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ORIGINAL ARTICLE

Comparison of two formulae for the calculation of glomerular filtration in the dosage of zoledronic acid

E. Ramírez Herráiz,^{a,*} N. Garrido Peño,^a R. Díez Fernández,^a A.M. Iglesias Bolaños,^b and M. Arteta Jiménez^a

^aServicio de Farmacia, Hospital Universitario de Getafe, Madrid, Spain

^bServicio de Farmacia, Hospital del Sureste, Madrid, Spain

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Abstract

Objective: To validate the use of a formula that does not require the patient's weight (Levey formula) for calculating creatinine clearance in the adjustment of the dosage of zoledronic acid.

Method: Prospective observational study in which zoledronic acid prescriptions in the Oncology and Haematology departments were recorded over the course of 8 months. The adjustment of the dose of zoledronic acid was carried out in accordance with creatinine clearance obtained using 2 different equations; the Cockcroft-Gault equation which is based on medical records, and the Levey formula which does not require the patient's weight for the calculation. The results of zoledronic acid dosage from both equations were compared using the SPSS statistics programme, via the comparison of the 2 measurements using the t Student-Fisher (t test).

Results: The t test provided a t test value of $t=-3.366$, with 112 degrees of freedom and a degree of bilateral importance of $P=.001$. The difference between both measurements was $d=-0.051[0.162]$ and the confidence interval was 95%, -0.082 to -0.021 . From the data obtained in the t test, the degree of bilateral importance ($P=.001 < .05$) indicated that the results of the test were statistically significant.

Conclusions: The difference between the dosages obtained when comparing both methods of glomerular filtration is statistically significant, although not clinically relevant, therefore the MDRD-4 formula (Levey) could be used if the patient's weight is not available.

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*Corresponding author.

E-mail address: rdiez.hugf@salud.madrid.org (E. Ramírez Herráiz).

PALABRAS CLAVE

Ácido zoledrónico;
Aclaramiento de
creatinina;
Bisfosfonatos;
Hipercalcemia;
Metástasis óseas;
Filtración glomerular;
Dosificación

Comparación de dos fórmulas de cálculo de filtrado glomerular en la dosificación del ácido zoledrónico

Resumen

Objetivo: Validar la utilización de una fórmula que no requiera del peso del paciente (fórmula de Levey) para el cálculo del aclaramiento de creatinina en el ajuste de la dosificación del ácido zoledrónico.

Método: Estudio observacional prospectivo en el que se recogen durante un período de 8 meses las prescripciones de ácido zoledrónico realizadas en los servicios de Oncología y Hematología. Se realiza el ajuste de la dosis de ácido zoledrónico de acuerdo con el aclaramiento de creatinina obtenido mediante 2 ecuaciones diferentes: a) la fórmula de Cockcroft-Gault, que es la propuesta en la ficha técnica del medicamento, y b) la fórmula de Levey, que no requiere del peso del paciente para su cálculo. Se comparan los resultados de dosificación de ácido zoledrónico de ambas ecuaciones con el programa estadístico SPSS, mediante la prueba de comparación de 2 medias calculando la t de Student-Fisher (t test).

Resultados: La prueba t proporcionó un valor $t = -3,366$, con 112 grados de libertad y un grado de significación bilateral $p = 0,001$. La diferencia entre ambas medias $\pm$ desviación estándar fue de $-0,051 \pm 0,162$, y el intervalo de confianza del 95 %, $-0,082$ a $-0,021$.

A partir de los datos obtenidos en la prueba estadística t test, el grado de significación bilateral $p = 0,001 < 0,05$ indicó que el resultado de la prueba era estadísticamente significativo.

Conclusiones: La diferencia de dosis obtenida al comparar ambos métodos de cálculo del filtrado glomerular es estadísticamente significativa, aunque sin relevancia clínica, con lo que se podría utilizar la fórmula de la Modification of Diet in Renal Disease 4 (Levey), si no disponemos del peso del paciente.

