Evaluation of glomerular filtration rate estimation by Cockcroft–Gault, Jelliffe, Wright and Modification of Diet in Renal Disease (MDRD) formulae in oncology patients

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Background: The aim was to evaluate the accuracy of Cockcroft–Gault, Jelliffe, Wright and Modification of Diet in Renal Disease (MDRD) formulae as a substitute for the gold standard measure of glomerular filtration rate (GFR) using chromium 51 EDTA.

Patients and methods: Retrospective analysis of GFR measurements in oncology patients from a University Teaching Hospital over 3 years was carried out. Bias and precision of estimates of GFR were compared with measured GFR.

Results: Six hundred and sixty patients with measured GFR (median 90 ml/min, range 23–179 ml/min) were identified. Cockcroft–Gault produced the smallest bias (median percentage error −1.4%) and highest precision (median absolute percentage error 14.0%) and was the most accurate for carboplatin dosing. For patients >30% over their ideal body weight (IBW), using IBW + 30% in the Cockcroft–Gault formula was more precise than using actual body weight or IBW. The Wright formula was most accurate for patients aged 70 + years and patients with a body mass index (BMI) ≥30 but overestimated GFR when GFR < 50 ml/min.

Conclusions: When measured GFR is unavailable, we advise estimating GFR using the Cockcroft–Gault formula and using IBW + 30% for patients weighing >30% over their IBW. If the GFR is ≥50 ml/min and the patient is >70 years and/or BMI ≥30, the Wright formula gives the best estimate of GFR.

Key words: carboplatin, Cockcroft–Gault, estimation, formula, glomerular filtration rate

Introduction

Many patients having therapy for cancer require assessment of renal function for dosing of cytotoxic chemotherapy agents. Carboplatin in particular is calculated using a targeted area under the plasma carboplatin concentration time curve (AUC) instead of using body surface area (BSA) [1]. The Calvert equation is used for dosing carboplatin and incorporates the glomerular filtration rate (GFR) as its key variable (Figure 1). It is therefore essential to establish an accurate GFR. Early trials used 24-h urine creatinine collection and inulin excretion;
however, these are unreliable [2, 3]. The most common methods to calculate GFR use radioisotopes such as chromium 51 EDTA and technetium-99m diethyl trimamine penta-acetic acid or a nuclear camera renogram [4–6]. The chromium 51 EDTA clearance method [4] is accurate, reproducible and commonly used. These methods are expensive and not always immediately available, especially when treatment is being delivered in the district hospital setting.

Multiple formulae have been devised to estimate the GFR as a substitute for measurement (Figure 1). Cockcroft–Gault [7] is the most commonly used formula and the modified Jelliffe formula [8] has been used in some Gynaecological Oncology Group trials. Both of these formulae use patient characteristics, e.g. age, sex, weight and serum creatinine, and assume that creatinine is eliminated entirely by glomerular filtration. The Wright formula was developed via a population kinetic method derived from chromium 51 EDTA GFR in an oncology population [9]. It can be complicated to calculate with different versions incorporating creatine kinase and adjustments for laboratory methods of calculating serum creatinine (enzyme or Jaffe method).

The Modification of Diet in Renal Disease (MDRD) formula is commonly used in clinical practice since the UK Guidelines for the Identification, Management and Referral of Adults with Chronic Kidney Disease recommended that an estimated GFR should be calculated with every request for serum creatinine in patients >18 years. The estimated GFR (Figure 1) is calculated using the abbreviated MDRD equation [10] rather than the six-variable version [11] (which includes urea and albumin as well as age, sex, creatinine and race). The MDRD formula results are reported as ml/min/1.73 m² as BSA is not part of the equation. The MDRD formula was not derived from patients with serious illness and is not currently recommended for oncology drug dosing.

BSA using the Dubois formula: \(0.007184 \times Wt \times Ht\)

Calvert[2]: \(\text{Carboplatin dose} = \text{AUC} \times (\text{GFR} + 25)\)

BMI: \(\frac{Wt}{\text{Height (m)}^2}\)

Ideal body weight using Devine formula:
- Male: \(50.0 + (0.906 \times (Ht - 152.4))\)
- Female: \(45.5 + (0.906 \times (Ht - 152.4))\)

Creatine Clearance

Cockcroft–Gault (mls/min) [7]: \(\frac{1.40 \times \text{Age} \times Wt\times(1.0 - 0.15 \times \text{Sex})}{Cr \times 0.814}\)

Jelliffe (mls/min) [8]: \(\frac{98.0 \times 0.8 \times (\text{Age} - 20) \times (1 - 0.1 \times \text{Sex}) \times (\text{BSA}/1.73)}{Cr \times 0.0113}\)

