Journal of Drug Metabolism and Toxicology

Tesfaye, J Drug Metab Toxicol 2016, 7:2
DOI: 10.4172/2157-7609.1000209

Case Report Open Access

Serum Creatinine Levels May Not Necessarily Reflect a True Renal Function to Adjust Amikacin Dose in Paraplegic Patient: A Case Report and Literature Review

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Received date: May 24, 2016; **Accepted date:** June 05, 2016; **Published date:** June 15, 2016

Abstract

To estimate glomerular filtration rate as an indicator of kidney function, clearance of endogenous creatinine is usually used despite its unreliability due to influence of several factors including age, gender, muscle mass and interferences within methods. Although there is emergence of better markers like serum cystatin-C, creatinine clearance continues to be used routinely as a marker of renal function to date. In the present case study we describe only slightly elevation of serum creatinine associated with high serum drug concentration 27 mg/L "trough" and 41 mg/L "peak", respectively in a paraplegic patient treated with initially reduced dose (500 mg/day) of an aminoglycoside antibacterial drug (amikacin). The relatively little increment of serum creatinine in this case might be related to underlying pathology resulting in low production of creatinine, which does not essentially reflect the true renal function. Methodological challenges during GFR estimation and risk of renal impairment in Spinal Cord Injury (SCI) patents are also discussed in context with literature review.

Keywords: Spinal cord injury; Serum creatinine; Amikacin dose adjustment

Introduction

Serum creatinine measurement with its clearance calculation is being used as kidney function indicator for many decades. Nevertheless the reliability of this biomarker is questioned due to influential factors existing to in individuals both at health and disease conditions [1]. Under physiological conditions, creatinine does not bind to plasma proteins, and is freely filtered by the renal glomeruli, so that the differences in serum creatinine and its renal clearance may reflect the differences in glomerular filtration rate [2]. Methods of analysis and equipment used may also be cause of bias leading to inaccurate estimation of the renal function [3]. The Jaffe method for instance is affected by numerous interferants that can cause creatinine levels to be falsely increased or decreased [4]. Advances of kinetic enzymatic methods may eliminate the error caused by interferences for instance in Jaffe method, while the challenges caused by other natural or disease factors remain untouched. Illness leading to long time in bed stay and paralysis are reported to be associated with rapid deterioration in muscle mass [5,6] as a result of limited or absent activity. Failure to consider variation in creatinine production due to differences in muscle mass, diseases, and other conditions impact on serum creatinine, and inaccuracy in measurement can lead to inaccurate conclusion. The misinterpretation of low serum creatinine can lead to undesired outcomes, especially in patients with chronically reduced renal function such as the patients with spinal cord injury characterized by decreased GFR that can affect the safety of the drugs [7]. In the present paper we describe a case of paraplegic patient with relative renal impairment overdosed even by half reduced dose of an aminoglycoside antibiotic with significant serum drug accumulation with only slightly increment of actual serum creatinine.

Case Description

A Caucasian male (age 66 years, body weight 90 kgs, lean body mass 67.1 kgs, height 186 cm, body mass index 26.01 kg/m^{-2}, body surface area 2.15 m^2) has undergone vascular operation (stent graft) aiming ascendant aortal segment replacement introduction of an artificial vale for underlying dilatation of ascending aorta and aortal valve insufficiency 9 years ago. In November of 2014 he complained of abdominal pain, and further examination revealed dissection of aorta. The new finding was initially aimed to be managed conservatively, but the aortal arch replacement was conducted just three weeks later. However, otherwise unresolved bleeding enforced stent-graft placement of descending aorta, after which the patient demonstrated paraplegic lesion with neurological level of injury at T3. The lesion was AIS grade "A" according to the international standards for neurological classification of spinal cord injury [8] most probably as a result of ischemic damage during the stent-graft procedure. The clinical state was further complicated by repeated episodes of respiratory infection necessitating tracheotomy and temporary ventilation support. Later renal function impairment indicated intermittent dialysis, with slow improvement and persistently abnormal renal parameters. Exacerbated tachyarrhythmia has been repeatedly resolved by electrical cardioversion. The patient also has acquired Clostridium caused enterocolitis. In March 2015 the patient was referred to the spinal cord unit for further care. After admission, lab tests revealed evident alteration of renal function (Blood urea nitrogen/BUN=24.4 mmol/L, Serum creatinine 170 μmol/L). To eradicate respiratory and urinary tract infection three antibacterial drugs (Tienam 1 g/6 hr, Amikacin