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Introduction

Zoledronic acid is a bisphosphonate that acts mainly in the bone and inhibits osteoclastic bone resorption. Its selective bone activity is due to its great affinity for mineralised bone; however the exact molecular mechanism is not clear. As well as being a powerful inhibitor of bone resorption, zoledronic acid also has anti-tumour properties that may contribute to its general efficacy in the treatment of bone metastases.¹

The therapeutic indications described in the technical data sheet approved by the Spanish Agency for Medicines and Health Products (AEMPS) are the prevention of skeletal related episodes in patients with advanced neoplasias with bone disease and the treatment of tumour-induced hypercalcaemia.²

Zoledronic acid reaches concentrations in the bone which are 100 times greater than those in the plasma and this significantly reduces 6 weeks after administration. There is no evidence of biotransformation and it is eliminated exclusively via the kidney, however this is reduced to 50% after 6 months and 60% one year after administration. This is indicative of the long retention period that zoledronic acid has in the bone.³

Nephrotoxicity induced by zoledronic acid requires control of kidney function via creatinine clearance and, occasionally, interruption to treatment, as indicated in the technical data sheet.² Furthermore, poor kidney function can cause kidney failure, precipitate the need for dialysis and can cause death in some patients.⁴

The US Food and Drug Administration (FDA) recorded 72 cases of kidney dysfunction associated with zoledronic

acid during the period from August 2001 to March 2003. Twenty-seven of these patients required dialysis and 18 died.⁴ In addition, there are retrospective studies that show substantial deterioration of kidney function with zoledronic acid. Therefore, the technical data sheet for zoledronic acid warns of nephrotoxicity, as well as the need to adjust the dose depending on creatinine clearance.² These studies reveal that the incidence of kidney dysfunction is greater in patients with multiple myeloma and those treated with pamidronate, compared to those treated with zoledronic acid.^{4,5}

A proper pharmaceutical assessment of prescriptions for zoledronic acid should include a review of patients' kidney function based on creatinine clearance and correct adjustment of the drug dosage.

The technical data sheet recommends a series of adjustments to the dose (Table 1) depending on creatinine clearance, calculated using the Cockcroft-Gault formula. This formula (Table 2)⁶ requires some demographic (age and sex) and anthropometric (weight) variables.

Given that zoledronic acid is not dosed based on the patient's weight, this is often not specified in the medical prescription. If weight is not known, the Cockcroft-Gault formula cannot be used and the pharmacist must use other formulas to calculate creatinine clearance.

There are several equations that estimate glomerular filtration based on creatinine concentrations in the serum.^{6,7} However, the most well known and most-widely validated in different population groups are the Cockcroft-Gault equation and that developed by the Modification of Diet in Renal Disease (MDRD) study group, also known as the Levey formula.⁸ There are abbreviated versions of the

Table 1 Dosage of zoledronic acid based on creatinine clearance according to the technical data sheet

Basal creatinine clearance, mL/min	Recommended dose of zoledronic acid, mg
>60	4
50-60	3.5 ^a
40-49	3.3 ^a
30-39	3.0 ^a

^aThe dose adjustment was calculated taking into account that the clearance of zoledronic acid depends on creatinine clearance; it is assumed that the appropriate area under the curve is 0.66 mg/h/L (area under the curve obtained with creatinine clearance of 75 mL/min).

Table 2 Equations for estimating glomerular filtration (conventional units)**MDRD-4**

Estimated GF = $186 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ for women}) \times (1.210 \text{ for black race})$

MDRD-6

Estimated GF = $170 \times (\text{creatinine})^{-0.999} \times (\text{age})^{-0.176} \times (\text{urea} \times 0.467)^{-0.170} \times (\text{albumin})^{0.318} \times (0.762 \text{ for women}) \times (1.180 \text{ for black race})$

Cockcroft-Gault

estimated creatinine clearance = $[(140 - \text{age}) \times \text{weight} / (72 \times \text{creatinine})] \times (0.85 \text{ for women})$

$$Cl_{\text{creatinin}} = \left[\frac{(140 - \text{age}) \times \text{weight}}{(72 \times \text{creatinine})} \right] \times (0.85^a)$$

Creatinine clearance, mL/min; albumin: albumin concentrations in the serum, g/dL; creatinine: creatinine concentrations in the serum, mg/dL; age: years; GF: glomerular filtration, mL/min/1.73m²; MDRD: Modification of Diet in Renal Disease; weight: kg; urea: urea concentrations in the serum, mg/dL.

^aFor women.

formula, depending on the number of variables contained in the equation: MDRD-6 and MDRD-4 (Table 2).⁹ Previous studies have shown the validity of the Levey formula, which does not require the patient's weight to calculate creatinine clearance.⁹ The advantages of this formula over the Cockcroft-Gault one are as follows⁹:

- Overestimates glomerular filtration (GF) to a lesser extent for values under 15 mL/min/1.73m²
- Greater diagnostic accuracy for GF values between 15 and 60 mL/min/1.73m²
- It is more precise for any GF value

The purpose of this study is to validate the use of the Levey formula to calculate creatinine clearance in the adjustment of the zoledronic dose.

