ESTIMATING GFR IN ONCOLOGY PATIENTS RECEIVING CISPLATIN CHEMOTHERAPY : PREDICTED CREATININE CLEARANCE AGAINST Tc-99m DTPA METHODS

by

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ABBREVIATIONS

99mTc-DTPA	99mTechnetium- diethylene triamine pentaacetic acid
51Cr-EDTA	51Chromium-ethylenediaminetetraacetic
CG	Cockroft-Gault
MDRD	Modification of Diet in Renal Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
PSC 1	Plasma One Sampling
PSC 2	Plasma Two Sampling
GFR	Glomerular Filtration Rate
BSA	Body Surface Area
ECV	Extracellular Volume
ERPF	Effective Renal Plasma Flow
ROI	Region of interest
ICC	Intraclass Correlation Coefficients

UNITS

MBq	Mega Becquerel
mSv	milli Sievert

ABSTRAK

Tajuk:

Mengukur kadar penapisan glomerulus di kalangan pesakit onkologi yang menerima kemoterapi Cisplatin : Perbandingan antara kaedah pengiraan kreatinin dengan kaedah 99mTc-DTPA.

Objektif:

Menganalisa insiden kerosakan ginjal berikutan rawatan kemoterapi Cisplatin di kalangan pesakit onkologi melalui kaedah pengiraan kadar penapisan glomerulus sebelum dan selepas kemoterapi menggunakan persampelan plasma 99mTc-DTPA sebagai rujukan dan dibandingkan dengan kaedah pengiraan kreatinin dengan kaedah 99mTc-DTPA.

Metodologi:

Satu kajian prospektif yang melibatkan 33 pesakit yang telah dirujuk ke Jabatan Perubatan Nuklear, Hospital Pulau Pinang untuk skan 99mTechnetium-diethylenetriamine pentaasetic asid antara 1 February 2014 and 30 April 2015. Kajian ini telah dijalankan bagi menganalisa insiden kerosakan ginjal berikutan rawatan kemoterapi Cisplatin di kalangan pesakit onkologi melalui kaedah pengiraan kadar penapisan glomerulus sebelum dan selepas kemoterapi menggunakan persampelan plasma 99mTc-DTPA sebagai rujukan dan dibandingkan dengan kaedah pengiraan kreatinin dengan kaedah 99mTc-DTPA. Daripada 33 pesakit yang dirujuk, hanya 21 orang sahaja yang layak dimasukkan ke dalam kajian ini.

Keputusan:

Dari seramai 21 orang pesakit yang dikaji, 16 (76.2%) adalah lelaki manakala 5 (23.8%) adalah wanita. Usia purata pesakit adalah 55.1 tahun (10.80). Dos Cisplatin yg diberikan adalah sebanyak 75mg/m^2per pusingan kemoterapi untuk 3 pusingan. Perbezaan purata GFR oleh PSC 2 sebelum dan selepas kemoterapi adalah sebanyak 13.38 (-4.60, 31.36) ml/min/1.73m2 (*p* 0.136). Daripada 21 pesakit, 3 orang telah didapati mengalami kerosakan buah pinggang akut yang didefinisikan sebagai GFR < 50ml/min/1.73m^2. Jumlah ini telah membentuk peratusan sebanyak 14.3% daripada keseluruhan insiden kerosakan buah pinggang. Plot Bland-Altman telah menunjukkan hanya metod PSC 1 mematuhi metod PSC 2. Intraclass Correlation Coefficients (ICC) pula menunjukkan metod PSC 1 memiliki kebolehpercayaan yang tinggi terhadap metod PSC 2 ($p< 0.001$). Manakala kaedah-kaedah lain yg menggunakan asas serum kreatinin dalam formula GFR seperti CG, MDRD dan CKD-EPI serta Gates menunjukkan tidak ada persetujuan serta kebolehpercayaan jika dibandingkan dengan metod PSC 2 ($p> 0.05$).