500 mg/ 24 hr and Entizol 500 mg/8 hr) were concomitantly prescribed. Amikacin starting dose is usually 1000 mg in our clinical setting for adults, whereas despite dose reduction by half, amikacin trough level after 3 doses revealed evident accumulation towards potentially toxic concentrations(trough 27 mg/L, peak 41 mg/L) urging temporary drug withdrawal in this case Serum creatinine concentrations measured by less affected enzymatic method before amikacin therapy and almost on daily basis after intervention for eight consecutive days including post drug withdrawal revealed (baseline 159 µmol/L, 1st day 176 µmol/L, 2nd day 155 µmol/L, 3rd day 151 µmol/L, 4th day 143 µmol/L, 5th day 145 µmol/L, 6th day 137 µmol/L, 8th day 130 µmol/L, respectively as illustrated in Figure 1.

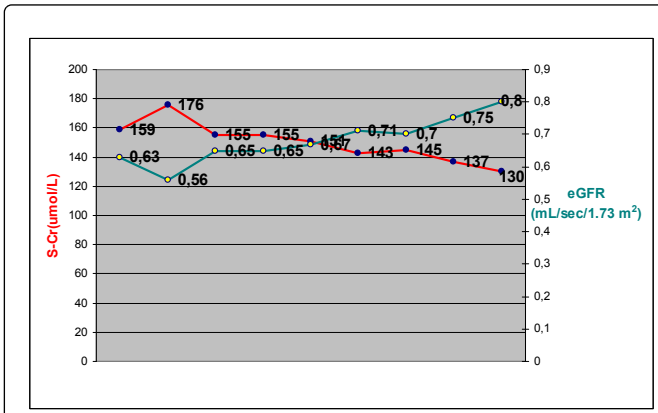

Figure 1: Decline and improving of eGFR inversely corresponding with serum creatinine levels in paraplegic patient treated with reduced and extended interval amikacin doses (500 mg/24 hours).

Initial glomerular filtration rate estimated according to the Modification of Diet in Renal Disease (MDRD) formula was >0.63 mL/sec/1.73 m^2 or 41.6 mL/min/1.73 m^2. On the 3rd day, trough amikacin level as determined by fluorescent polarization immunoassay (FPIA) was unacceptably high reaching 27 mg/L (Figure 2) provided that concentrations exceeding 5-10 mg on once-daily (extended interval dosing regimen) is considered potentially toxic referring to therapeutic range guidelines.

Although the peak amikacin level of 41 mg/L may be advantageous for concentration dependent bacterial killing effect, it certainly carries high risk of nephrotoxicity in the patient with evidence of chronic renal function impairment. Recorded serum creatinine levels of this patient theoretically indicated relatively good clearance (33.5 mL/min/1.73 m^2) using Jelliffe II. Formula, which has been incorporated in MW/PHARM version 4 CZ pharmacokinetic program used for dose adjustment. The case simply demonstrates that eGFR based on serum creatinine in paraplegic subjects may overestimate the renal function leading to undesired drug overdose unless therapeutic drug monitoring with skillful/careful interpretation is used to assist in the appropriate and safe dose adjustment.

Discussion

There is no doubt about that determination of endogenous creatinine serum level is the most widely used indirect measure of glomerular filtration rate as it is convenient and cheap, although is of low sensitivity even to substantial renal function impairment in addition to problematic interpretation [9], so that serum creatinine that falls in the so-called "normal" value in a young, healthy individual may in an elderly patient indicate a significant reduction in GFR due to old age or disease state [10].

