CASE DESCRIPTION

A 78-year-old man with prostate cancer needed intravenous treatment with amikacin for a suspected gram-negative bacillary respiratory infection. He had a body surface area of 1.97 m², weight of 78 kg, and body mass index of 29 kg/m². Laboratory test results are shown in Table 1. Because the initial renal function was judged to be normal and the patient was considered overweight, the antibiotic was empirically administered at 12 mg/kg once daily (1000 mg/24 h).

Predose and peak concentrations (obtained 0.5 h after completion of the intravenous dose of amikacin) were measured by a homogeneous immunoassay (Cobas Integra®, Roche) to confirm that the dosage was correct. Concentrations were fitted to a 1-compartment model using Bayesian analysis (PKS®, Abbott). Because the new estimated glomerular filtration (GFR)³ rate equations, such as Modification of Diet in Renal Disease–isotope dilution mass spectrometry (MDRD-IDMS) or CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), are not included in the software, estimations for dose adjustment were carried out using the creatinine clearance (CrCl) calculated by the Cockcroft-Gault (CG) formula. Serum creatinine (sCr) was measured by the compensated Jaffe kinetic method (IDMS-traceable assay). Adjustment of aminoglycoside dosage sought to maintain concentrations within the therapeutic intervals.

Fig. 1 shows amikacin concentrations determined in our patient as well as the dosage regimens. On the fifth day from the beginning of the antibiotic treatment, the amikacin volume of distribution and clearance estimated by applying the population pharmacokinetic equations and taking into account the CrCl were 0.25 (0.07) L/kg by applying the population pharmacokinetic equations.

Another pharmacokinetic control was carried out on the 13th day and the observed predose and peak concentrations were considered to be adequate. CysC was also measured the same day and a CKD-EPICys of 28 mL/min was recommended. To evaluate the performance of the Bayesian estimation, the measured amikacin concentrations were compared with the predicted ones, generated on the basis of the estimates of the CrCl and that estimated by the CKD-EPICys equation. The predicted (SD) concentrations were 1.11 (0.6) and 30.40 (3.30) mg/mL by using the sCr-based estimates, and 1.25 (0.71) and 34.02 (3.95) mg/mL by using CysC-based estimates. Prediction of amikacin serum concentration was more accurate when the estimation was 0.3 μg/mL, which was lower than the observed concentration in our patient (10.6 μg/mL). The presence of drug interactions with comedication was ruled out by using the Lexi-Interact™ online database. However, the patient also suffered from liver injury (Table 1). Because it has been proven that in advanced liver diseases or liver cirrhosis an overestimation of the GFR occurs when sCr is used, the measurement of serum cystatin C (CysC) was recommended to detect a possibly impaired renal function. Pending this measurement, a new dosing scheme of 750 mg/36 h was recommended.

CASE FOLLOW-UP

Serum CysC was 2.29 mg/L, measured by an immunephelometric method (Immage®, Izasa) on the ninth day. The GFR calculated by using the CKD-EPI equation was 24 mL·min⁻¹·(1.73 m²)⁻¹, corresponding to 27 mL/min according to the body surface area of the patient. This value was very similar to the estimated amikacin clearance on the fifth day (28 mL/min).

QUESTIONS TO CONSIDER

1. Under what circumstances is Cr a poor predictor of renal function and leads to overestimation of GFR?
2. If renal impairment is suspected and Cr is not increased, what other marker is suggested by Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines to estimate GFR?
3. What family of antibiotics could also be considered as markers of renal function?
was carried out by entering the CKD-EPIcys \((r^2, \text{3.2835 vs 1.6009})\).

An increase of Cr (1.3 g/dL) was observed 9 days after the end of the treatment with amikacin, which was compatible with the presence of acute kidney injury.

**DISCUSSION**

Low peak concentrations of amikacin cannot achieve the desired antimicrobial effect and have been related to increasing failure rates. On the other hand, high amikacin predose concentrations cause nephrotoxicity and ototoxicity. Because amikacin has a narrow therapeutic range, it is believed that therapeutic drug monitoring is appropriate for amikacin therapy to ensure adequate concentrations and, therefore, drug efficacy and safety \((1)\).

