A comparison of bedside renal function estimates and measured glomerular filtration rate (Tc$^{99m}$DTPA clearance) in cancer patients

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Background: The aim of this study was to compare measured glomerular filtration rate (GFR) with estimates of GFR derived from the population pharmacokinetic methods of Martin and Wright, and the creatinine clearance (CrCl) estimates of Cockcroft and Gault, and Jelliffe.

Patients and methods: GFR was determined by technetium-99m diethyl triamine penta-acetic acid (Tc$^{99m}$DTPA) clearance in adult cancer patients. Height, actual body weight and serum creatinine were measured, and GFR and CrCl estimates calculated.

Results: One hundred and twenty-two patients were included. The mean measured GFR was 87 ml/min (range 30–174 ml/min). The mean bias (mean percentage error) was 2, 1, –10 and –17%, and the mean precision (mean absolute percentage error) was 18, 19, 21 and 23% for the Wright, Martin, Cockcroft and Gault, and Jelliffe formulas, respectively. The Martin formula significantly underestimates GFR for females (mean bias –10%) and overestimates GFR for males (mean bias 8%) (P <0.001 for bias of males versus females). The Wright and Martin formulas significantly overestimate GFR <50 ml/min (mean bias 39 and 30%; P = 0.03 and 0.05, respectively) and all formulas underestimate GFR >100 ml/min (mean bias –18, –16, –24 and –32% for Wright, Martin, Cockcroft and Gault, and Jelliffe formulas, respectively; P <0.001).

Conclusions: All the assessed estimates for renal function were found to have significant limitations.

Key words: Cockcroft and Gault formula, creatinine clearance, glomerular filtration rate, technetium-99m diethyl triamine penta-acetic acid (Tc$^{99m}$DTPA)

Introduction

An assessment of renal function is desirable when determining the dosage of drugs with a narrow therapeutic index and those that are renally excreted, in particular cytotoxic chemotherapeutic agents. Ideally, a bedside method for estimating glomerular filtration rate (GFR) is required.

An accurate measurement of GFR is possible by measuring the clearance of radiolabelled isotopes such as technetium-99m diethyl triamine penta-acetic acid (Tc$^{99m}$DTPA) and chromium 51 EDTA (Cr$^{51}$EDTA) [1–4]. Nonetheless, these methods are invasive and expensive, and are not readily available in all clinical settings.

In routine clinical practice, indirect methods are used to approximate GFR. The most frequently applied approximation is endogenous serum creatinine concentration (SCr).

However, interpretation is limited as the measured level is influenced by many non-renal factors including the muscle mass and age of the individual as well as the actual method of measurement [5, 6]. Creatinine clearance (CrCl) measurement, through 24-h urine collection, is also used to estimate renal function; however, the reliability of this method is very much dependant on accurate and complete urine collection [1, 7–12].

Various equations and nomograms have been developed to estimate creatinine clearance from serum creatinine concentration. In 1976, Cockcroft and Gault [13] published a formula derived from simultaneous linear regression to approximate CrCl as measured by 24-h urine collection. The formula includes the covariables of gender, age, body weight and SCr. In 1973, Jelliffe [14] published a similarly derived formula that includes the same covariables, but incorporates body surface area (BSA) rather than weight alone. The Cockcroft and Gault formula has been the most frequently used, although several analyses have demonstrated limitations in the accuracy and applicability of this estimate [6, 15]. In an attempt to...
improve on the estimates derived from the available bedside formulas to predict GFR in cancer patients, using the population pharmacokinetic approach [16, 17]. A comparison of these formulae as a direct measurement of GFR has not yet been published by an external group.

The aim of this study was to compare GFR, measured by Tc99mDTPA clearance, with estimates of GFR derived from the population pharmacokinetic methods of Wright et al. [16] and Martin et al. [17], and the CrCl estimates of Cockcroft and Gault [13] and Jelliffe [14].

**Patients and methods**

**Setting**

This was a retrospective study of adult patients with cancer who had GFR measured by Tc99mDTPA clearance at the Peter MacCallum Cancer Institute [15].