Kesimpulan:

Kaedah menggunakan radionuklid dalam menilai GFR adalah merupakan kaedah yang paling sensitif dalam mengesan kejadian kerosakan buah pinggang disebabkan oleh Cisplatin. Seramai 3 orang daripada sejumlah 21 orang pesakit telah didapati mengalami kerosakan buah pinggang akut (GFR < 50ml/min/1.73m2) oleh kedua dua metod PSC 1 dan PSC 2. Kaedah PSC 1 adalah kaedah yang boleh dipercayai dan digunapakai dalam penilaian GFR serta boleh boleh dijadikan pengganti kepada metod PSC 2. Kaedah-kaedah lain seperti CG, MDRD, CKD-EPI dan juga Gates tidak boleh digunapakai utk mengesan kejadian

kerosakan buah pinggang berikutan rawatan Cisplatin. Kami mengesyorkan penggunaan PSC 1 utk penilaian GFR bagi pemantauan kes rawatan kemoterapi Cisplatin.

ABSTRACT

Topic:

Estimating glomerular filtration rate in oncology patients receiving Cisplatin chemotherapy : Predicted creatinine clearance against 99mTc-DTPA methods

Objective:

To analyze the incidence of Cisplatin induced nephrotoxicity in oncology patients through GFR estimation pre and post chemotherapy using 99mTc-DTPA plasma sampling as reference method and to compare with predicted creatinine clearance and Tc-99m renal scintigraphy.

Methodology/ Study Design:

A prospective study of 33 patients referred to the Department of Nuclear Medicine, Hospital Pulau Pinang for 99mTc-DTPA scan between 1 February 2014 and 30 April 2015. This study was performed to analyze the incidence of cisplatin induced nephrotoxicity among the oncology patients via the radionuclide and creatinine-based method of GFR estimation. Out of 33 adults referred, only 21 are included in the study.

Results:

From the 21 patients included in the study, 16 (76.2%) are male and 5 (23.8%) are female. The mean age of patients is 55.1 (10.80). The dose of Cisplatin given was 75mg/m^2 for each cycle up to three cycles. The mean difference of GFR pre and post chemotherapy as given by the PSC 2 method was 13.38 (-4.60, 31.36) ml/min/1.73m2 (p 0.136). Of 21 patients, 3 were found to have severe nephrotoxicity (GFR < 50ml/min/1.73m^2) contributing 14.3% of incidence. Bland-Altman plot showed only PSC 1 is in agreement with PSC 2 technique. Intraclass Correlation Coefficients (ICC) also showed that PSC 1 has high degree of reliability in comparison to PSC 2 method (p< 0.001). The rest of the methods, namely the CG, MDRD, CKD-EPI and Gates methods do not show reliability and agreement in comparison to PSC 2 method (p< 0.05).

Conclusion:

Radionuclide method for evaluating GFR is the most sensitive method for the detection of Cisplatin induced nephrotoxicity. 3 of 21 patients were found to develop severe nephrotoxicity (GFR < 50ml/min/1.73m2) in this small number of samples by both PSC 1 and PSC 2 methods. PSC 1 method was found to be a reliable substitute of PSC 2. The rest of the methods, namely the CG, MDRD, CKD-EPI and Gates are not reliable for detection of early nephrotoxicity. We will recommend the use of one plasma sampling method (PSC 1) for GFR estimation in monitoring post Cisplatin chemotherapy patients.

1.INTRODUCTION

The recent data published in 2011 which was based on GLOBOCAN 2008 indicates that the numbers of cancer cases are on the rise worldwide. Among the risk factors identified are aging and unhealthy life style. The data shows 12.7 million of cancer cases with 7.6 million of deaths estimated to have occurred in 2008 (Ferlay et al., 2010, Jemal et al., 2011). Those are identified as solid tumours and the use of Cisplatin chemotherapy as neo-adjuvant treatment has been shown to have a higher cancer response by 2 to 3 fold compared to after radio-surgery (Stathopoulos, 2013).

Cisplatin remains as one of the best anticancer agent for the treatment of solid tumour over the last 30 years (Stathopoulos, 2013). Cisplatin in its full name is known as dichlorodiamino platinum and had been used for the treatment of various malignancies involving the head and neck, lung, breast, liver, testis, ovarian and bladder (Kodama et al., 2014a). Despite its well-known desirable effect on cancer treatment per se, its full therapeutic potential has been limited by its potential toxicity. Many articles reported that the incidence of nephrotoxicity following high dose cisplatin chemotherapy happens in the range of 20 to 25% (Yao et al., 2007, Gonzalez et al., 2004). Since Cisplatin remains as a promising therapeutic anticancer therapy up to date, on-going researches are being done to develop concurrent renoprotective agent that can reduce the effect of nephrotoxicity. Numerous efforts are being done to evaluate other chemotherapeutic agents and targeted therapies that can be alternative to Cisplatin with more or less similar therapeutic effect but lesser toxicity (Stathopoulos, 2013). Injury to the kidney could happen even after a single dose of 50 to 100mg/m^2 of Cisplatin, however, most of the cases are reversible with conservative treatment of volume expansion or saline diuresis with early detection while a small percentage of patients will continue to have progressive decline in renal function. Worst case scenario has been described in the literature whereby repetitive courses of Cisplatin at high doses may lead

to irreversible kidney damage if it fails to be detected and treated at early stage (Yao et al., 2007).