This antibiotic is eliminated through the kidney, so it is very important to have an accurate estimation of the patient’s renal function to establish an individualized dose \((2)\). It is well known that the most sensitive laboratory indicator to reflect the renal function is GFR. The GFR used to be estimated by CrCl in 24-h urine but this is a time-consuming and imprecise method. Nowadays equations for estimated GFR using serum measurements are considered to be more accurate than CrCl. Among them, the CG equation has been recommended for dose adjustment of drugs because the estimated CrCl is expressed in milliliters per minute. However, standardization of analytical methods of Cr (IDMS) makes this equation overestimate GFR. Thus, the best equations for this purpose are MDRD-IDMS and CKD-EPI \((3)\). In our patient, the CrCl values estimated by CG, MDRD-IDMS, and CKD-EPI at the beginning of the therapy were 76 mL/min, 87 mL/min \((76 \text{ mL} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1})\) and 85 mL/min \((75 \text{ mL} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1})\), respectively. KDIGO guidelines recommend the use of CKD-EPI or, alternatively, CKD-EPIcys to reduce bias at estimated GFR >60 mL/min.

Our patient represented a case in which sCr and the CrCl did not accurately predict the serum amikacin predose concentration. Because the estimated CrCl showed no renal impairment, an initial standard empirical dose was established. However, the observed antibiotic predose concentration after 5 days from the beginning of the treatment was much higher than expected taking into account the administered doses and the GFR. This high concentration indicated a low amikacin clearance and a large half-life, leading to antibiotic accumulation. This finding was probably due to the overestimation of GFR when sCr was used as a marker of renal function \((4)\). Our patient was 78 years old, critically ill, and had hepatic injury and, therefore, sCr was not a reliable marker of renal function. Consequently, a more accurate marker was needed for the appropriate use of amikacin in this oncologic patient.

When precision is required for dosing (e.g., due to narrow therapeutic range) and/or estimates may be unreliable (e.g., due to low muscle mass), KDIGO 2012

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**Table 1.** Laboratory results during and after the treatment with amikacin.

<table>
<thead>
<tr>
<th>Parameter, reference or therapeutic interval</th>
<th>Day of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Amikacin predose concentration, 1–4 μg/mL</td>
<td>–</td>
</tr>
<tr>
<td>Amikacin peak concentration, 25–30 μg/mL</td>
<td>–</td>
</tr>
<tr>
<td>Amikacin clearance, mL/min(^a)</td>
<td>–</td>
</tr>
<tr>
<td>Cr, 0.7–1.2 mg/dL</td>
<td>0.96</td>
</tr>
<tr>
<td>CG clearance, mL/min</td>
<td>76</td>
</tr>
<tr>
<td>CysC, 0.63–1.44 mg/L</td>
<td>–</td>
</tr>
<tr>
<td>CKD-EPI(_{cys}), mL \cdot min(^{-1}) \cdot (1.73 m(^2))^(^{-1})</td>
<td>–</td>
</tr>
<tr>
<td>CKD-EPI(_{cys}), mL/min</td>
<td>–</td>
</tr>
<tr>
<td>Albumin, 3.2–4.6 g/dL</td>
<td>–</td>
</tr>
<tr>
<td>Total bilirubin, 0.2–1.1 mg/dL</td>
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</tr>
<tr>
<td>Aspartate aminotransferase, 19–48 U/L</td>
<td>86</td>
</tr>
<tr>
<td>Alanine aminotransferase, 10–40 U/L</td>
<td>63</td>
</tr>
<tr>
<td>Alkaline phosphatase, 40–129 U/L</td>
<td>1489</td>
</tr>
<tr>
<td>γ-Glutamyl transpeptidase, 2–30 U/L</td>
<td>957</td>
</tr>
</tbody>
</table>

\(^a\) Nonlinear least-squares fitting (PKS, Abbott).

