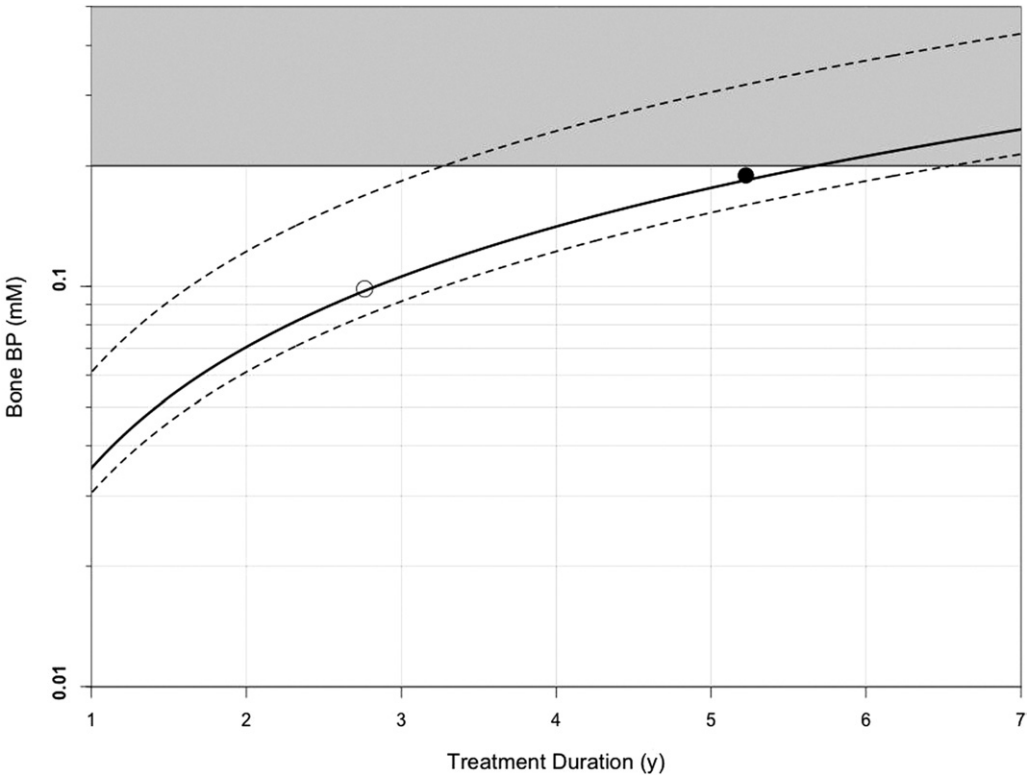

Fig. 2. Simulated bone bisphosphonate (BP) concentrations versus duration of therapy in years. The shaded box at the top represents the region of potential BP-related osteonecrosis of the jaw (BRONJ) bone toxicity above a threshold bone BP concentration of 0.2 mmol/L. The dashed lines are the medians of 1000 model-predicted accumulation profiles in patients with a bone mineral content (BMC) of 1.5 kg (upper line) or 3.0 kg (lower line). The solid line is the median of 1000 simulated profiles for the mean BMC in the study population. The open circle is the mean of the predicted bone BP concentrations for study subjects who did not have BRONJ based on each individual's treatment duration and BMC. Similarly, the closed circle is the mean of predicted bone BP concentration based on the study subjects with BRONJ, based on their individual treatment durations and BMC.

tical power to assess association with any specific cancer type.

Results for the multivariate model predicting risk of BRONJ in our population are shown in Table II. Race, age, duration of therapy, and weight were considered in the development of the predictive model. Only variables with $P < 0.05$ were retained. The multivariate data showed that after adjusting for age and duration of therapy, compared with Caucasians, Hispanics were 1.07 times as likely to experience BRONJ (95% confidence interval [CI]: 0.38-3.03), African Americans were 2.42 times as likely to experience BRONJ (95% CI: 0.46-12.59), and Asians were 5.21 times as likely to experience BRONJ (95% CI: 2.11-12.88, $P < 0.001$).

