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ORIGINAL ARTICLE

Michael Joseph Dooley · Susan Gaye Poole

Poor correlation between body surface area and glomerular filtration rate

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Abstract *Purpose*: The aim of this study was to determine the correlation between body surface area (BSA) and glomerular filtration rate (GFR) measured by Tc-99m DTPA clearance in adult patients with cancer. *Methods*: GFR was determined by Tc-99m DTPA clearance in adult patients with cancer. Height and actual body weight were measured. Ideal body weight was calculated. BSA was calculated using the Du Bois and Du Bois linear method using both actual and ideal body weight. *Results*: Included in the study were 122 patients. The mean GFR measured by Tc-99m DTPA clearance was 87 ml/min (range 30–174 ml/min). The mean BSA (actual weight) was 1.76 m^2 (median 1.73 m^2, range 1.31–2.58 m^2). The mean BSA (ideal body weight) was 1.63 m^2 (median 1.63 m^2, range 1.20–2.00 m^2). The overall correlation between BSA (actual weight) and GFR in this adult population was $r = 0.24$, and the 95% confidence interval was 0.06–0.4. The correlation between BSA (ideal body weight) and GFR was $r = 0.22$. The correlation between BSA and GFR excluding patients with a BSA < 1.5 m^2 or > 2.0 m^2 was 0.12. When patients with GFR < 50 ml/min or > 100 ml/min were excluded, the correlation with BSA was 0.07. The correlations between GFR and height, actual weight and ideal weight were 0.22, 0.21 and 0.22, respectively. *Conclusions*: This study demonstrated a poor correlation between GFR determined by Tc-99m DTPA clearance and BSA calculated using the Du Bois and Du Bois linear method. The 95% confidence interval for the correlation between BSA and GFR was 0.06–0.4 indicating that a strong applicable clinical correlation is very unlikely.

Key words Body surface area · Glomerular filtration rate · Ideal body weight · Actual body weight · DTPA · Clearance

M. J. Dooley (✉) · S. G. Poole
Pharmacy Department,
Peter MacCallum Cancer Institute,
St Andrews Place, East Melbourne,
Victoria 3002, Australia
e-mail: mdooley@petermac.unimelb.edu.au
Tel.: +613-9656-1212; Fax: +613-9656-1405

M. J. Dooley
Department of Pharmacy Practice,
Victorian College of Pharmacy (Monash University),
Parkville, Victoria, Australia

Introduction

A relationship between renal function and body surface area (BSA) was first postulated in 1928 [13]. This relationship is based on the observation that the total number of glomeruli and kidney weight, in various species of mammals, is directly proportional to BSA, but not body weight. The ratio of kidney weight to BSA is almost identical for various species. Urea excretion is also correlated with kidney weight [23]. BSA has also been shown to be proportional to blood volume [1].

The rationale for the use of BSA as the criterion on which to base the calculation of doses of chemotherapy was proposed in 1958 based on this evidence [19]. Subsequent to this, BSA has been used in dose calculation and currently its use in calculating doses of most cytotoxic agents is standard practice. BSA has been estimated using both actual and ideal body weight [8]. A number of formulas and nomograms are used to estimate BSA [4, 22]. The Du Bois and Du Bois linear method for estimating BSA has been shown to be accurate and is used routinely in both clinical trials and routine practice [2, 7].

This application of BSA as a means of individualizing chemotherapy doses has come under scrutiny due to limited supportive pharmacokinetic data and evidence that other anthropometric characteristics may be more suitable [9, 10, 11, 17, 21]. Despite these data, current practice continues to rely on BSA as the method of determining chemotherapy drug dosage. An accurate measurement of glomerular filtration rate (GFR) is possible by measuring the clearance of technetium-99m

diethyl triamine pentaacetic acid (Tc-99m DTPA) [5, 18]. The accuracy of this methodology has been validated at this institute [15]. The aim of this study was to determine the correlation between BSA and GFR measured by Tc-99m DTPA clearance in adult patients with cancer.

Materials and methods

Eligible patients were adults with cancer at the Peter MacCallum Cancer Institute. GFR was determined by Tc-99m DTPA clearance [15].