Wright (mls/min) [9]: \(\frac{6580 - 38.8 \times \text{Age} \times \text{BSA} \times (1 - 0.168 \times \text{Sex})}{Cr}\)

MDRd(mls/min/1.73m²) [10]: \(32788 \times (Cr)^{1.154} \times (\text{Age})^{0.206} \times (0.742 \times \text{Sex})\)

Key: BSA: body surface area, Sex: Male = 0, Female = 1, Age: Age in years, Cr: serum creatinine μmol/L, Ht: Height in centimetres, Wt: Weight in kilograms, BMI: Body mass index

Figure 1. Calculations.

In patients who weigh >30% above their ideal body weight (IBW), pharmacists can correct for weight by using IBW in the Calvert equation. This correction, however, can result in some patients being administered lower carboplatin doses compared with those weighing only slightly less. As a pragmatic rather than evidence-based approach, some pharmacists use IBW + 30% in the calculation of GFR.

This study evaluates the accuracy and precision of the Cockcroft–Gault, modified Jelliffe, Wright and MDRD formulae in estimating GFR compared with a gold standard measurement of GFR using chromium 51 EDTA GFR. We aim to determine which formula is the best substitute for this gold standard and evaluate the effect on carboplatin dosing in a general cancer population. In the subgroup of patients weighing >30% above their IBW, we evaluate three weight corrections: actual body weight (ABW), IBW or IBW + 30%.

**Methods**

**Patients**

Details were obtained retrospectively of all oncology patients who had undergone measurement of GFR by chromium 51 EDTA in the Department of Nuclear Medicine at our institute over a 3-year period from January 2003 until January 2006. The first recorded GFR was used for patients with multiple records, except for six patients where errors had been noted. Patient demographics were recorded at the initial visit. Body mass index (BMI), BSA and IBW were calculated (Figure 1).

**Laboratory methods and GFR calculations**

Single-sample GFR measurements were used until January 2005 and subsequently a three-sample GFR was introduced. GFR was measured following the intravenous injection of 2 MBq chromium 51 EDTA.

Serum creatinine was measured using the kinetic Jaffe method in Addenbrookes Biochemistry Department within 4 weeks of the measured chromium 51 EDTA GFR. The estimated GFR was calculated using the Cockcroft–Gault, modified Jelliffe, Wright and MDRD formulae (Figure 1). An adjustment for ethnicity was not included in the MDRD calculations, as >95% of our population is Caucasian.

**Statistical methods**

The degree of bias for each GFR formula from measured GFR (chromium 51 EDTA) was assessed by percentage error (PE), i.e. the percentage difference between the estimated and measured GFR. Precision was
assessed using absolute percentage errors (APEs), i.e. the absolute difference between the estimated and measured GFR as a percentage of measured GFR. Box and whisker plots for PE and APE were constructed.

In the subgroup of patients weighing >30% above their IBW, the APEs from using different body weights in the estimated GFR formulae were compared using a Wilcoxon signed rank test. This assumes that underestimating or overestimating measured GFR by the same amount is equivalent. If any IBW correction significantly improved the performance of the GFR estimation over using ABW, then this correction was used in all subsequent analyses. Bland and Altman [12] plots were constructed for the difference in estimated and measured GFR against measured GFR after log transformations. Regression lines for the expected value of the difference and appropriate limits of agreement were obtained [12].

An AUC 5 (mg/ml/min)/carboplatin dose was calculated for each GFR measure using the Calvert dosing equation (Figure 1). Calculated doses were compared with doses obtained using measured GFR in terms of PE and APE. An APE of >20% was considered to be a clinically relevant difference in the carboplatin dose.

results

Patient characteristics for the 660 patients identified are given in Table 1. The median age was 56 years (range 16–88 years) and 53% were male. Four hundred and thirty-nine patients had cachexia, but no reasons were identified in the other 17 cases.

