and its Summary of Product Characteristics lists neurotoxicity as an extremely rare event. However, we have observed 3 episodes similar to that described by Quiñones et al in patients on haemodialysis receiving acyclovir-valacyclovir for metameric herpes zoster.

Case 1. Female patient aged 61 years treated with oral acyclovir at 800mg/12 hours. After the third dose, she experienced a psychotic reaction with visual hallucinations and dysarthria. Antiviral treatment was suspended and the psychiatric symptoms resolved completely in 3 days.

Case 2. Male patient aged 66 years undergoing treatment with oral valacyclovir (500mg/12 hours). After the second dose, he presented dysarthria and reduced consciousness. In light of a possible case of herpesviral encephalitis, treatment was changed to IV acyclovir at 400mg/day, with no noticeable response. The level of consciousness improved after each haemodialysis session, and then decreased again. When we suspected neurotoxicity caused by the antiviral agent, we reduced the acyclovir dose to 200mg/day and started daily haemodialysis sessions; the patient improved progressively and had recovered completely by the ninth day.

Case 3. Female patient aged 83 years who was treated with valacyclovir at 1g/12 hours as prescribed by her general practitioner. Dysarthria began following the third dose. Valacyclovir was suspended and the patient underwent daily haemodialysis during 3 days, the speech disorder resolving completely.

This last patient received a high dose of valacyclovir, but in the other two patients, acyclovir and valacyclovir doses were adjusted according to the stage of renal failure. A correlation between toxicity and plasma drug levels is under debate. Some authors state that there is a higher risk of toxicity when levels exceed 20 micromoles per litre,[2] but others claim not to have witnessed symptoms in patients with levels greater than 30 micromoles, and it is therefore impossible to establish a safe therapeutic range.[3] Furthermore, the early onset of the neurological symptoms was remarkable in our three cases: in all of the patients, symptoms appeared on the second day of treatment after the second or third oral dose, which would suggest that the cause was drug idiosyncrasy rather than drug accumulation.

Haemodialysis was effective in reducing the levels of acyclovir and its metabolites.[4] This is the most effective treatment for this type of neurotoxicity, and it is an important tool for the differential diagnosis of acyclovir neurotoxicity and viral encephalitis.[2,5]

The appearance of neurological or psychiatric changes in these patients should be taken into account in order to prevent misdiagnosis, as occurred in our own case 2 and in the case described by Quiñones et al.

Conflicts of interest

The authors declare they have no potential conflicts of interest related to the contents of this article.

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Estimating glomerular filtration rate in order to adjust drug doses: confusion abounds

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To the Editor,

Two recent events led to our writing this letter.

One. For 2 or 3 years now, our local biochemistry laboratories calculate the estimated glomerular filtration rate (eGFR) by means of the MDRD-IDMS formula (formerly MDRD) and the isolated creatinine value, as per National Kidney Foundation recommendations.[1]

Yet in October 2011, we still observe the following:

- The constant used by some biochemistry laboratories for the MDRD-IDMS formula is 186, when it should be 175 since the calculation for the serum creatinine value is standardised by IDMS.
- Some laboratories deliver MDRD-IDMS results in ml/min instead of ml/min/1.73 m^2. Although it is dependent on an individual's body surface area, this could lead one to

assume that the measurement is absolute, which could have consequences when adjusting doses.

Two. While the new formula for measuring glomerular filtration rate (GFR),[2] CKD-EPI, seems to improve on the current MDRD-IDMS formula in both accuracy and precision, it is likely to make things even more confusing when it comes to choosing an equation to adjust a drug dose.

Furthermore, an article recently published in this journal comparing the MDRD-IDMS and CKD-EPI formulas in a Spanish population[3] contained what appears to be an erratum in Table 1, which describes the formulas used to calculate CKD-EPI: for males with creatinine levels >80 micromoles/litre, it states to divide by 0.7, and we believe that it should be by 0.9.

In light of all of the above, we would like to make the following observation:

From the 1980s until quite recently, GFR was estimated using the formula published by Cockcroft and Gault (CG) in 1976.[4] The result of this equation (an estimation of creatinine clearance) was used to evaluate renal function and adjust the doses of any drugs that so required. We would like to stress that the value obtained by this formula is absolute. This means that it accounts for the individual's size (since it includes weight among its variables) and gives a result in ml/min (if the body surface area differs greatly from the mean, using ideal rather than true weight is recommended.)

