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Rapid decline of serum creatinine and a challenge of aminoglycoside dosing: a case of post bilateral lung transplantation cystic fibrosis patient

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SUMMARY

Serum or plasma creatinine level determination has been serving for decades as the most commonly used marker of renal function. However, creatinine levels are affected by a number of other factors not related to renal function, particularly age, gender, muscle mass, starvation, wasting diseases, post surgical states, and activity or exertion. Alternatives for the assessment of renal function or glomerular filtration rate (GFR), through measurement of the clearance of exogenous substances like, inulin, ^{51}Cr-ethylendiaminotetraacetate (^{51}Cr-EDTA), ^{99m}Tc-diethylenetriaminepentaacetic acid or iohexol are more accurate, but too complex, laborious, and not suitable for routine clinical use. Therefore, serum creatinine measurement yet remains the most common method to estimate renal function in routine clinical practice. In the presented case study, nearly 50% decline in serum creatinine level as measured by enzymatic colorimetry method according to the manufacture's recommendation is described. Relatively rapid serum creatinine concentration decline from 67 μmol/L baseline value to 30 μmol/L within 4 days in a CF patient post bilateral lung transplantation, who, was on courses of essential immunosuppressive, antimycotic, and antibacterial drugs including an aminoglycoside (amikacin) was observed. The change in serum creatinine level within four consecutive days after bilateral lung transplantation (mean difference, -49.25 % μmol/L; with 95% confidence interval, -29 to -37 μmol/L) was significant. Herein, the event is not essentially reflecting better renal function, since amikacin trough level was unacceptably high (20 mg/L) at the same time, rather explaining probably low production of creatinine as a result of underlying pathology in cystic fibrosis. Patient related explanations and existing methodological challenges have also been discussed.

Key words: serum creatinine, amikacin dosing, cystic fibrosis, lung transplantation.

SOUHRN

Tesfaye H., Průša R., Kolářová J., Šimonek J., Lischke R.: Rychlý pokles sérového kreatininu a obtížné dávkování aminoglykosidu – kazuistika pacientky s cystickou fibrózou po oboustranné transplantaci plic

Hladina sérového nebo plazmatického kreatininu slouží již desítky let jako nejčastější používaný ukazatel renální funkce. Přesto je koncentrace sérového kreatininu ovlivněna jinými, s funkcí ledvin nesouvisejícími faktory (věk, pohlaví, svalová hmota, stav výživy, nemoci poškozující organismus, pooperační stavy, tělesná aktivita nebo vyčerpávající fyzický výkon). Alternativy pro zjištění renální funkce/gromerulární filtrace (GFR) pomocí podání exogenních látek (inulin, ^{51}Cr-ethylendiaminotetraacetát (^{51}Cr-EDTA), ^{99m}Tc-diethylenetriaminepentaacetát nebo iohexol) jsou přesnější, ale zároveň velmi složité, pracné a nehodí se pro rutinní praxi. Měření sérového kreatininu proto stále zůstává běžnou metodou k odhadu renální funkce v rutinní klinické praxi. V tomto sdělení popisujeme cca 50% pokles sérového kreatininu měřeného enzymatickou metodou s kolorimetrickou detekcí podle návodu výrobce. Relativně rychlý pokles sérového kreatinu z 67 μmol/l na 30 μmol/l v průběhu 4 dnů byl pozorován u pacientky s cystickou fibrózou po oboustranné transplantaci plic, s náležitou imunosupresivní, antimykotickou i antibakteriální léčbou včetně aminoglykosidů (amikacin). Změny v hladině sérového kreatininu během 4 dnů (průměrný rozdíl 49, 25 %, při 95% intervalu spolehlivosti, -29 až -37 μmol/l) jsou významné. Tento jev přesto nemusel být odrazem lepší clearance vzhledem k nepřijatelně vysoké „trough" hladině amikacinu a nejspíše poukazuje na možné snížení produkce kreatininu v souvislosti s cystickou fibrózou. Autoři v článku diskutují o stavu nemocné a probírají metodologická úskalí.