Table 2. Percentage errors and absolute percentage errors for the four different GFR formulae using ABW, IBW and IBW + 30% in the calculations for the patients weighing ≥30% over their IBW

<table>
<thead>
<tr>
<th>GFR formula</th>
<th>Percentage error, median (IQR)</th>
<th>Absolute percentage error, median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft–Gault</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABW</td>
<td>11.5 (−2.8 to 26.3)</td>
<td>15.9 (6.4–27.2)</td>
</tr>
<tr>
<td>IBW</td>
<td>−26.3 (−36.4 to −16.0)</td>
<td>26.7 (17.8–36.7)</td>
</tr>
<tr>
<td>IBW + 30%</td>
<td>−4.2 (−17.3 to 9.2)</td>
<td>12.6 (6.0–25.8)</td>
</tr>
<tr>
<td>Jelliffe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABW</td>
<td>−10.7 (−24.1 to 2.1)</td>
<td>18.0 (8.4–28.8)</td>
</tr>
<tr>
<td>IBW</td>
<td>−25.9 (−36.9 to −14.4)</td>
<td>26.0 (17.6–37.0)</td>
</tr>
<tr>
<td>IBW + 30%</td>
<td>−17.2 (−29.4 to −4.3)</td>
<td>20.1 (11.6–30.4)</td>
</tr>
<tr>
<td>Wright</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABW</td>
<td>4.0 (−10.2 to 19.2)</td>
<td>13.2 (6.3–24.7)</td>
</tr>
<tr>
<td>IBW</td>
<td>−12.9 (−23.8 to 1.8)</td>
<td>17.3 (10.4–26.8)</td>
</tr>
<tr>
<td>IBW + 30%</td>
<td>−2.6 (−14.9 to 13.9)</td>
<td>14.4 (6.6–24.4)</td>
</tr>
<tr>
<td>MDRD</td>
<td>−15.7 (−32.0 to 2.7)</td>
<td>22.2 (9.8–33.4)</td>
</tr>
</tbody>
</table>

ABW, actual body weight; GFR, glomerular filtration rate; IBW, ideal body weight; IQR, interquartile range. For all patients, the Cockcroft–Gault formula exhibited the estimates with the least bias (median PE −1.4%; Table 3; Figure 2). The Wright formula tended to underestimate GFR (median PE 8.1%). The MDRD and Jelliffe formulae tended to overestimate GFR (median PE −5.2% and −9.5%, respectively; Table 3).

Table 3. Percentage errors and absolute percentage errors for the four different GFR formulae with the appropriate weight calculation for the patients weighing ≥30% over their ideal body weight

<table>
<thead>
<tr>
<th>GFR measure</th>
<th>GFR measurement, median (IQR)</th>
<th>Percentage error, median (IQR)</th>
<th>Absolute percentage error, median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium 51 EDTA GFR</td>
<td>90 (71–111)</td>
<td>−1.4 (−13.5 to 14.8)</td>
<td>14.0 (6.1–24.9)</td>
</tr>
<tr>
<td>Cockcroft–Gault</td>
<td>86 (66–116)</td>
<td>−9.5 (−20.3 to 4.2)</td>
<td>15.8 (8.0–26.2)</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>80 (63–101)</td>
<td>−8.1 (−3.4 to 25.1)</td>
<td>14.5 (6.1–26.0)</td>
</tr>
<tr>
<td>Wright</td>
<td>96 (76–121)</td>
<td>−5.2 (−21.2 to 11.3)</td>
<td>17.1 (7.4–29.9)</td>
</tr>
<tr>
<td>MDRD</td>
<td>81 (67–102)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease.
Figure 2. Box and whisker plots of (A) percentage errors and (B) absolute percentage errors for the four different GFR formulae with the appropriate weight calculation for the patients weighing ≥30% over their IBW. CG, Cockcroft–Gault; GFR, glomerular filtration rate; IBW, ideal body weight; MDRD, Modification of Diet in Renal Disease.

(Figure 3). The variability of the differences remained stable across all GFR values for all formulae, with all having fairly similar precision, although MDRD estimates were slightly more dispersed.

Clinical relevance
Using the Cockcroft–Gault formula produced the least bias (median PE −1.9%) and most precise (median APE 10.9%)
The GFR estimates using the Jelliffe formula were most accurate with younger patients aged < 40 years (Table 5; Figure 4). In patients aged 70 + years, the Wright formula gave the least biased (median PE 4.3%) and slightly more precise estimates of GFR (median APE 15.3%). Cockcroft–Gault produced the least bias estimates for the 40- to 70-year olds (median PE −2.0%).

glomerular filtration rate

Cockcroft–Gault was the most accurate formula over the full range of GFR measurements (Table 5; Figure 4). In the 46 patients with low GFR (< 50 ml/min), the Wright formula produced the most biased and imprecise estimates (median PE 28.1%, median APE 28.1%). Over a normal GFR range of 50–100 ml/min, estimates of GFR using the MDRD had the least

Table 4. Carboplatin AUC 5 doses, percentage errors, APEs in carboplatin dose and the number (percentage) of patients with an APE >20% compared with doses obtained using chromium 51 EDTA GFR for the four different GFR formulae with the appropriate weight calculation for the patients weighing ≥30% over their ideal body weight