In 1999, 23 years after the CG formula was published, Levey published a new formula for estimating GFR: the MDRD.[5] Shortly afterwards, in 2002, the KDOQI proposed using this formula for early detection and classification of chronic kidney disease so that patients in earlier stages would have better access to nephrology care.[1] The result given by this formula is dependent on body surface area (ml/min/1.73m^2), as is also the case with the recently improved MDRD-IMDS and CKD-EPI formulas.[6,2] Since the result is dependent on a surface area of 1.73 m^2, we only need the variables age, sex, serum creatinine and race. This formula was recommended by such societies as the Spanish Society of Clinical Biochemistry and Molecular Pathology (SEQC) and the Spanish Society of Nephrology (S.E.N).[7]

Nevertheless, although generalised use of the MDRD method seems appropriate for categorising individuals in different stages of chronic kidney disease, it causes some problems in adjusting drug doses, especially if the value given by the laboratories is interpreted as an absolute value.

If we consider only the relative results (ml/min/1.73m^2) given by MDRD, MDRD-IMDS or CKD-EPI –those results given by biochemical laboratories– individuals with a body surface area >1.73m^2 will have a higher absolute eGFR value. This could lead to underdosing the patient. If the patient's body surface area is less than 1.73m^2, the absolute eGFR will be lower, which could lead to overdosing the patient (Tables 1 and 2).

On the other hand, the required dose of a certain drug may vary considerably depending on the equation used to estimate GFR, and this may have clinical repercussions.[8] With this in mind, most published drug adjustment guidelines recommend a dose and/or drug interval according to the Cockcroft-Gault formula; very few guidelines make use of MDRD.[9] In two recent examples, regulatory authorities based their recommendations on the CG formula:

- The Spanish Agency for Medicines and Health Products (AEMPS) followed the European Medicines Agency recommendation and modified the SmPC for Pradaxa® (dabigatran) and issued an informative note on 27 October 2011 reminding doctors of the importance of checking renal function before and after treatment with this new drug. They informed that before starting dabigatran treatment, renal function must be assessed in all patients by calculating creatinine clearance (CrCl) in order to exclude patients with severe renal failure (CrCl<30ml/min).[10]
- The Food and Drug Administration (FDA)'s safety update of 1 September 2011 stated that the SmPC had been changed and issued a reminder that "Reclast should not be used (is contraindicated) in patients with creatinine clearance less than 35ml/min".[11]

The FDA guidelines for the industry simply cite the CG and MDRD equations as being the most commonly used.

However, experts do not agree on which of the formulas should be used for adjusting doses in patients with renal

Table 1. Recommended dabigatran dose adjustments according to the glomerular filtration rate estimated by different equations

Formula used to estimate GFR	Results	Units	Recommendation as SmPC
Cockcroft-Gault	31.3	ml/min	Indicated
MDRD-4v	28.6	ml/min/1.73m^2	Contraindicated
MDRD-4v adjusted for body surface area	35.1	ml/min	Indicated
CKD-EPI	26.3	ml/min/1.73m^2	Contraindicated

White male 85 years of age, 180cm height, 90kg, with a serum creatinine level of 2.2mg/dL. Estimated body surface area 2.1m^2. GFR=Glomerular filtration rate

Table 2. Recommended daptomycin dose adjustments according to the glomerular filtration rate estimated by different equations

Formula used to estimate GFR	Results	Units	Recommendation as SmPC
Cockcroft-Gault	21.6	ml/min	/48h
MDRD-4v	33	ml/min/1.73m^2	/24h
MDRD-4v adjusted for body surface area	27.5	ml/min	/48h
CKD-EPI	31.5	ml/min/1.73m^2	/24h

White female 85 years of age, 150cm height, 50kg, with a serum creatinine level of 1.5mg/dl. Estimated body surface area 1.4m^2. GFR=Glomerular filtration rate

failure. Some advocate using the equation recommended by the pharmaceutical manufacturer, particularly in the case of elderly patients,[12] while others[13,14] state that the MDRD and CG equations are completely interchangeable.

In summary, and as a general rule, using the equation recommended by the pharmaceutical manufacturer (mainly CG) seems reasonable. If there is no specific recommendation, the most reliable method of estimating GFR in the target population should be should.

Regardless of which equation is used, we must remember that dose adjustments must be made using absolute GFR values, especially for patients whose body surface area differs greatly from 1.73m^2.

Conflicts of interest

The authors declare they have no potential conflicts of interest related to the contents of this article.

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