To address this issue, current clinical practice requires close monitoring of the kidney function pre and post chemotherapy to anticipate any significant decline of renal function. Therefore, estimating the glomerular filtration rate (GFR) has been accepted at large as a parameter to represent the functional status of the kidney (Itoh, 2001). There are various techniques which has been proposed to estimate GFR using endogenous or exogenous markers, but the most important aspect in choosing which method to use will have to take into account the simplicity, cost and availability without compromising the accuracy of the result. The development of various techniques has taken place from calculating the endogenous to exogenous substances excreted by the kidneys over the years, and until today it is still well accepted that measurement of the inulin clearance for assessment of GFR remains as the gold standard. Nevertheless, this method has gained less popularity in view of its complexity and invasive procedures to perform. Therefore, since the era of 1970s, radionuclide techniques have been developed as an alternative to inulin for measurement of GFR (Filler, 2008).

At present, the most frequent technique to assess bedside GFR is still by measuring the serum creatinine. The result is incorporated into various formulas in order to generate GFR. However, of note, the interpretation result of this method is susceptible to many variations by multiple non renal factors, namely the muscle mass, age, race and not forgetting the dietary intake (Millward et al., 1996). This holds true that in our centre, estimation of GFR using serum creatinine and Cockroft-Gault (CG) formula is still the preferred choice here in view of its simplicity to be performed bedside at an affordable cost.

The main aim for performing this study is to encourage early detection of nephrotoxicity post Cisplatin chemotherapy among the selected oncology patients. This is achieved via various methods for comparison namely the creatinine based method againts the 99mTc-DTPA method. Radionuclide method has been shown to be a potential alternative to inulin (Biggi et al., 1995). With this, 99mTc-DTPA with two plasma sampling method (PSC 2) has been chosen as the standard of reference. In this study, we attempt to evaluate the reliability of the creatinine based equations and 99mTc-DTPA single plasma sampling (PSC 1) in comparison to the PSC 2. We also attempt to justify the use of PSC 1 as an alternative to PSC 2 in view of the less invasive technique with only single blood sampling without compromising the accuracy of the GFR reading. This is in accordance with the recent study conducted in 2010 which aim to find a simplified yet accurate way of determining GFR among children in order to reduce the physical and psychological trauma to the patients following repetitive blood sampling (Gutte et al., 2010). In order to evaluate possibility of nephrotoxicity at earlier stage, this study will be conducted in 3 stages; pre chemotherapy to get baseline GFR, post mid cycle chemotherapy (after 3 cycles of chemo) to measure how much fall in GFR from baseline and at post completion of 6 cycles of chemotherapy to further evaluate the trend in GFR reading. The ideal situation is to conduct this study before and after every Cisplatin dose with the intention to get serial GFR reading. However, due to limited resources and logistic problems, the justification of this study design is made based on an article published in 2010 to perform the test to at least post third chemotherapy for accurate detection of early kidney injury (Fatima N., 2010).

2.LITERATURE REVIEW

2.1 Brief anatomy of the kidney

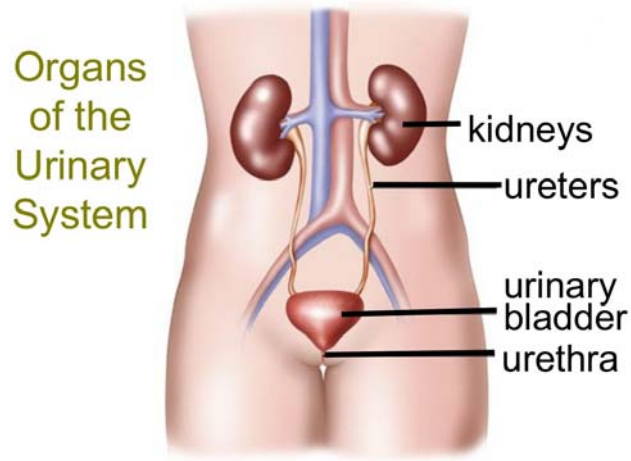

Figure 1.0 Front view of urinary tract

(Adapted from www.slideshare.net on 1.8.2015)