Tc-99m DTPA was prepared 30–60 min prior to injection using fresh eluate and a current DTPA kit. Instant thin-layer chromatography was performed on all DTPA preparations approximately 30 min after reconstitution of the kit, and at the time of dose administration. Radioactivity was sampled in a Well scintillation counter to confirm labelling efficiency of greater than 98%.

Tc-99m DTPA (400 MBq) was administered via a three-way tap and cannula to enable correlation with renal imaging. A 10-ml 0.9% sodium chloride flush per dose ensured no dose residue in any of the apparatus. The dosing apparatus and injection site were checked for dose residue using a scintillation probe. Blood samples (10 ml) were taken at baseline and at 2, 3 and 4 h after injection. Plasma was separated and counts obtained. The clearance of Tc-99m DTPA was calculated from a single exponential derived from the blood samples between 2 and 4 h after injection as described by Fawdry et al. [5]. The GFR was calculated without correction for BSA.

Height and actual body weight were measured. Ideal body weight was calculated [25]. Age and gender were recorded. BSA was calculated using the Du Bois and Du Bois linear method using both ideal and actual body weight [4]. Relationships between BSA (actual and ideal body weight) and GFR (all patients, those with GFR greater than 50 ml/min and equal to or less than 100 ml/min, as well as those with BSA equal to or greater than 1.5 m^2 and equal to or less than 2.0 m^2) were assessed statistically using the Pearson correlation coefficient. The 95% confidence intervals were calculated using the atanh transformation. For a strong correlation to exist between BSA and GFR, a correlation coefficient greater than 0.8 would be desirable [11].

Results

Included in the study were 122 patients (70 male, 52 female). The mean age was 61.4 years (range 21–83 years). The mean GFR measured by Tc-99m DTPA clearance was 87 ml/min (median 82.5 ml/min, range 30–174 ml/min). The mean BSA (actual weight) was 1.76 m^2 (median 1.73 m^2, range 1.31–2.58 m^2). The mean BSA (ideal body weight) was 1.63 m^2 (median 1.63 m^2, range 1.20–2.00 m^2).

The overall correlation between BSA (actual weight) and GFR was $r = 0.24$, and the 95% confidence interval was 0.06–0.4 (see Fig. 1 and Table 1). The correlation between BSA (ideal body weight) and GFR was $r = 0.22$. The correlation between BSA and GFR with the exclusion of patients with a BSA < 1.5 m^2 and > 2.0 m^2 was 0.12. When patients with GFR < 50 ml/min or > 100 ml/min were excluded the correlation with BSA was 0.07. The correlation between GFR and height, actual weight and ideal weight was 0.22, 0.21 and 0.22 respectively.

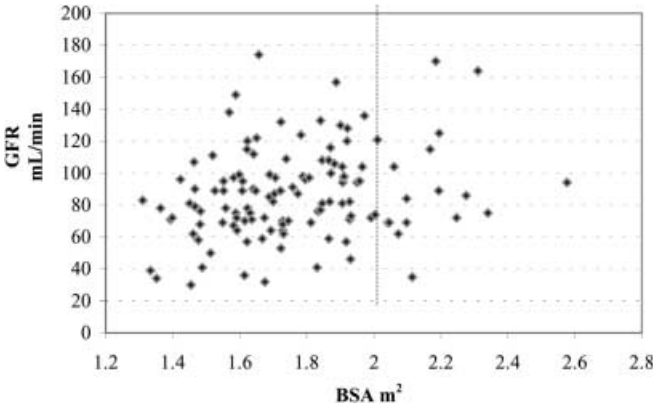

Fig. 1 Clearance of Tc-99m DTPA versus BSA estimated by Du Bois and Du Bois linear method (actual body weight)

Discussion

An accurate measurement of GFR is possible by measuring the clearance of radiolabelled Tc-99m DTPA or Cr-51 EDTA [5, 6, 15, 20]. The use of Tc-99m DTPA is preferred in many facilities because of greater convenience and lower cost. The precision of these estimates depends on accurate and reproducible radiopharmaceutical preparation and the method used to calculate clearance. Local factors relating to the source and extent of protein binding of Tc-99m DTPA can also influence the accuracy of results. The methodology utilized in this study, of Tc-99m DTPA clearance determined by absolute blood clearance from repeated blood sampling has been shown to be accurate [5]. This method has also been simultaneously compared with Cr-51 EDTA clearance at this centre and has been shown to be precise ($r = 0.98$), the regression line having a slope of near unity (1.02) and an intercept close to zero [15]. The methodology used in the study by Millward et al. [15] was replicated in the same laboratory using the same source of radiopharmaceutical.