<table>
<thead>
<tr>
<th>GFR measure</th>
<th>Carboplatin AUC 5 dose (mg/ml/min), median (IQR)</th>
<th>Percentage error, median (IQR)</th>
<th>APE, median (IQR)</th>
<th>APE &gt; 20%, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium 51 EDTA</td>
<td>580 (480–680)</td>
<td>−1.9 (−11.0 to 10.9)</td>
<td>10.9 (4.6–19.0)</td>
<td>142 (22)</td>
</tr>
<tr>
<td>Cockcroft–Gault</td>
<td>555 (460–705)</td>
<td>−7.7 (−16.8 to 2.7)</td>
<td>12.2 (6.0–20.2)</td>
<td>168 (25)</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>520 (440–630)</td>
<td>−3.2 (−3.2 to 18.4)</td>
<td>11.1 (4.7–19.7)</td>
<td>154 (23)</td>
</tr>
<tr>
<td>Wright</td>
<td>600 (510–730)</td>
<td>−4.6 (−17.0 to 8.1)</td>
<td>13.6 (6.0–22.9)</td>
<td>212 (32)</td>
</tr>
<tr>
<td>MDRD</td>
<td>530 (460–630)</td>
<td>−4.9 (−10.2 to 4.9)</td>
<td>12.5 (6.0–22.9)</td>
<td>218 (34)</td>
</tr>
</tbody>
</table>

APE, absolute percentage error; AUC, area under the plasma carboplatin concentration time curve; GFR, glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease.
The Jelliffe formula includes BSA and has been shown to have a greater bias than other formulae, particularly when the BSA is small [16]. In our study, the Jelliffe formula consistently underestimated GFR in most situations, except in patients with a low GFR < 50 ml/min or BMI < 18.5. These findings are supported by other studies [9, 17, 18].

The Wright formula was developed in an oncology population; we would therefore have expected this formula to be the most accurate in estimating GFR in our population [9]. It has been shown in some studies to be more accurate than other formulae [9, 19, 20]. This is in contrast to what we have found in our study except within the subgroups of age 70+ and BMI >30. In the study by Wright et al. [9], using the same Wright formula as we have used (not incorporating creatine kinase and the Jaffe method of measuring creatinine; Figure 1) produced similar precision to our study (15% versus 14.5%, respectively) but underestimated the GFR by 5% compared with an overestimation of 8.1% in our study. The Wright study had few patients with GFR < 50 ml/min and so does not recommend that it be applied to a population with significant renal impairment. Our study and also a study by Poole et al. [17] have shown that in patients with a GFR < 50 ml/min, the Wright formula considerably overestimated the GFR. We included patients with a GFR < 50 ml/min to allow the evaluation of the formulae in a representative oncology population.

In UK, an estimated GFR using the abbreviated MDRD equation, derived from patients with chronic renal disease, is calculated with every request for creatinine in patients aged >18 years but is not currently recommended for chemotherapy dosing [10]. The accuracy of the MDRD formula in a non-oncology population has been extensively studied in a variety of different patient groups [13–15, 21–26]. It is more accurate than Cockcroft–Gault in non-cancer patients with chronic renal disease [11, 14, 15, 22, 24, 27]; we, however, found the converse was true for cancer patients. In patients with a normal GFR range, the evidence is equivocal as to which of the two formulae is best at estimating GFR [13, 14, 25, 26], and our data and Chew et al. [28] also suggest minimal differences. A few studies have examined all the formulae specifically in an oncology population [20, 29–32]. Barraclough et al. [19] reported that in an oncology population with a mean measured GFR of 81 ml/min (367 patients), the Cockcroft–Gault formula underestimated GFR by 2% while the Wright formula overestimated it by 2% but was the most precise (APE 19%). With the inclusion of 252 patients with a measured GFR < 50 ml/min, all the formulae had similarly poor accuracy [19].

We evaluated the formulae in subgroups of patients based on age, weight and GFR. Marx et al. [18] found in a study of an elderly oncology population (225 patients) that the Wright formula was the least biased (bias 0%, precision 16%) and the MDRD formula overestimated GFR whereas Cockcroft–Gault and Jelliffe underestimated GFR. These findings are confirmed by us and a number of other studies [33–35]. In patients who are overweight, our findings were similar to a study by Verhave et al. [34] in that Cockcroft–Gault overestimates GFR whereas the Jelliffe and MDRD formulae underestimate GFR. Our
results suggest that the Wright formula has the least bias for patients with a BMI ≥30.