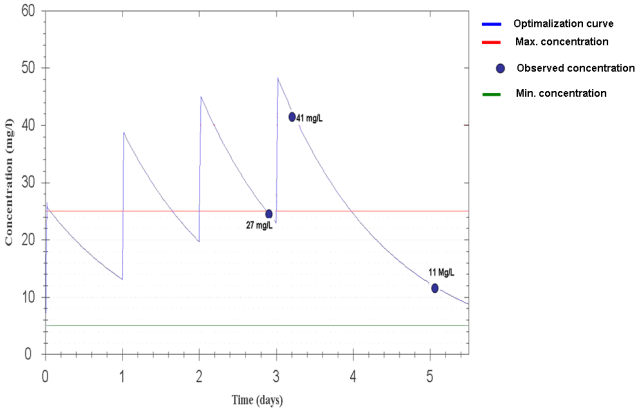

Figure 2: Cumulative amikacin concentration despite initially reduced dose by half till withdrawal followed by gradual elimination in a paraplegic patient with renal function impairment.

Long time follow-up on ability of plasma creatinine value in individuals, who have sustained spinal cord injury has already confirmed that plasma creatinine is a poor detector of early stage renal function deterioration [11] Meanwhile, progressive renal impairment after spinal cord injury is well documented [12] at least for acute stage of the injury and may be associated with many changes that can affect disposition of drugs such as aminoglycosides. Therefore, dosing of aminoglycosides in such patients can be challenging due to changes in some important pharmacokinetic parameters such as volume of distribution, clearance, and half-life of these drugs. Considerable differences in the disposition of amikacin have found in persons with chronic SCI in comparison to controls suggesting that amikacin dosing regimens developed for healthy subjects may demonstrate inaccuracy when extrapolated uncritically to these patients [13]. There is enough evidence that indicates serum creatinine and various GFR estimation equations are not accurate for assessing true renal function in this case, whereas using markers like Cystatin C may be better option to substitute creatinine [14], although its use is limited in routine practice to date. Determining appropriate, dosage in patients with SCI is very challenging because such patients exhibit multiple changes so that monitoring of aminoglycoside concentrations and calculation of patient-specific pharmacokinetic values can help guide dosage in this patient population [15]. Overestimation of drug clearance by the frequently employed GFR estimation methods necessitated developing an alternative method of estimating drug clearance in spinal cord injury patients to produce better results with less variability [16]. As previously mentioned, Mirahmadi et al. [17] also reported that both serum creatinine and mean urinary creatinine excretion were markedly lower in paraplegics compared with ambulatory subjects. Not only the original Cockcroft and Gault formula appears misleading; when applied to SCI patients, it is also published that both MDRD and CG equations overestimate GFR in patients with chronic SCI at all stages of chronic kidney disease, particularly in quadriplegic subjects [18]. There were incidents, where our group earlier published cases of patients with apparently low serum creatinine, who suffered drug overdose and toxicity [19,20]. In critically ill patients, where serum