**GFR determination**

Tc99mDTPA was prepared 30–60 min prior to injection using a current DTPA kit (Amscan™ Pentetate II Agent; Amersham Healthcare, Buckinghamshire, UK). Instant thin layer chromatography was performed on all DTPA preparations, ~30 min after reconstitution and at the time of administration. Radioactivity was sampled to confirm labelling efficiency of >98%. A dose of 400 MBq Tc99mDTPA, followed by 10 ml sodium chloride 0.9% flush, was administered and correlated with renal imaging. Residues in dose apparatus and the injection site were assessed using a scintillation probe. If the cumulative residue for an individual patient exceeded 1% of the total dose then the procedure was considered void and was repeated in full. Blood samples were taken at baseline, and at 2, 3 and 4 h post-injection. Plasma was separated and counts obtained. The clearance of Tc99mDTPA was calculated from a single exponential derived from the blood samples between 2 and 4 h after injection, as described by Fawdry et al. [3]. The calculated GFR was not corrected for body surface area [1].

**Formula calculation of renal function estimates**

Height and actual body weight (ABW) were measured. Age and gender were recorded. SCR was measured using an alkaline picrate-kinetic method (Jaffe method). Body surface area was calculated using the formula of DuBois and DuBois [18]. GFR approximations were calculated using the formulae proposed by Wright et al. [16] and Martin et al. [17]. Creatinine clearance approximations were determined using the Cockcroft and Gault formula [13] and the Jelliffe formula [14] not standardised for BSA.

Wright et al. [16] (using the formula derived for GFR with the Jaffe method of SCR measurement without the inclusion of creatine kinase):

\[
\text{GFR (ml/min)} = \frac{[6550 - (38.8 \times \text{Age})] \times [1 - (0.168 \times \text{Sex})]}{\text{ABW}^{0.425} \times \text{Height}^{0.725}}
\]

where ABW is measured in kilograms and SCR is measured in micromoles per litre. BSA = 0.007184 × ABW\(^{0.425}\) × Height\(^{0.725}\) [18]. BSA is measured in square metres, Height in centimetres, Age in years (nearest 10 years rounded). GFR approximations were calculated using the Jaffe method. Body surface area was calculated using the formula of DuBois and DuBois [18]. GFR approximations were calculated using the Cockcroft and Gault [13] and Jelliffe [14].

**Assessment of obesity**

Body mass index (BMI) was calculated and obese patients were identified as those with a BMI >30 kg/m\(^2\), as defined by the World Health Organization [19].

**Statistical analysis**

Pearson’s correlation was used to assess relationships between measured GFR (Tc99mDTPA clearance) and estimated clearances using the four formulae. Plots of the difference between the measured GFR and estimated clearances compared with measured GFR were examined to determine whether prediction error was independent from measurement magnitude. Analyses of differences were used to determine bias and precision [20]. Bias was assessed by mean percentage error (MPE), calculated as the percentage difference between the estimated clearances for each formula and measured GFR. A positive bias indicates overestimation of GFR, and a negative bias indicates underestimation. Ninety-five per cent confidence intervals (95% CI) were calculated. Precision was assessed by the mean absolute percentage error (MAPE). Relationships were also assessed by gender and varying levels of renal function: reduced (GFR <50 ml/min), normal (GFR 50–100 ml/min) and high (GFR ≥100 ml/min). The statistical significance of differences between the estimated clearances and measured GFR was assessed using the paired Student’s t-test.

**Results**

One hundred and twenty two patients were included in the analysis (71 males and 51 females). GFR was determined for 119 patients prior to planned treatment with carboplatin, while in three cases it was prior to treatment with cisplatin. Table 1 lists the patient characteristics, and the measured and formula-based estimates of renal function.

The relationships between the formula estimations of renal function and measured Tc99mDTPA clearance are displayed in Figure 1. The mean differences (ml/min), bias (MPE) and precision (MAPE) are shown in Table 2. Bias is displayed graphically in Figure 2.

The paired Student’s t-test indicated that the estimates from the Wright (P = 0.11) and Martin (P = 0.14) formulae were not statistically significantly different from the Tc99mDTPA clearance. Conversely, both the Cockcroft and Gault (P <0.001) and Jelliffe (P <0.001) formulae provided estimates that were statistically significantly different.

When separate analyses were performed for males and females, the correlation, bias and precision did not alter significantly for the Wright, Cockcroft and Gault or Jelliffe formulae. However, the Martin formula was found to significantly underestimate GFR for females (mean bias −9%) and overestimate GFR for males (mean bias +8%) (P <0.001 for bias of males versus females) (Table 3).

Both the Wright formula and the Martin formula significantly overestimated GFR <50 ml/min (P = 0.03 and 0.05,
respectively). All of the formulae underestimated GFR for patients with GFR >100 ml/min ($P <0.001$ for all formulae) (Table 4).