This study demonstrated a poor correlation between GFR, determined by Tc-99m DTPA clearance, and BSA, measured by the Du Bois and Du Bois linear method. For BSA to be suitable for use in the estimation of the clearance of renally excreted drugs, a correlation of greater than 0.80 is desirable. The 95% confidence interval for the correlation was 0.06–0.4, demonstrating that this is statistically significantly less than the desired value of 0.8. This indicates that a strong applicable clinical correlation is very unlikely.

The correlation was not improved when ideal body weight was used instead of actual body weight. The use of ideal body weight in practice is not common. The primary reason for using ideal body weight is to avoid overdosing obese patients. However, ideal weight has been shown to be lower than national averages or the weight of the average cancer patient [8]. In a large retrospective study in which doses of chemotherapy administered to 3732 patients were reviewed, it was

Table 1 Correlation between BSA and GFR measured by Tc-99m DTPA clearance

	Patient group	Number of patients	Correlation (r)
Actual body weight	All patients	122	0.24
	BSA >1.5 to <2 m^2	86	0.12
	GFR >50 to <100 ml/min	82	0.07
Ideal body weight	All patients	122	0.22
	BSA >1.5 to <2 m^2	93	0.11
	GFR >50 to <100 ml/min	82	−0.03

shown that actual weight was greater than ideal in 69% of all patients. This was clinically relevant in only 8% of patients, in that the dose calculated using actual weight would have been more than 25% greater than that calculated using ideal body weight [8]. In this study actual weight was greater than ideal weight in 93 patients (76%). Needless to say, whether ideal or actual weight is used, the correlation between BSA and GFR is poor. It is worth noting that the correlation between GFR and actual weight and ideal weight was 0.21 and 0.22, respectively, not greatly dissimilar to that of BSA. It has been postulated that lean body mass may be a better surrogate for individualizing doses than BSA or total body mass [16, 17]. Lean body mass was not measured in this study.

It has been demonstrated that the correlation between Tc-99m DTPA clearance and creatinine clearance, estimated using the Cockcroft and Gault formula, is poor for GFR >100 ml/min [3, 15]. Correlation was still very poor even when GFRs >100 ml/min and <50 ml/min were excluded. Only nine patients had a GFR <50 ml/min and none had a GFR <30 ml/min.

In many studies, and clinical settings, patients with a BSA of >2 m^2 have the dose of chemotherapy calculated at a ceiling of 2 m^2. There is no scientific basis for this practice. In this study BSA was not rounded down to 2 m^2. In analysing the results, it was not surprising that the correlation between BSA and GFR did not improve when BSA <1.5 m^2 and >2 m^2 were excluded.

Many authors have quoted an apparent relationship between BSA and GFR that stems from the work published in 1951 [24]. However, the original derivation for this postulated relationship is from much earlier work [13]. This work involved the study of urea excretion and the influence of body size on urea output in a very small number of patients. The conclusion of the authors was that urea clearance values in children, when normalized to a BSA of 1.73 m^2, fell within the range of clearances observed in normal adults. Normalization of GFR to BSA has since become standard practice in many settings. However, this practice has been questioned [12, 14, 26].

A number of studies examining pharmacokinetic parameters have also questioned the application of BSA as a means of individualizing chemotherapy doses [9, 10, 11, 21]. There is some evidence that BSA does correlate with some pharmacokinetic parameters in drugs that are not extensively renally excreted [10]. However, numerous studies have failed to show direct correlations between BSA and pharmacokinetic parameters for renally excreted agents. This is not surprising in light of the findings of this study.

This study further highlights that the convention of utilizing BSA as the criterion for dosing of cytotoxic chemotherapy agents has many limitations. Improved approaches to dosage calculation including pharmacokinetic modelling and toxicity-adjusted dosing must continue to be explored [10].

In summary, there was no correlation between BSA and GFR measured by Tc-99m DTPA clearance. The routine use of BSA as a method of dosage calculation needs to critically evaluated.

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