creatinine has low sensitivity to detect early renal function impairment Cockcroft–Gault and MDRD equations using cratinine are not also good enough to show true renal function [21] Comparison of measured endogenous creatinine clearance with the predicted creatinine clearance revealed that the predicted values in the spinal cord injury patients consistently exceeded the measured values [17], so that the original Cockcroft and Gault formula; when applied to SCI patients can be very misleading. As better alternative, the serum cystatin C is considered a convenient and more reliable surrogate marker of GFR and may enable early detection of renal impairment [22] and could be applied also for the spinal cord injury patients [23,24]. Unfortunately there are no ready universal guidelines to apply it as replacement for serum creatinine measurements although a virtually assay-independent simple cystatin-C based and biologically oriented equation for estimation of GFR [25]. Cystatin-C level was not readily available to assess renal function also in our patient before amikacin dosing. Generally, renal failure and complications such as urinary tract infections due to abnormal bladder emptying and catheterizations are common among SCI patients [26]. When nephrotoxic agent like amikacin is administered to prone patients with SCI, appropriate aminoglycoside dosing is a difficult task as such patients exhibit changes that lead to abnormal aminoglycoside pharmacokinetic profiles. In such circumstances, careful and timely monitoring of aminoglycoside concentrations and calculation of patient-specific pharmacokinetic values can help guide dosage adjustment [15]. Considering serum creatinine as the major variable in calculating GFR one may expect the creatinine level and GFR to be of corresponding values. In contrast, amikacin trough level was more than five-fold (27 mg/L)higher than usually observed or recommended trough value (<5 mg/L), despite only slightly increased serum creatinine and initial reduction of amikacin dose by half in the case described here. Several plasma constituents can interfere with creatinine measurement, however, in the present case, possible analytical error has been excluded by using less interfered enzymatic method according to the manufacturer, Siemens Diagnostics, Japan. Some liver abnormalities can interfere with serum creatinine levels [27,28] as also unmasked liver alteration may be considered in any patient with SCI provided that relatively high frequency of liver disease in association with SCI exists [29,30]. However, bilirubin, liver transaminases, as well as total protein and albumin levels were not remarkable in our patient. There have been many attempts to transform mathematically or correct serum creatinine aiming that it may more accurately reflect glomerular filtration rate in several formulae widely used in the past and to date [31-35] as listed in Table 1, but none of them are suitable for SCI patients In later detailed report [36] it has been concluded that GFR should be estimated using MDRD study equation that using standardized serum creatinine. However, later published paper [37] is in disagreement with MDRD formula applicability to all populations even post creatinine standardization. More recent equation is also published [38], but its universal application and validity is not without challenges since the biomarker used in the new equation also includes plasma creatinine level, whose shortcomings as a marker of glomerular filtration rate are not completely avoided. Nevertheless, very recently published alternative [16] as modified equation for renal function estimation may be appropriate for spinal cord injury patients provided that the new equation estimates drug clearance more accurately in chronic spinal injury patients.

Name of Method	Formula	References
Schwartz	k (Height in cm)/Serum creatinine in mg/dL where, k = constant = 0.33 (in premature infants) = 0.45 (in term infants to 1 year) = 0.55 (in children up to 13 years) = 0.70 (in adolescent males) = 0.55 (in adolescent females)	[31]
Cockcroft & Gault	a. For men: CrCl = [(140 – $Age_{(years))}$ x Weight (kg)]/SCr x 72 b. For women: CrCl = ([(140 - $Age_{(years))}$ x Weight (kg)]/SCr x 72) x 0.85	[32]
Jelliffe II.	a. For men: (100/SCr) - 12 b. For women: (80/SCr) - 7	[33]
MDRD	170 x SCr-.999 x $Age_{(years\ )}$ -.176 x (0.762 if female) x (1.180 if black) x SUN-.170 x Alb.318	[34,35]

Table 1: Different formulae developed in the past for glomerular filtration rate estimation based on serum creatinine clearance. KEY to abbreviations in the table: SCr serum creatinine (mg/dL); Wt=Body weight (kg); SUN=Serum urea nitrogen (mg/dL); Alb=Serum albumin (g/dL), CrCl=Creatinine clearance.

Conclusion

Dosing nephrotoxic drugs like amikacin just on the basis of estimated GFR using creatinine clearance as a maker is not anymore wise step towards safe therapy in paralysis patients. Skilful assessment of the clinical state and awareness of drug accumulation is very important in particular in patients with spinal cord injury with chronic renal impairment. Most importantly drug disposition assessment without delay through Therapeutic Drug Monitoring (TDM) method for adequate dose adjustments is mandatory both to prevent toxicity resulting from overdosing as well as therapy failure due to inadequate dose

Conflict of Interest

All the authors declare that they have no conflict of interest pertaining to this case report.

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