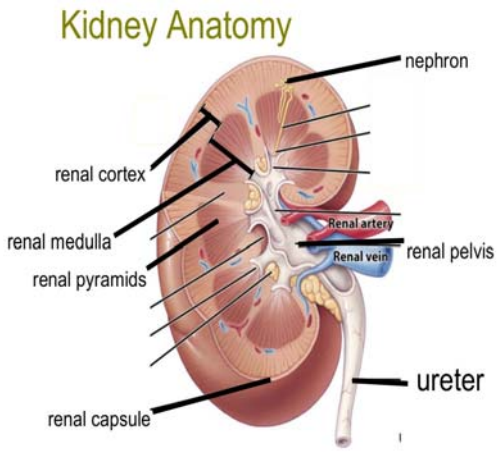

Figure 2.0 Anatomy of the kidney

(Adapted from www.slideshare.net on 1.8.2015)

The kidneys are bean shaped organ located retroperitoneally that play important roles in vertebrates. They maintain body homeostasis such as regulation of blood pressure, electrolytes and acid-base balance as well as site for hormones production such as calcitriol, erythropoietin and renin.

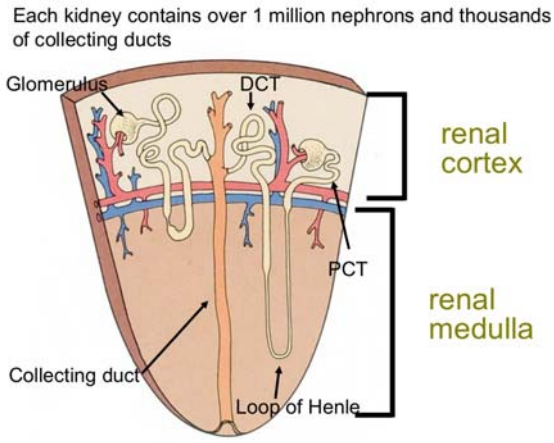

Figure 3.0 Cross-sectional view of renal cortex and renal medulla

(Adapted from www.slideshare.net on 1.8.2015)

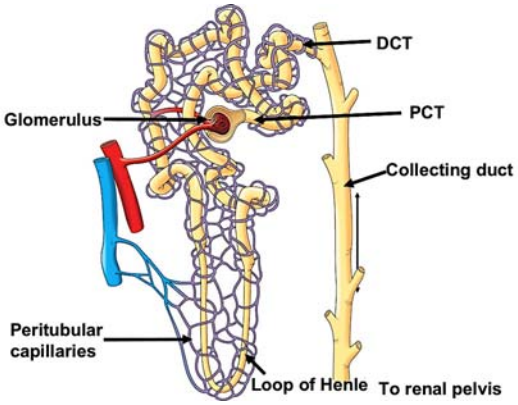

Figure 4.0 Anatomy of the nephron

(Adapted from www.slideshare.net on 1.8.2015)

Inside kidney, there is one single basic structure and functioning unit known as nephron. Each nephron is made up of a filtering component namely the renal corpuscle and the renal tubule with specific functions for reabsorption and secretion. On the other hand, the renal corpuscle by itself is responsible for filtering out solutes from the blood and delivering water and small solutes to the renal tubule for further processing. This unique structure is made up of a glomerulus and Bowman's capsule and it marks the beginning of the nephron's initial filtering component (Tortora and Derrickson, 2009).

The glomerulus is made up of a tuft of capillary with blood supply coming from the afferent arteriole of the kidney circulation. In glomerulus, water and solutes will be filtered through the glomerular wall into the Bowman's capsule and this is made possible by a pressure force known as glomerular blood pressure. This is where the glomerular filtration occurs in the kidney. In addition to that, the filtration of fluid from the blood in the glomerulus is done by the podocytes which forms the visceral inner layer of the Bowman's capsule. Following this, the resulting glomerular filtrates will then undergoes further processing along the nephron to form the urine (Tortora and Derrickson, 2009).

2.2. Overview of renal physiology

In the kidney, the single basic structure and functioning unit is known as nephron. It serves three important basic processes which are the glomerular filtration, tubular reabsorption and tubular secretion (Tortora and Derrickson, 2009).