Seventeen of the 122 patients were identified as being obese, with a BMI >30 kg/m². In these patients, the mean ratio ($\pm$ SD) between the formula-based estimates and Tc⁹⁹mDTPA clearance was 0.99 ($\pm$0.19), 1.16 ($\pm$0.23), 1.06 ($\pm$0.26) and 0.83 ($\pm$0.20) for the Wright, Martin, Cockcroft and Gault and Jelliffe formulas, respectively. As this does not differ significantly from unity, it would indicate that obesity did not contribute to the bias observed.

**Discussion**

There are many clinical scenarios where an accurate assessment of renal function is required. This is particularly the case

### Table 1. Mean demographic characteristics of study patients ($n = 122$)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.4 ± 11.5</td>
<td>21–83</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 8.7</td>
<td>143–188</td>
<td></td>
</tr>
<tr>
<td>Actual body weight (kg)</td>
<td>68.3 ± 17.0</td>
<td>41.6–135</td>
<td></td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.77 ± 0.23</td>
<td>1.31–2.58</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine concentration (µmol/l)</td>
<td>80 ± 20</td>
<td>50–230</td>
<td></td>
</tr>
<tr>
<td>Tc⁹⁹mDTPA clearance (ml/min)</td>
<td>87 ± 28</td>
<td>30–174</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Relationships between renal function estimates and measured GFR (Tc⁹⁹mDTPA clearance)

<table>
<thead>
<tr>
<th>Formula</th>
<th>$r$</th>
<th>Mean difference [ml/min (range)]</th>
<th>Bias [MPE (95% CI)]</th>
<th>Precision (MAPE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright</td>
<td>0.71</td>
<td>−3 (−78 to +56)</td>
<td>2 (−2.9 to +6.4)</td>
<td>18</td>
</tr>
<tr>
<td>Martin</td>
<td>0.66</td>
<td>−3 (−88 to +52)</td>
<td>1 (−3.5 to +6.0)</td>
<td>19</td>
</tr>
<tr>
<td>Cockcroft and Gault</td>
<td>0.68</td>
<td>−12 (−90 to +61)</td>
<td>−10 (−14.2 to −5.9)</td>
<td>21</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>0.70</td>
<td>−18 (−90 to +38)</td>
<td>−17 (−21.0 to −13.2)</td>
<td>23</td>
</tr>
</tbody>
</table>

### Table 3. Mean percentage differences in renal function estimates compared with measured GFR, by gender

<table>
<thead>
<tr>
<th>Formula</th>
<th>All</th>
<th>Males</th>
<th>Females</th>
<th>$P$ (males versus females)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias (MPE)</td>
<td>95% CI</td>
<td>Bias (MPE)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Wright</td>
<td>+2</td>
<td>(−2.9 to +6.4)</td>
<td>+4</td>
<td>(−2.5 to +10.5)</td>
</tr>
<tr>
<td>Martin</td>
<td>+1</td>
<td>(−3.5 to +6.0)</td>
<td>+8</td>
<td>(+2.3 to +14.5)</td>
</tr>
<tr>
<td>Cockcroft and Gault</td>
<td>−10</td>
<td>(−14.2 to −5.9)</td>
<td>−9</td>
<td>(−14.7 to −3.8)</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>−17</td>
<td>(−21.0 to −13.2)</td>
<td>−19</td>
<td>(−24.0 to −13.3)</td>
</tr>
</tbody>
</table>
Figure 1. Measured GFR (Tc<sup>99m</sup>DTPA clearance) versus renal function estimates. *p*, Student’s *t*-test for formula estimate versus GFR (Tc<sup>99m</sup>DTPA clearance). (A) Measured GFR versus GFR estimate (Wright). (B) Measured GFR versus GFR estimate (Martin). (C) Measured GFR versus CrCl estimate (Cockcroft and Gault). (D) Measured GFR versus CrCl estimate (Jelliffe).