In patients who weigh >30% above their IBW, IBW is often used in the estimating GFR formulae. In an attempt to correct for potential underdosing, pharmacists in our institution use IBW + 30% in the estimation of GFR. There are no published studies confirming the appropriateness of using IBW + 30%.

Sparreboom et al. [36] evaluated the benefits of using alternative weights for obese patients in the dose calculations of anticancer drugs. They found in patients receiving carboplatin that the average of IBW and ABW was the best predictor of carboplatin clearance. A study by Ekhart et al. [37] suggested that flat dosing of carboplatin in obese patients should be used.

In our subgroup of 160 patients who weighed >30% above...
IBW, using IBW in all the formulae underestimated GFR and we would therefore not recommend using IBW in calculations of GFR. When using the Cockcroft–Gault formula, we would, however, recommend using IBW + 30%. A large prospective study is required to validate these recommendations.

There is debate about using Cockcroft–Gault or MDRD as a substitute for chromium 51 EDTA in oncology drug dosing [29, 30, 38, 39]. Some studies have found little difference between them, although both were inaccurate [29, 39]. Others have found MDRD most accurate [38], especially in patients who had poor general status [30]. Conversely, we found that an additional 10% of patients would have received a >20% difference in carboplatin dose using the MDRD than the Cockcroft–Gault formula. The question of what level of difference is clinically significant varies between studies (between 5% and 20%). In our study, ~75% of the patients would receive a >5% difference in dose to that calculated by chromium 51 EDTA GFR (data not shown), but this was as high as 85% in the study by de Lemos et al. [29]. The effects of underdosing are unclear; however, the toxicity from overdosing includes thrombocytopenia, neutropenia and the requirement for dose alterations. One study observed no variation in the rates of toxicity or number of dose modifications despite 48% of patients having a >20% difference in the carboplatin dose (using MDRD compared with the Cockcroft–Gault formula and not chromium 51 EDTA GFR) [40].

A limitation of our retrospective study is that the method for chromium 51 EDTA GFR was altered from single-sample estimation to three-sample estimation in January 2005; therefore, approximately two-thirds of patients had a chromium 51 EDTA measurement that may have been less accurate. However, the distribution of the chromium 51 EDTA GFR measurements was similar for both groups (one sample: median 90 ml/min (range 26–165) versus three samples: median 91 ml/min (range 23–176)). It is also difficult to directly compare results between studies as patient factors and methods for measuring GFR and serum creatinine vary. Due to the retrospective nature of our study, we were unable to correct for the many variables in our patient population. These include factors such as muscle mass (which will affect creatinine), low albumin, poor nutrition, oedema, ascites, co-morbidities (e.g. renal problems), prior treatments and other medications. Ideally, we would prospectively review side-effects and differences due to carboplatin doses calculated by the different formulae.

Finally, the MDRD formula, as obtained in the clinical setting, performed worse in patients that were under- or overweight. This highlights the problem of the MDRD formula being based on the average BSA of a patient and not the individual’s BSA. Therefore, in its current form it would be considered unsuitable for estimating GFR for the patients in the extreme weight categories. The performance of the MDRD formula may be improved with an appropriate modification to adjust the formula for the patients’ BSA but this should not be left to treating clinicians in busy clinics to adjust.

conclusions

This study is one of the largest to evaluate the accuracy of four commonly used formulae in an oncology population. It highlights the inaccuracy of estimating GFR and the variability seen in clinical practice throughout UK. It is the first study to investigate weight corrections for patients who weigh >30% above their IBW and to provide evidence to support current clinical practice.

All the formulae examined show a degree of bias and imprecision in estimating GFR and there is no perfect substitute for chromium 51 EDTA GFR. Overall, in our study, the Cockcroft–Gault formula is both the least biased and the most precise formula and we would therefore recommend using this formula for calculation of estimated creatinine clearance/GFR and subsequent drug dosing when chromium 51 EDTA GFR is unavailable. In patients who weigh >30% above their IBW, our data support the use of IBW + 30% in the Cockcroft–Gault formula. The Wright formula could be considered in patients aged 70 + years or in obese patients with a BMI ≥30 if the GFR is >50 ml/min. We would not recommend using the Jelliffe or MDRD formula for estimating GFR to dose chemotherapy drugs. All the available formulae have limitations especially in the lower GFR range (GFR < 50 ml/min) and measured creatinine clearance (e.g. using chromium 51 EDTA) should continue to be used in this subgroup until a more reliable formula is developed.

disclosure

The authors declare no conflict of interest.