Based on these results we considered a potential population sampling bias, particularly with respect to Asians. We evaluated the racial composition of Los Angeles County and of our dental school population as a whole during the same 5-year span as our study patients. Of 10,000 dental patients at our institution, Asians comprise 12% of the patient population. According to U.S. Census Bureau data for Los Angeles County, Asians comprise approximately 14% of the population, whereas African Americans represent 9%, Hispanics 48%, and Caucasians 50%; some people report more than 1 ethnicity, so the total of all categories is more than 100%.[13] These percentages closely match our control population (Table I), except for the Hispanics, whose categorization may differ according to whether ethnicity is considered in addition to race. Overall, our random sampling scheme was not biased with respect to race.

DISCUSSION

The pathogenesis of BRONJ is considered multifactorial and usually involves oral surgery or trauma with subsequent delayed wound healing and a biofilm-mediated infection; the only consistent etiologic agent shared by the majority of patients who experience this condition is BP therapy.[14,15] Oral surgical procedures tend to expose bound BP from both superficial and deep layers of bone, releasing the drug into the local milieu where

Table II. Risk of bisphosphonate-related osteonecrosis of the jaw

	Control	*Case*	*Odds ratio**	*95% confidence interval*	*P value*
Hispanic	18	9	1.07	0.38–3.03	0.9
African American	4	3	2.42	0.46–12.59	0.3
Asian	12	34	5.21	2.11–12.88	<0.001
Test for trend†					0.6

*Adjusted for age and duration of therapy in years.
†Likelihood-ratio test (2df).

it inhibits wound healing and increases the binding affinity of oral bacteria to bone.[16] Our results show that oral or intravenous BP can reach toxic thresholds for potential induction of BRONJ with enough accumulation in jawbone depending on the duration of the therapy in addition to other PK–PD parameters or risk factors such as age, weight, and race.

At present, there are no guidelines or consensus on optimal dosage and duration of oral BP therapy. We established a toxic BP threshold in bone of 0.2 mmol/L and PK modeling to evaluate BRONJ risk over time to allow practitioners a quantitative method for assessing potential toxic accumulation of BP. The molecular features of all nitrogen-containing BP drugs (e.g., the drugs taken by all patients in this study) are similar and confer similar PK properties for the purposes of this study, allowing for comparisons between drugs such as pamidronate (used for model development) and other nitrogen-BP drugs taken by study patients.[17,18] This preliminary work attempts to define individualized endpoints for BP therapy based upon parameters such as age, weight, race, or total BMC that can be estimated from lean body weight or measured by dual-emission x-ray absorptiometry (DEXA). Because we did not have data for consistently measured total BMC by DEXA for many patients in our study, this was a limitation. Therefore, to evaluate similar data for every patient and minimize variability, we did not use any DEXA scores in our modeling, but were able to draw meaningful conclusions with an estimated BMC from readily available clinical indexes such as height, weight, and lean body mass. A study similar to ours that includes DEXA-measured BMC data for patients as a covariate for PK modeling would be beneficial in the future. For BRONJ specifically, measured density of the jawbones could provide more useful information for disease risk because these bones are thought to preferentially take up BP drug because of their relatively high density, particularly the denser mandible, where most cases of disease occur, compared with the maxilla.

For the purposes of this pilot study, we made several assumptions that we recognize may limit the power of our model and findings. These assumptions include presuming a uniform bone density in patients, that there is a fixed drug bioavailability, and that unknown internal and external variables affecting drug bioavailability and disease risk were relatively equally distributed between cases and controls. For the purposes of our modeling, the statistical noise in our system is minimally confounding, but future studies using prospective data acquisition, larger population sizes, additional covariate analysis, balancing of groups for known risk factors, and restricting analysis to intravenous administered BP (e.g., zoledronate) could address confounders, variability in drug bioavailability, and systemic exposure. Nonetheless, this first BRONJ-related PK–PD modeling we created illustrates the value of this methodology and of incorporating readily available information into mathematical calculations for potential use in clinical application. Predictive modeling allowed us to confirm some known, and identify some new, covariates associated with BRONJ.