2.2.1 Glomerular filtration

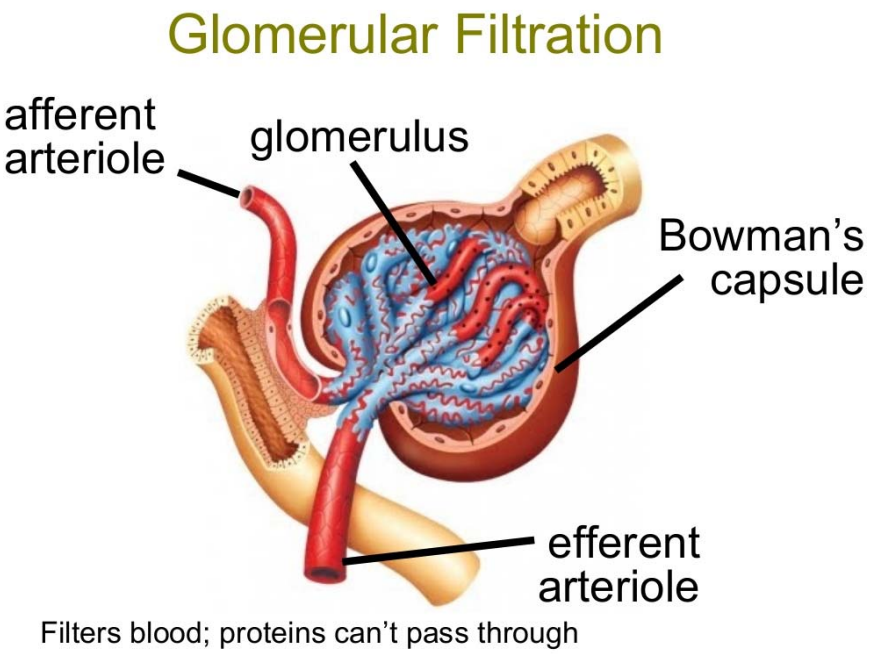

Figure 5.0 Anatomy of the glomerulus

(Adapted from www.slideshare.net on 1.8.2015)

Fluid that enters the capsular space is known as glomerular filtrate. Filtration happens when there is a driving force to push the fluid and solutes out of the afferent arteriole through a membrane in the capillaries. On average, daily volume of glomerular filtrate in adults is 150 liters in female and 180 liters in male. Except for blood cells, platelet, most plasma proteins and any substance, which have larger diameter than the entry pores in the membrane, most substances in blood plasma can easily pass through the glomerular filter.

For further information, there are 3 main pressures involved in glomerular filtration, namely the glomerular blood hydrostatic pressure, capsular hydrostatic pressure and blood colloid osmotic pressure. Each of them carries specific function.

Glomerular blood hydrostatic pressure promotes filtering out of the glomerular capillaries into Bowman's capsules whereas capsular hydrostatic and blood colloid osmotic pressure force the filtration from the capsules into the glomerular capillaries. Glomerular filtration rate is defined as the amount of filtrate formed in both kidneys per minute. The rate itself is determined by renal auto regulation, neural and hormonal regulation.

2.2.2. Tubular reabsorption and secretion

Any substances which are needed by the body will be reabsorbed back into the blood and any subtances which are no longer needed will be secreted into the tubule and excreted out of the body. For better understanding, reabsorption denotes the process of absorbing back the substances from the renal tubule into the blood stream whereas secretion denotes the process of excretion of substance from the blood into the renal tubule.

2.3. Evaluation of kidney function

Assessing the kidney function requires evaluation of both quality and quantity endogenous substance such as urea and creatinine in the blood as well as the urine level. GFR, being the most popular marker of kidney function, is resembling the number of functioning nephrons. This means that GFR will be reduced in case of reducing functioning renal mass.