\(^b\) Measured on the same blood sample.
guidelines recommend direct measurement of GFR (4), which is very difficult in clinical practice, or to use methods based on CysC to estimate GFR by the CKD-EPI_Cys equation. These recommendations are based on many studies that have shown that CysC is superior to sCr in determination of GFR because it is not affected by hepatic dysfunction, inflammation, body surface area, age, sex, diet, and muscle mass (5). However, CysC has not been widely adopted, partly because it is a more expensive test than sCr but also because many clinicians do not believe its utility.

Several studies have revealed improved predictability of serum concentrations of antibiotics eliminated mainly via renal excretion by using CysC (6, 7, 8, 9). As a result, we decided to measure CysC to determine the renal function. In fact, the suspected renal impairment was confirmed when GFR according to the CKD-EPI_Cys was calculated.

Pharmacokinetic models that are used for Bayesian analysis in therapeutic drug monitoring include an index of renal function such as CrCl to describe drug clearance. As a result, the goodness of fit and predictive performance of the models could be better if they include a more accurate index of renal function. Hermida et al. (6) have previously addressed significant differences for pharmacokinetic parameters of amikacin when using the GFR values predicted by sCr and CysC in the Abbott PKS program in patients with hepatic dysfunction. As might be expected, in our patient the prediction of amikacin predose concentration on the 13th day was more accurate when the estimations were carried out by entering the CKD-EPI_Cys. An improvement in the estimation of amikacin peak concentration was not observed because, in general, this concentration is more affected by the apparent volume of distribution than the predose concentration.

sCr is not a good marker of early renal impairment because it takes a long time to increase above the upper limit of the reference interval. On the other hand, it has been proposed that aminoglycosides might be used to estimate renal function (10). In fact, aminoglycosides are ideal markers because they are freely filtered, are neither secreted nor reabsorbed by the kidney, and have little nonrenal clearance. In our patient, during the 14 days of
amikacin treatment no increased sCr was found and it was possible to detect renal impairment only by using CrCl 9 days after the end of the therapy. However, we could detect amikacin accumulation and decreased antibiotic clearance on the first samples tested.

We conclude that, under some circumstances, neither sCr nor estimated GFR using sCr are good markers for monitoring renal function during amikacin therapy. When observed antibiotic concentrations cannot be explained by the estimated GFR, basing aminoglycoside dosage on GFR estimated using CysC should be considered.

**POINTS TO REMEMBER**

- CrCl estimated by the CG equation should not be used for dose setting of drugs because it overestimates GFR. The best equations for this purpose are MDRD-IDMS and CKD-EPI based on Cr or CysC.
- sCr leads to overestimation of GFR in several conditions, such as decreased muscle mass, malnutrition, and hepatic dysfunction, and in elderly individuals.
- Alternatively, KDIGO 2012 guidelines suggest the CKD-EPI equation to estimate renal function in patients with suspected renal impairment who need dose setting of drugs with narrow therapeutic range.
- Aminoglycosides are freely filtered, neither secreted nor reabsorbed in the kidney, and have little nonrenal clearance. High concentrations of these antibiotics despite the use of standard doses corrected for estimated GFR should lead to suspicion of renal impairment.

**Clinical Case Study**

**Commentary**

Paul E. Stevens*

This case beautifully illustrates why KDIGO CKD guidelines recommend that for patient safety and medication management in CKD, if precision is required for dosing because of a narrow therapeutic or toxic range, then estimation of GFR through methods based on CysC or direct measurement of GFR should be used.

In clinical practice, especially in the acute setting, direct GFR measurement is impractical and there is a clear requirement for a rapid, simple, and repeatable estimate of GFR. The ideal filtration marker is a substance exclusively excreted by the kidney that is freely filtered at the glomerulus, is neither reabsorbed, metabolized, synthesized, nor secreted by the kidney, and does not influence kidney function. Although high concentrations of aminoglycosides, despite the use of standard doses corrected for Cr-based GFR estimates, may indicate renal impairment, this is akin to shutting the stable door long after the horse has gone. We therefore need biomarkers for dose setting of drugs because it overestimates GFR. The best equations for this purpose are MDRD-IDMS and CKD-EPI based on Cr or CysC.

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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**References**