Because the amount of BP in bone appears to be a significant risk factor for BRONJ development, measuring the content of BP in the jawbone of patients to determine whether they have reached the toxic threshold for induction of BRONJ would be clinically valuable. At the time of the study presented here, there was no way to accurately measure BP in bone. Recently, we developed a method for the quantification of BP in jawbone using energy dispersive x-ray spectroscopy[19]; in this pilot study comprising a small number of patients with BRONJ, we found importantly that all patients with BRONJ had BP concentrations at or above the toxic threshold. Accordingly, future PK–PD studies can potentially involve direct measurements of jawbone BP concentration to evaluate the association with BRONJ risk at the population level.

The frequency of BRONJ in osteoporosis patients taking oral BP in our study is significant and likely reflects the fact that we are a tertiary-care dental hospital with patients undergoing invasive dental procedures that are commonly associated with BRONJ. We may also have referral bias in this context. However, it is important to note that the correct population to study for an accurate understanding of oral BP-related BRONJ epidemiology is a dental patient population and not a medical or oncological patient population, because BRONJ pathogenesis usually follows invasive dental procedures. Additionally, our results help ex-

plain why patients taking oral BP, who are considered by most at little risk for developing BRONJ, could accumulate enough drug in the skeletal compartment over time to be at an increased risk for BRONJ similar to shorter-term intravenous BP patients. We have shown here and in previous studies that even oral BP therapy for as little as 1 year may be associated with BRONJ.[20] Our nonparametric Bayesian-based modeling represents a rational approach to understanding this time-to-event endpoint clinically based on PK–PD parameters and also allows for calculations of the time period required for oral dosing to reach parity with intravenous dosing. Importantly, similar PK–PD approaches can be applied to the analysis and compartmental quantification of any nitrogen-BP on the market.

In this pilot study, we found that Asians were disproportionately affected by BRONJ and showed the highest risk compared with other races. Our results suggest that this could be related to not only PK–PD but also pharmacogenomic (PG) factors. For example, in our study Asians had a lower body weight overall and thus a smaller skeletal compartment. For a given extent of drug accumulation, this could result in greater bone drug concentrations over time and increase toxicity-related events such as BRONJ. Because weight was not significant in our multivariate model, genotypic differences in Asians compared with other races may partially account for these findings and warrant further investigation. There is no evidence to support that Asians access dental care less frequently than other races, which could have confounded our findings.

Recently, PG analysis of polymorphisms has emerged as a promising tool for identifying patients with a higher risk of drug-related adverse events. In the context of BRONJ, recent genotypic analysis has identified potential biomarkers and predictors related to BRONJ development and risk such as the aromatase polymorphism.[21] Genome-wide association studies have elucidated potential genetic susceptibilities to BRONJ development such as the RBMS3 gene polymorphism.[22] Interestingly, this study did not identify any relevant signal on the major histocompatibility complex region; human leukocyte antigen haplotype variation is often associated with adverse drug reactions that have an immune-related pathogenesis. Human leukocyte antigen variants are mainly related to a drug-specific predisposition and can also be detected by genome-wide association studies with a small number of affected cases, but given the absence of such a signal, the authors speculated that BRONJ is more likely to be a toxic adverse drug reaction, which is corroborated by the fact that patients exposed to higher cumulative doses of BP are at a greater risk for developing BRONJ.[21] Our findings are consistent with this notion.

Further investigations into genetic predictors of BRONJ, combined with population PK results from studies such as ours, can ultimately lead to personalized BP therapy that is predicated on individual genotype and phenotype. This line of translational research could lead to PK–PD–PG model-based, individual dosing for patients taking BP drugs, leading to safer and more optimal dosing regimens that still provide antiresorptive benefits but reduce the risk of adverse effects like BRONJ.

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