2.3.1 Glomerular filtration rate (GFR)

GFR has been largely used as a measure of kidney function in clinical practice and it represents the volume of fluid filtered through the nephrons per unit time during formation of the urine (Schwartz and Furth, 2007). It is said to be the best overall

measure of renal function in both healthy or diseased kidney (Smith, 1951). The normal level of GFR varies according to age, sex and body size. In young adults, it measures approximately 120 to 130ml/min/1.73m^2 and this value reduces with age. Some other author has published the reference range of GFR in adulthood to be approximately 105ml/min/1.73m^2 of BSA (Levey et al., 2003). Although declining GFR value with age is considered part of normal aging process (Lindeman et al., 1985), this factor has been found to be independent predictor of adverse sequelae, for example death or cardiovascular diseases (Manjunath et al., 2003). Therefore, the prevalence of chronic kidney disease by definition increases with age in view of the adverse outcomes associated to it. There is estimated 17% of the elderly aged above 60 years old have GFR of less than 60ml/min/1.73m^2 (Coresh et al., 2003). This is an important point to be taken pertaining to the treatment option for chemotherapy and associated GFR level since the risk of developing carcinoma is also increasing with age. In children, GFR value slowly increases approaching the adult value over the first 2 years of life (Murray et al., 2013).

In clinical practice, the measurement of GFR has may uses which include evaluation and monitoring of kidney in chronic renal disease, during the course of administration of nephrotoxic drugs, calculation of myelotoxic chemotherapy drug doses that is excreted through the glomerular filtration, potential renal donor evaluation, single kidney renal function evaluation, pre and post-operative follow up as well as prediction or assessment for the need of dialysis (Murray et al., 2013).

There are many options available to measure GFR and many methods are developed to meet this purpose using either endogenous or exogenous markers. The main interest of this study is to show the use of radionuclide method as a reliable GFR marker to detect evidence of nephrotoxicity following Cisplatin chemotherapy.

Radionuclide method has been shown to exhibit a comparable result and can be an alternative to the cumbersome inulin measurement in daily practice (Fawdry and Gruenewald, 1987, Rehling and Thamdrup, 1984).

GFR normalization is an important component to be performed in obtaining the final measurement. It is done to eliminate the individual variation from patient to patient pertaining to the different renal masses in order to establish the reference value across the individuals with different demographic characteristics (Murray et al., 2013). There are two ways of performing GFR normalization; one is via Body Surface Area (BSA) method which is the most widely used method in clinical practice and the other one is the Extracellular Fluid Volume (ECV) which is less popular compared to the former method. Though BSA is the preferred method, there is an issue that comes along with it in which the physiologic relevance has been questioned (Turner and Reilly, 1995). In opposed to ECV method, it has been said to have a better dimensional relationship (volume- based) to GFR (Brøchner-Mortensen, 1980) and has gained more superiority against BSA method especially in children (Bird et al., 2003).

The BSA and ECV normalizations equations are as follows:

$$GFR_{BSA} = GFR_{NON} \times \frac{1.73\ m^2}{BSA},$$

$$GFR_{ECV} = GFR_{NON} \times \frac{12.9\ L}{ECV},$$

Figure 6.0 BSA and ECV equations

(Adapted from Assessment of glomerular filtration rate measurement with plasma sampling: A technical review, Journal of nuclear medicine technology 2013 41(2): 67-75))

where GFR_{BSA} is in ml/min/1.73m^2, GFR_{ECV} is in ml/min/12.9, BSA is in m^2 and ECV is in litres.

The two most commonly used BSA estimation methods are the Dubois formula for adults (Du Bois and Du Bois, 1989) and the Haycock formula for both adult and children (Haycock et al., 1978). Both formulas area given as follows:

For Dubois formula,

$$BSA = 0.007184 \times height^{0.725} \times weight^{0.425}$$

For Haycock formula,

$$BSA = 0.024265 \times height^{0.3964} \times weight^{0.5378}$$

Figure 7.0 Dubois and Haycock's equations

(adapted from Assessment of glomerular filtration rate measurement with plasma sampling: A technical review, Journal of nuclear medicine technology 2013 41(2): 67-75)

where BSA is in meters squared, height is in centimetres and weight is in kilograms.

2.3.2 Effective renal plasma flow (ERPF)

ERPF is another way of quantifying renal function other than GFR. ERPF is a technique used to measure renal plasma flow thus estimating the renal function. It is measured using plasma clearance technique. Paraaminohippurate (PAH) is the best substance to measure ERPF with the extraction ratio nearly 1. Historically, I-131 OIH and I-123 OIH have been used to quantify ERPF whereby the urinary clearance of I-131 OIH is approximately 85% of PAH. However, at present 99mTc-MAG3 has been used to replace hippuran. Nevertheless, its efficacy for ERPF measurement has been

documented at about 60% of hippuran since it does not undergo glomerular filtration and slightly reduced level of tubular secretion. However, a lot of studies has been conducted and prove that 99mTc-MAG3 is able to produce an accurate ERPF result once corrected for the different extraction fraction (Ziessman et al., 2013).