Klíčová slova: sérový kreatinin, dávkování amikacinu, cystická fibróza, transplantace plic.

Introduction

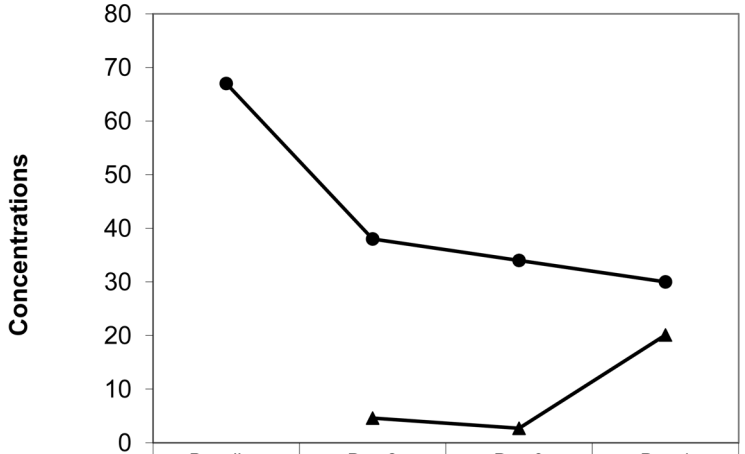
Creatinine is a small molecular weight (113 Daltons) metabolic product of creatine and phosphocreatine, which are both found almost exclusively in muscle. Thus, creatinine production is proportional to muscle mass and varies a little from day to day. However, production can change over longer periods of time if there are changes in muscle mass and other conditions [1]. Although diet ordinarily accounts for only a relatively small proportion of overall creatinine excretion, it is another source of variability in serum creatinine levels. Creatine from ingested meat is converted to creatinine and it is also partly the source of creatinine excretion. Thus, variability in meat intake can also contribute to variability in serum creatinine levels. The conversion of creatine to creatinine can occur with cooking. Since creatinine is readily absorbed from the gastrointestinal tract, ingesting cooked meat can lead to a rapid increase in serum creatinine levels. Creatinine does not bind to plasma proteins, and is freely filtered by the renal glomeruli. However, it has long been appreciated that creatinine is also secreted by the renal tubule. Even if tubular secretion of creatinine were constant, the differences in serum creatinine

and renal clearance could still reflect the differences in glomerular filtration rate, so that the secretion of creatinine varies substantially both in the same individuals over time and between different individuals [2]. One of the problems with using creatinine or its inverse as a measure of glomerular filtration rate is that interpatient and intrapatient differences in creatinine production itself. Particularly troublesome is the fact that the proportion of total renal creatinine excretion due to tubular secretion increases with decreasing renal function, which could have a dampening effect on serial measurements in individuals, because glomerular filtration rate could fall more rapidly than indicated by either serum creatinine or creatinine clearance. Nevertheless, method of determination as well as analyzing apparatus may also be source of significant bias leading to wrong estimation of the renal function [3]. The Jaffe method is affected by numerous interferents that can cause creatinine levels by this method to be falsely increased or decreased [4].The advance of kinetic enzymatic methods has reduced the error in creatinine measurement caused by the presence of various interferents in Jaffe method. However, variations in creatinine production due to age- and gender-related differences in muscle mass remain unavoidable challenges. It is generally accepted that bed rest and paralysis are also associated with rapid deterioration in muscle mass [5, 6]. Failure to consider variation in creatinine production due to differences in muscle mass, diseases, and other conditions including potential effects of tubular secretion on serum creatinine, and unaccuracy in measured values frequently lead to misinterpretation of serum creatinine levels, which affects the clinician to believe that renal function is better than it actually is, especially in patients with reduced renal function. The increase in extrarenal creatinine degradation, which is attributed to its conversion to carbon dioxide and methylamine by bacteria in the intestine at time of declining renal function, may lead to underestimation of declines in glomerular filtration rate. Herein we present unexplained apparent decline in a cystic fibrosis female patient, whose amikacin trough level was unacceptably high.