Table 4. Bias of renal function estimates for low, normal and high levels of GFR

<table>
<thead>
<tr>
<th>Formula</th>
<th>GFR (total) (n = 122)</th>
<th>GFR &lt;50 ml/min (n = 9)</th>
<th>GFR 50–100 ml/min (n = 83)</th>
<th>GFR &gt;100 ml/min (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias (% difference)</td>
<td><em>P</em> value</td>
<td>Bias (% difference)</td>
<td><em>P</em> value</td>
</tr>
<tr>
<td>Wright</td>
<td>+2</td>
<td>0.11</td>
<td>+39</td>
<td>0.03</td>
</tr>
<tr>
<td>Martin</td>
<td>+1</td>
<td>0.14</td>
<td>+30</td>
<td>0.05</td>
</tr>
<tr>
<td>Cockcroft and Gault</td>
<td>−10</td>
<td>&lt;0.001</td>
<td>+11</td>
<td>0.38</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>−17</td>
<td>&lt;0.001</td>
<td>+14</td>
<td>0.34</td>
</tr>
</tbody>
</table>
in patients with declining renal function, those with altered muscle mass, when determining the need for renal dialysis, and when treating with drugs eliminated by renal clearance [21, 22]. When determining doses of renally cleared drugs, the clinician’s interest most frequently focuses on the quantification of the degree of renal function that has been lost, so that an appropriate dosage reduction may be made to account for this reduction in clearance. However, there are circumstances when an increase in drug dosage may be required to account for rapid renal elimination. An example of this in the oncology setting is in the use of carboplatin, which is eliminated primarily by renal means. Current practice is to dose carboplatin to a target area under the concentration–time curve (AUC) [1, 23–26]. The most frequently used method is application of the formula developed by Calvert et al. [23] that incorporates measured GFR. For patients with rapid renal clearance, the target AUC will not be achieved if a proportionally larger dose is not administered.

For widespread clinical application, the assessment of renal function needs to be accurate, convenient and inexpensive. An accurate, non-invasive formula-based method that does not require multiple blood samples or tedious urine collection would be ideal. The Cockcroft and Gault [13] and Jelliffe [14] formulae are used routinely in practice, but their accuracy has been questioned. Assessment of the clinical applicability of the newer population-derived formulae is necessary.

The Cockcroft and Gault and the Jelliffe formulae were derived using simultaneous linear regression methods. Both formulae incorporated similar covariables to estimate creatinine clearance from the 24-h urine collection [13, 14]. The population pharmacokinetic approach was used in the development of both the Wright [16] and the Martin [17] formulae. The resultant estimates of GFR were derived using $^{51}$Cr-EDTA clearance and covariables similar to those in the Cockcroft and Gault and Jelliffe formulae [16, 17]. Both the Wright and Martin formulae were developed from data derived from patients with cancer.

Figure 2. Percentage difference between renal function estimates and measured GFR (Tc$^{99m}$DTPA clearance). (A) Percentage difference between GFR estimate (Wright) and measured GFR (Tc$^{99m}$DTPA clearance) versus measured GFR. (B) Percentage difference between GFR estimate (Martin) and measured GFR (Tc$^{99m}$DTPA clearance) versus measured GFR. (C) Percentage difference between CrCl estimate (Cockcroft and Gault) and measured GFR (Tc$^{99m}$DTPA clearance) versus measured GFR. (D) Percentage difference between CrCl estimate (Jelliffe) and measured GFR (Tc$^{99m}$DTPA clearance) versus measured GFR.
Wright et al. [16] developed four formulae for estimating GFR based on two different methods of measuring serum creatinine, namely the enzymatic method and the Jaffe method, and including or excluding an additional covariate creatine kinase. They concluded that all four derived formulae provide a suitably reliable estimate that is significantly less biased than the Cockcroft and Gault or Jelliffe formulae. The formula selected for comparison in this study was the one that utilised no additional parameters other than those included in the Cockcroft and Gault or Jelliffe formulas. The Wright formula selected includes serum creatinine measured using the Jaffe method, but without creatine kinase.

In this group of adults with cancer, the correlation between Tc99mDTPA clearance and the GFR/creatinine clearance estimates of Wright, Martin, Cockcroft and Gault and Jelliffe were deficient. Although the formulae by Wright and Martin do provide an improved net bias when compared with either the Cockcroft and Gault or Jelliffe formulae, there are significant limitations to both new methods that restrict the clinical applicability.