Method

An observational prospective study was carried out, in which all prescriptions from the oncology and haematology department for zoledronic acid received in the pharmacy department from November 2006 until June 2007 were recorded. Creatinine clearance was calculated based on the Levey formula (MDRD-4) for all prescriptions.

For those patients whose weight was known, this was also calculated using the Cockcroft-Gault formula.^{6,8} Based on the clearance obtained, and in accordance with recommendations published in December 2004 by the FDA and incorporated in the European technical data sheet in March 2006, the adjusted doses of zoledronic acid were recorded. The dose adjustment was calculated taking into account that the clearance of zoledronic acid depends on creatinine clearance; it is assumed that the appropriate area under the curve is 0.66 mg/h/L (area under the curve obtained with creatinine clearance of 75 mL/min).²

During the study period, the pharmacist validated a total of 200 prescriptions of zoledronic acid. Weight could only be obtained in 113 of these based on prescriptions for other concomitant treatments, mainly chemotherapy.

The data recorded for each patient were: age, weight, height, creatinine, gender, illness, and creatinine clearance, obtained from the pharmacotherapeutic history.

The quantitative variables, weight, creatinine and height do not follow normal rules according to the Kolmogorov-Smirnov test and therefore these were expressed according to their average and interquartile range.

The statistical comparison of 2 averages was performed using SPSS version 13, with the *t* Student-Fisher (*t* test) for associated samples, for the purpose of checking whether there were differences in the dosage, depending on the formula used to calculate clearance in the 113 prescriptions and their statistical significance.

Results

Of the 113 prescriptions analysed, 69.03% corresponded to women (78/113) and the remaining 30.97% to men (35/113), with a corrected average age in time of 55.5 years (range, 34-88) and 65.5 years (range, 18-74), respectively, weight of 66 (range, 60-73, height of 1.55 (range, 1.51-1.63), and creatinine levels of 0.79 (range, 0.71-0.95) (Figures 1-3).

A total of 67.26% of prescriptions came from the oncology department, while the remaining 32.74% from haematology. There follows a list of the illnesses presented by the patients: multiple myeloma (35/113), breast cancer (4/113), metastatic breast cancer (46/113), non-small cell lung cancer (19/113), gallbladder cancer (1/113), prostate cancer (5/113), gastric cancer (2/113), and bladder cancer (4/113).

Tables 3 and 4 show the results of the statistical analysis performed using the SPSS program.

The *t* test showed a value of *t*=−3.366, with 112 degrees of freedom and a degree of bilateral significance *P*=.001. The difference between both averages (standard deviation) was −0.051 (0.162) and the 95% confidence interval was, −0.082 to −0.021.

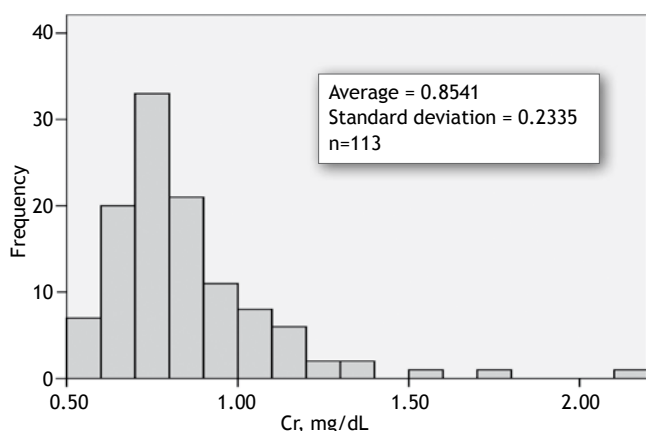


Figure 1 Creatinine (Cr) histogram.

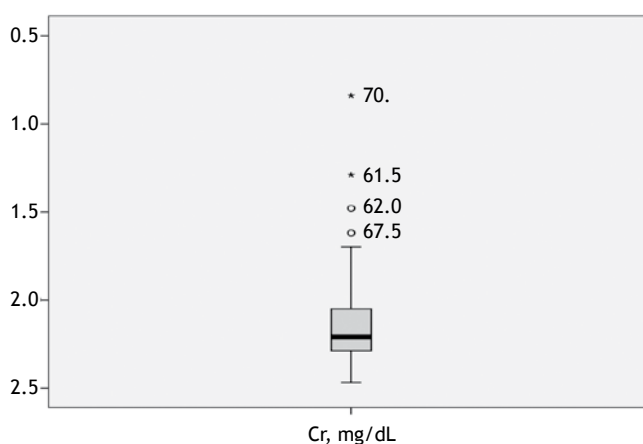


Figure 2 Creatinine (Cr) box graph.