Case description

A Caucasian female (age 18 years, body weight 55 kg, lean body mass 47.9 kg, height 155 cm, body mass index 22.89 kg/m^2, body surface area 1.53 m^2) underwent bilateral lung transplantation indicated for progressive lung disease with underlying genetical defect defined as cystic fibrosis. The patient was on long-term aminoglycoside antibiotic in combination with betalactams due to chronic *Pseudomonas species* colonization before transplantation.

After successful bilateral lung transplantation from a cadaver donor, the usual immunosuppressive regimen was started with tacrolimus. Tacrolimus levels were within recommended therapeutic ranges throughout the follow-up. Preoperative host lung specimen from the bronchial trees revealed *Aspergillus species*, necessitating antimycotic therapy with amphotercin-B, inhalation, i. v. voriconazole, which was switched to oral voriconazole after sputum from the grafted lungs proved negative within four days. Voriconazole levels determined at extra-mural laboratory were reportedly within conventional therapeutic limit. Complying with the usual protocol the patient was prescribed tazocin (a betalactam with tazobactam component) and amikacin 450 mg every 8 hours since the patient was considered prone to *Pseudomonas* infection. Serum creatinine concentrations measured by less affected enzymatic method on daily basis for four consecutive days reveald (baseline 67 µmol/l , 2nd day 38 µmol/L , 3rd day 34 µmol/L, 4th day 30 µmol/L, respectively). Amikacin trough levels were also monitordy starting the the 2nd day of therapy. Intial gromelural filtration estimate according to MDRD was > 1.5 mL/sec. On the 4th day, trough amikacin level as determined by fluorescent polarization immunoassay (FPIA) was unacceptably high (20 mg/L). Serum creatinine levels theoretically indicated high clearance (196 mL/min or 222.7 mL/min/1.73m^2) using Jelliffe – II. formula incorporated in MW/PHARM 3.60 NL, pharmacokinetic program used for dose adjustment. However, the serum creatinine levels were not corresponding to the amikacin trough concentrations as demonstrated in Figure 1. In this case serum creatinine concentrations



	Baseline	Day 2	Day 3	Day 4
Serum creatinine (umol/L)	67	38	34	30
Serum amikacin trough (mg/L)		4,6	2,7	20,1

Fig. 1. Significant decline of serum creatinine level in a CF patient after bilateral lung transplantation, where trough serum amikacin level shows inverse relation to serum creatinine levels

measured by less affected enzymatic method was surprisingly lower than might be expected in a patient under concomitant treatment with potentially nephrotoxic drugs. Finally, the dosing interval was prolonged to 12 hours and acceptable trough level (4.7 mg/L) was achieved after this individual drug pharmacokinetic guided intervention. *Aspergillus* was eradicated within four days, but oral voriconazole doses were continued as prophylactic maintenance therapy, overall due to positive sputum culture for *Candida glabrata*. Further, the patient was maintained by this regimen and we have no reports of other complications, pertaining to renal function or graft versus host disease.