2.3.3 Exogenous GFR markers

There are few exogenous substances which can be used for measurement of GFR. Among them are the inulin and the radioactive tracers such as the 99m-Tc DTPA and 51-Cr EDTA. Inulin, a group of naturally occurring polysaccharides produced by many types of plants, has the properties of an ideal tracer. It is neither secreted nor reabsorbed at the nephron allowing accurate GFR to be calculated. It is the gold standard for measuring GFR but is rarely used clinically due to its technical difficulty, expensive, time consuming, require multiple urine samples and is problematic to be done in patients with urologic disease and in children. Though it still remains as the gold standard method, it has lost its popularity due to its cumbersome procedure and technically difficult to be performed (Murray et al., 2013).

Radionuclide method using plasma sample clearance has been found to produce accurate GFR measurement (Brøchner-Mortensen, 1978). However, Itoh et. al concluded that this technique is laborious and therefore its use is reserved for specific indication that strictly requires accurate quantification of renal function (Itoh, 2003). After all, we need to understand that the ideal characteristics of tracer properties used in GFR measurement shall include:

i) It undergoes only glomerular filtration and thus has identical plasma and urinary clearance.

ii) It has a low molecular weight and small molecular size to allow free filtering through the glomerular membrane.

iii) It has no entry into the intracellular space.

iv) It has no interference with renal function.

v) It has no extrarenal excretion or clearance to other organs.

vi) It has no tubular secretion or absorption.

vii) It has no nephrotoxicity.

Theoretically, a tracer that follows any processes other than glomerular filtration is not an ideal tracer and the resulting GFR is not equal to its plasma clearance. Those processes include radionuclide dissociation, metabolic degradation, plasma protein binding, tubular reabsorption and secretion. This phenomenon may lead to inaccuracy in GFR reading resulting from unwanted retention or clearance of the tracer. However, in real clinical practice, it is almost impossible to have an ideal tracer exactly as discussed above. Nevertheless, we still have the option of using near ideal properties to deal with the difficulty and impracticality of using an ideal tracer (Murray et al., 2013).

Radionuclide based techniques allow for the rapid and reliable measurement of GFR from plasma samples taken following IV bolus of radiotracer (Kuster, Cristol et al. 2014). The tracer diffuses across the capillary endothelium and between intravascular and extra vascular spaces and mixes throughout the extra vascular fluid volume (ECV). GFR can be measured through the quantification of plasma and standard-volume sample activity using a gamma counter. These techniques hold the

central assumption that the tracer is cleared solely by glomerular filtration (Murray et al., 2013).

Two of the most frequently used tracers for GFR measurement with near ideal properties are Cr-51 EDTA and Tc-99m DTPA. Cr-51 allows more time between the drawing of blood and counting of the samples due to its relatively long half-life of 27.7 days. However, the disadvantage of using Cr-51 is that not only it is expensive, it also has associated tubular reabsorption as well as issue in handling storage of Cr-51 waste. A reported practical advantage for Cr-51 EDTA studies is that any plasma samples with an existing Tc-99m concentration can be left to decay until no Tc-99m remains before processing. Whereas for Tc-99m DTPA, it has the advantage that it is readily available and can be produced with a Mo-99/Tc-99m generator already in house for diagnostic work thus reducing expenses. Its disadvantage is that processing is required within 24 hours of taking plasma samples due to its shorter half life of 6 hours (Murray et al., 2013).

There is still a big challenge to get simple yet accurate method for GFR determination. Another radionuclide technique using gamma camera uptake known as Gates method where GFR is calculated without blood or urine sampling. This method has been the most common in routine setting, although diagnostic accuracy of gamma camera is debatable (Itoh, 2003). Due to that the same author has conducted a study to assess the clinical validity of single-sample methods and gamma camera uptake methods with Tc-99m DTPA for the estimation of GFR in patients with various degree of renal dysfunction. The reference for the "true" GFR (GFR*t*) was determined from plasma clearance by means of the two-compartment model curve fitting 10 plasma samples. The author found out that the single sample method in GFR ≥30ml/min was more accurate than the gamma camera method, and the gamma