Based on the data obtained in the statistical *t* test, the degree of bilateral significance $P=.001 < .05$ indicated that the test result was statistically significant.

Discussion

In a recent cohort study performed on prescriptions for zoledronic acid and its adjustment by the pharmacist (based on creatinine clearance calculated using the Cockcroft-Gault formula), the authors concluded that it would be useful to perform clinical studies using the MDRD-4 formula (Levey) to assess kidney function. In this way, they can recommend dose adjustments based on this formula.¹⁰

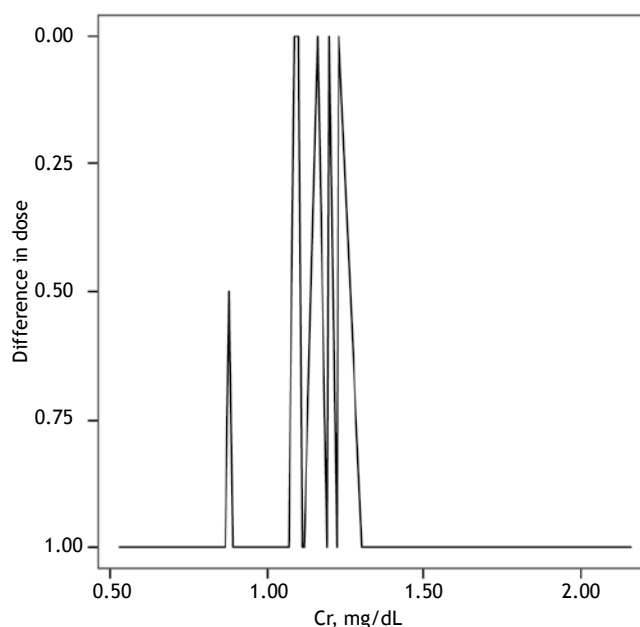


Figure 3 Interactive dispersion graph. Cr: creatinine.

Table 3 Results of statistical study. *t* test for related samples

	No.	Average dose	Standard deviation	Standard error in the average
CG group	113	3.89	0.266	0.025
Levey group	113	3.95	0.198	0.019

CG indicates Cockcroft-Gault.

One disadvantage in the use of the Levey formula is its reliability for GF values equal to or greater than 60 mL/min/1.73 m², since, in those cases, it underestimates the actual filtration rate. In certain clinical situations, such as strict vegetarian diets, muscular diseases, paralysis, acute hepatopathy, oedema, ascitis, etc, estimating GF based on an equation is inadequate and must be measured directly.¹¹

At present, due to its easy implementation in laboratory reports and sensitivity to early detection of chronic kidney disease, the MDRD-4 equation (Levey) is the formula recommended by the majority of scientific organisations.^{12,13} It is to be noted that the clinical trials performed to date generally use the Cockcroft-Gault formula to assess kidney function. Therefore, it may be useful for clinical trials

Table 4 T-test for related samples

	Average	Standard deviation	Standard error in the average	95% confidence interval for evidence		<i>t</i>	Degrees of freedom	Significance (bilateral)
				Inferior	Superior			
Dose CG-dose Levey	-0.051	0.162	0.015	-0.082	-0.021	-3.366	112	0.001

CG: Cockcroft-Gault.

to use the Levey equation to assess kidney function and recommend dose adjustments based on this formula.

The main limitation on the use of estimation equations comes from the lack of standardisation in methods for measuring creatinine. This fact has a greater impact on values of creatinine concentration which are near to the reference limits, resulting in higher inaccuracy in estimating GF greater than 60 mL/min/1.73m².

Standardisation of methods for measuring creatinine is essential, while also improving precision and accuracy, to be able to apply universal clinical decision criteria and reduce uncertainty in relation to estimated GF values greater than 60 mL/min/1.73m².

According to studies in phase I, II, and III prior to marketing of zoledronic acid, the difference in the 0.051 mg dose obtained in this study is not clinically relevant, according to the GF calculated using any of the 2 formulas. These studies were carried out with an increased dose of 0.1 mg (0.1-8 mg) and therefore the difference in doses obtained in this case is not relevant.^{14,15}

Consequently, the adjustment of the zoledronic acid dose may be performed indistinctly with the creatinine clearance obtained using both formulas. This allows the prescribing doctor and pharmacist validating the treatment to adjust the dosage of zoledronic acid in cases in which the patient's weight is not known.

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