Discussion

Serum creatinine is probably the most widely used indirect measure of glomerular filtration rate; its popularity may be attributable to convenience and low cost, despite its insensitivity to even substantial declines in glomerular filtration rate. In addition to the methodological quality challenges, the correct interpretation of serum creatinine in the clinical setting is problematic [7], so that serum creatinine that falls in the "normal" range may indicate a normal glomerular filtration rate in a young, healthy individual, whereas the same serum creatinine value in an elderly patient may indicate a significant reduction in GFR due to old age determined physiologic organ function deterioration in addition to reduced muscle mass and poor reserve conditioned by the disease itself [8]. Recently, the measurement of serum cystatin-C, a small 122-amino acid-containing protein, a cysteine protease inhibitor expressed in all nucleated cells is advocated to be a better marker of renal function [9], but there are no validity based ready guidelines to apply it as replacement for serum creatinine measurements. Considering serum creatinine as the major variable in calculating GFR, logically, one may expect the change in creatinine and GFR to be of corresponding magnitude, but that might not be the case here. In contrast, amikacin trough level was at least four-fold (20 mg/L) than usually observed or conventional trough value (< 5 mg/L) to our surprise, despite series of low serum creatinine records and the known fact that CF patients clear aminoglycosides faster than common population. Progressive renal impairment after lung transplantation is published [10], but the high amikacin trough coincidence with serum creatinine decline is not clear. Several plasma constituents can interfere with creatinine measurement causing the Jaffe colorimetric assay to yield falsely high creatinine values, but less falsely low values. In the present case, possible analytical error has been excluded by double control confirming that the values were reproducible, provided that newer techniques measuring true serum creatinine give levels that are slightly lower than those from the Jaffe assay method (the values we found were all determined by reportedly less interfered enzymatic method according to the manufacturer, Siemens Diagnostics, Japan). Very high serum bilirubin levels are known to be associated to low creatinine levels [11], while severe liver disease is reported [12] to cause low creatinine production; thus unmasked liver alteration may be concerned in CF patient too, as relatively high frequency of liver disease in association with cystic fibrosis has been published [13, 14]. However, bilirubin level, liver transaminases, as well as total protein and albumin levels were not remarkable in our patient. Muscle mass can also decline over a relatively short period of time especially in CF patient due to underlying malabsorption and immobility during hospitalization (in bed). The decline in creatinine excretion may be explained likely due to decreases in muscle mass from multiple causes, including the effects of immunosuppressive therapy in transplant patient. As a result of this decline in muscle mass, changes in serum creatinine may underestimate the measure of decline in renal function. The need to collect urine samples is a major limitation of the creatinine clearance technique. Therefore, there have been many attempts to transform mathematically or correct serum creatinine so that it may more accurately reflect glomerular filtration rate. Creatinine clearance, calculated by the Schwartz formula [15] for paediatric age, and Cockroft-Gault [16] for adult age respectively are used routinely to estimate renal function. Jelliffe or modified-Jelliffe formulae have also been used as a substitute for the GFR measurement [17]. All of these formulae have serum creatinine as a common variable, although have certain differences and limitations. The Jelliffe formula may have greater bias than the rest three formulae in estimating drug clearance. The Cockcroft and Gault formula does not take into account differences in creatinine production between individuals of the same age and gender or even in the same individual over time, extrarenal elimination, tubular handling, or inaccuracies in the laboratory measurement of creatinine, each contributing to error in the serum creatinine based estimate of glomerular filtration rate. As previously reported [18, 19], the Levey formula uses blood urea nitrogen (BUN), and serum albumin levels beside age and gender, which would not change over 2 days, so its recommendation is limited to patients with significantly reduced renal function. Later modified MDRD formula was considerd to be less biased, but a number of limitations associated with this method have been shortly published [20]. Recent paper by Delanye and Cohen [21] states that MDRD formula is not applicable to all populations, notably the healthy ones, and the patients with nutrition disorders, so that even cratinine standerdization may not eliminate the limitations. After discovering shortcomings in previous formula, Schwartz et al. [22] introduced new formula for better GFR estimation in paediatric chronic kidney disease, using height, gender, BUN, and cystatin-C as additional variables to serum creatinine.The recently published recommendation by two concerned scientific societies in the Czech Republic [23] emphasised more reliability of MDRD formula among others. Indeed, none of the shortcomings of using serum creatinine as a marker of glomerular filtration rate are avoided

completely to date. Under ideal conditions, glomerular filtration rate, as measured by a marker such as serum creatinine, should be equal to the inverse of the creatinine multiplied by a constant rate of creatinine excretion. However, such ideal situation is non-existing in clinical reality.

Conclusions

The advance of more accurate methods may reduced the error in creatinine measurement caused by the presence of various interferents.Whatever are the modifications in methods of determination or formulae for calculation of GFR estimation, skillful interpretation, and careful judgement should be done to use serum creatinine concentration as marker of renal function, since variations in creatinine level due to age and gender, muscle mass, and disease state related differences remain unavoidable challenges. In particular, drug dose adjustment should be based on complex evaluation of concomitant pathology in consistency with clinical findings, and drug disposition assessment in individual patient.

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