camera method was accurate than 24hour creatinine clearance. Due to that he concluded that the single sample method should be recommended for the accurate determination of the GFR with Tc-99m DTPA in a patient with mild to moderate renal dysfunction (Itoh et al., 2000). The same author again conducted another study aiming towards the assessment of clinical accuracy of single, two and multi sample methods. He proposed the use of single sample method at 180 min as the first choice in a routine practice in view of its accuracy and technical simplicity. The two-sample method at 120 min and 240 min is chosen selectively for a patient with severe renal failure where serum creatinine at the time of the test may help for the choice of either the single or the two-sample method (Itoh et al., 2000). This result is in agreement with the study conducted by Christensen and Groth among cancer patients referred for routine determination of Tc-99m DTPA clearance by comparing single and multiple plasma sample methods. The authors have concluded that the single method is accurate and that may prove useful as a routine method provided that the method is not used in patients with Tc-99m DTPA clearance less than 30ml/min and the plasma samples drawn between 180 to 300 min (Christensen and Groth, 1986).

In this study, the two plasma sampling method using Tc-99m DTPA has been used as the standard for comparison among other methods which are creatinine-based GFR. Its principle of GFR measurement is based on clearance of plasma radioactivity via single and two-blood sample using the well counter where by the blood was taken at 60 and 180 minutes post tracer injection and to compare with the clearance of radioactivity from plasma sampling taken at 180 minutes alone. Comparing to the study conducted by Waller and Keast, their measurement of GFR was taken from plasma radioactivity using single and two blood samples, tissue clearance with probe detectors, renal uptake and excretion using scintillation camera and combination of

single blood sample and external detector clearance rate. Those methods were compared with multiple plasma sampling where blood was taken at 1 hour post injection and again every 30 min for a period of 4 hour. Apart from comparing the individual accuracy of each method as well as its suitability for routine clinical use in the assessment of adult patients, the study was also done to assess how much data reduction was possible without impairing the accuracy of the result. From the analysis using 2 blood samples, the correlation with multiple-point plasma clearance was excellent, and in fact improved results was obtained by using the later blood samples. This was probably due to incomplete equilibration at earlier sampling times and this can be reduced by increasing the time between the samples. The results for single blood sample show inferior correlation compared with two blood samples taken at around the same time. However, the correlation improves when the time of sampling post injection is longer, reaching an optimum between 3 and 4 hour then deteriorating significantly at 5 hour. Meanwhile, the author did not recommend the use of less invasive external counter clearance rate without blood sampling since it does not correlate well enough with GFR (Waller et al., 1987).

On average, most of the studies conducted supported the use of single plasma sample of Tc-99m DTPA method for accurate measurement of GFR provided the GFR measured is ≥30 ml/min. This means that in view of its technical simplicity, time and cost saving, it is acceptable to implement this method in the clinical practice to evaluate kidney function where GFR is ≥ 30ml/min.

2.3.3.1 Clearance characterization

2.3.3.1.1 GFR Introduction

Plasma clearance assumes the biexponential model with 2 distinct compartments. It represents the fixed flow rates between constituent compartments. This can be illustrated further in the diagram below:

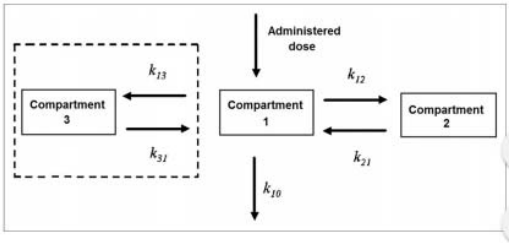

FIGURE 2. Two- and 3-compartment models with respective rate constants, k_{ij}. K_{10} is taken to be GFR clearance. Two-compartment model views compartment 1 as intravascular volume and compartment 2 as extravascular volume. Compartment 3 is considered to be present in patients with known third fluid compartments.

Figure 8: Two and three compartment model

(adapted from Assessment of glomerular filtration rate measurement with plasma sampling: A technical review, Journal of nuclear medicine technology 2013 41(2): 67-75)

After mixing has occurred between the 2 compartments, the slope of the clearance reflects solely renal clearance.

2.3.3.1.2 One-Compartment Characterization

Briefly, in this model, only the late exponential is characterized, and published corrections can be used to fill up for the missing early-compartment area under the curve (AUC). Only 2 to 4 samples are needed to calculate the GFR and this method is referred as slope intercept method.

The intercept of the late exponential is interpreted as instantaneous concentration of the tracer at the time of injection; instantaneous