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ORIGINAL ARTICLE

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

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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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PALABRAS CLAVE
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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 ± desviación estándar fue de —0,051 ± 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.

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