Our results demonstrate that the estimate of Wright et al. provides an improved estimate of GFR compared with either the Cockcroft and Gault or Jelliffe formulae, as the overall bias is close to zero. The results of the original paper by Wright et al. show similar results [16], with an overall MPE of –1% and a MAPE of 16%. This improvement, however, is primarily seen in patients with ‘normal’ renal function (i.e. GFR ≥50 ml/min and <100 ml/min), where the net bias is negligible, although the estimate is still imprecise. The formula does, however, have a significant positive bias for low GFR (i.e. overestimates) and a significant negative bias for high GFR (i.e. underestimates). From a clinical perspective this would significantly limit applicability. For example, if the Wright formula is substituted for measured GFR in the Calvert formula to calculate carboplatin doses, then from our data the dose would be overestimated by a mean of 23% for patients with GFR <50 ml/min and underestimated by a mean of 15% for patients with GFR >100 ml/min. The Wright paper did not provide an analysis for low, normal or high levels of renal function.

Our results confirm those of Martin et al. [17], who demonstrated that in a group of cancer patients their formula provides an improved estimate of GFR compared with the formula of Cockcroft and Gault. The bias and precision, when all ranges of GFR are considered, are comparable to that found for the Wright formula. Likewise, the Martin formula also results in similar excessive bias for high and low levels of GFR. In addition, the Martin formula also has a significant gender bias. The values for females are significantly underestimated (MPE -9%) and for males the GFR values are overestimated (MPE +8%). This may be due to the relatively small number of females in the samples used to derive and validate the formula, or undetected clinical differences between the males and females in the samples. Because of these inaccuracies we cannot recommend the use of this formula.

A number of groups have assessed the accuracy of the Cockcroft and Gault approximation in a variety of clinical settings. These assessments have usually been compared with creatinine clearance, determined by 24-h urine collection [21, 27–30]. There have also been a number of comparisons of the Cockcroft and Gault approximation with Tc99mDTPA, Cr51 EDTA and other direct measures of GFR [1, 5, 6, 16, 17, 31]. These assessments have almost uniformly concluded that the Cockcroft and Gault approximation underestimates GFR for normal and moderately reduced levels of renal function. For patients with significantly impaired renal function the Cockcroft and Gault formula overestimates renal function; this is due to the relatively high proportion of creatinine tubular excretion that occurs at low levels of renal function [6].

Our results confirm these conclusions and suggest that the use of the Cockcroft and Gault formula has significant limitations when an accurate assessment of renal function is required. A number of authors have presented data suggesting that the Cockcroft and Gault equation is adequate for clinical application, but these have been limited to patients with ‘normal’ renal function [5]. Our results demonstrate that the Cockcroft and Gault formula results in a statistically significant underestimation of GFR in the ‘normal’ range, and although the mean bias may be only –7%, the 95% CI is wide (–12.0% to –2.3%). This indicates that for some patients the estimate provided by the Cockcroft and Gault formula may underestimate true renal function by as much as 12%.

The Jelliffe formula provides a biased and imprecise estimate of GFR. Similar to the Cockcroft and Gault formula, it significantly underestimates renal function at normal and moderately impaired levels, and overestimates renal function for patients with significant impairment. From a clinical perspective both the Cockcroft and Gault and Jelliffe formulas result in clinically imprecise estimates, with a mean absolute percentage error in excess of 20%.

An assessment of the plots of all the formula-based renal function estimates compared with Tc99mDTPA clearance suggests that the relationship is extremely weak for Tc99mDTPA clearances <50 ml/min and >100 ml/min, and as such, none of the formula-based estimates can provide a reliable estimate for patients with renal impairment or for patients with rapid clearance. Several groups have acknowledged this as a limitation of the Cockcroft and Gault formula [5, 6]; however, neither Martin et al. or Wright et al. provided an analysis of their data stratified by GFR.

The use of the Jaffe method of serum creatinine measurement has been shown to influence the accuracy of the estimate. This variability has been quoted to be up to 20%, however, this is highly dependent on the specific methodology utilised [26, 32]. The methodology used in the laboratory for this study has been validated against enzymatic methods and showed <1.2% variability, indicating minimal influence on the results [33].
Conclusion

This study demonstrates that the renal clearance estimates of Wright, Martin, Cockcroft and Gault, and Jelliffe provide a biased and imprecise estimate of GFR. If any of these bedside estimates are to be used for dosage adjustment of renally eliminated drugs then the clinician must have an appreciation of the limitations of the methods. When an accurate estimate of GFR is required then clearance should be measured using a method such as \(^{99m}\)Tc-DTPA or Cr\(^{51}\) EDTA. Further research is required to develop more reliable methods for estimating renal function. Such research must include a specific analysis of the covariables for gender and also for differing levels of renal function.

References