Letter to the Editor

Interventional Cardiology

Positive and negative false estimates of serum creatinine

Accurate and precise measurement of serum creatinine is very important for assessment of kidney function. However, false estimates of serum creatinine have been found due to interference by both exogenous and endogenous substances which have been attributed to factors such as decreased or inhibited tubular secretion of creatinine, interference with serum creatinine assays and increased production of creatinine. Several drugs cause positive and negative interference through these mechanisms resulting in false positive and negative estimates of serum creatinine which may affect glomerular filtration rate (GFR) calculation also. Endogenous substances also affect the creatinine assay systems resulting in false estimate of serum creatinine concentration. Therefore, the awareness about the drug-induced or endogenous substance-induced false estimates of serum creatinine and preanalytical errors in blood sampling is important. Some remedial measures to avoid these interferences are: (i) avoiding blood draws from indwelling catheter, (ii) giving preference to fasting blood specimen and (iii) selecting the suitable analytical method for creatinine estimation (based on the information about the drugs being given to the concerned patient).

Keywords: False, Creatinine

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Submitted: June 21, 2017
Accepted: July 12, 2017
Published online: July 19, 2017

Introduction

Glomerular filtration rate(GFR) is considered as the best indicator of kidney function. An inverse relationship has been found between serum creatinine concentration and GFR and therefore, an elevated level of serum creatinine reflects a decrease in GFR and reduced kidney function. Moreover, GFR is generally calculated using equations which incorporate serum creatinine concentration. Therefore, the accurate measurement of serum creatinine is of utmost importance. However, false estimates (positive and negative) of serum creatinine do occur. This false estimate of serum creatinine may be due to interference by exogenous as well as endogenous substances and has been attributed to factors such as (1) decreased or inhibited tubular secretion of creatinine (normally about 15% of urinary creatinine comes from its secretion in the proximal tubules), (2) interference with serum creatinine assays and (3) increased production of creatinine [1].

Exogenous Substances

There are many drugs, which result in elevation of serum creatinine concentration without affecting GFR (Table 1). Therefore, it is very important to know how these drugs result in false elevation (overestimation) or sometimes false decline (underestimation) in serum creatinine levels to interpret the laboratory results correctly for diagnosis of renal function/disease. Perusal of Table 1 shows that drugs like cimetidine, ranitidine, famotidine, trimethoprim, pyrimethamine, salicylates, cobicistat and calcitriol inhibit tubular secretion of creatinine resulting in increased levels of serum creatinine [2]. Cimetidine, trimethoprim and salicylate therapy alter tubular secretion and result in increase in serum creatinine levels by 20%, 15-35% and 35-40% respectively [3]. However, this interference with tubular secretion of creatinine is reversible as withdrawal of these drugs brought the creatinine levels to preexisting ones. The increase in serum creatinine by these drugs

Table 1: Drugs/endogenous substances causing false estimates of serum creatinine (based on references mentioned in the text).

Inhibition of tubular secretion of creatinine	Interference with creatinine assay		
	Drugs/endogenous substances	Enzymatic	Jaffe's
Cimetidine (+) Famotidine (+) Ranitidine (+) Trimethoprim (+) Pyrimethamine (+) Salicylates (+) Cobicistat (+) Calcitriol (+)	Cefoxitin	NS	(+)
	Cephalothin	NS	(±)
	Cefpirom	NS	(+)
	Cephazolin	NS	(+)
	Lidocaine	(+)	(±)
	Flucytosine	(+)	NS
	Dopamine	(-)	(-)
	Dobutamine	(-)	(±)
	Acetohexamide	NK	(+)
	Furosemide	NS	(-)
	Aspirin	(-)	(+)
	Acetoaminophen	(-)	(+)
	Metamizole	(-)	(+)
	Streptomycin	NK	(+)
	Ethamsylate	(-)	NK
	Calcium dobesilate	(-)	NK
	S-aminolevulinic acid	NS	(+)
	Phenacemide	NK	(+)
	Bilirubin	(-)	(-)
	Glucose	(±)	(+)
	Haemoglobin	(-)	(+)
	Albumin	NS	(±)
	Pyruvate	NS	(+)
	Creatine	NS	(+)
	Acetoacetate	NS	(+)
	Haemoglobin F	NS	(-)
	B-hydroxy butyrate	(+)	(±)
	Lipemia	(-)	(+)
	proteins	(±)	(±)

(+): Positive Interference; (-): Negative Interference; (±): Positive or negative interference: NS: Non-specific interference; NK: Not Known

was usually within the normal range and hence has no clinical consequences but this increase could be more striking in patients with renal impairment, particularly when long-standing therapy is needed [2].

Fenofibrates-induced elevation of serum creatinine has been reported and fenofibrate has been postulated to alter intrarenal haemodynamics [4] as well as shown to cause tubular toxicity and increased production of creatinine [5]. However, the increase in serum creatinine due to fenofibrate therapy was found to be reversible after fenofibrate withdrawal.

Corticosteroides have been reported to increase GFR nonspecifically [6] but nevertheless the creatinine concentration increased by 10% [7]. This increase in creatinine is attributed to the catabolic state with protein degeneration and loss of muscle tissue induced by the steroid treatment [2]. The steroid induced diabetic state is also presumed to be the cause of increased serum creatinine in patients on steroids [8].

The list of drugs causing interference in creatinine assays is quite long (Table 1). The two most popular routine methods of creatinine estimation are Jaffe's kinetic method and enzymatic methods. Though the influence of interfering substances has been found to be less frequent with enzymatic methods [9] yet the Jaffe's method has the benefit of cost effectiveness.

The drugs of cephalosporin group generally cause positive interference or positive bias (over estimation) with Jaffe's method. However, the enzymatic methods of creatinine estimation resist this interference [3,9,10]. Lidocaine gives positive interference with enzymatic assays but less interference has been reported with Jaffe's method [3,9,11]. Fluocytosine gives falsely elevated creatinine values due to interference in enzymatic methods but not in Jaffe's method [12]. Therefore, Jaffe's based analytical systems should be used to analyze serum creatinine in patients receiving lidocaine or fluocytosine therapy [3]. On the other hand dopamine and dobutamine interfere negatively in both Jaffe's [10] and enzymatic methods [10,13]. However, Greenberg et al. [9] did not find any interference by

dopamine in both the methods but dobutamine caused positive interference with Jaffe's method but negative interference with enzymatic methods. Acetohexamide also gives falsely elevated serum creatinine in Jaffe's method [14]. Furosemide interferes negatively in Jaffe's method giving undetectable serum creatinine, which were detectable by enzymatic method [15].

There are some drugs, such as aspirin, acetoaminophen and metamizole, which interfere positively in Jaffe's method but negatively with enzymatic methods (Table 1). Streptomycin interferes positively with Jaffe's method but only in high doses (above therapeutic dose) [16]. Therefore, the selection of suitable method for creatinine estimation is important. Other drugs interfering in creatinine estimation are ethamsylate, calcium dobesilate and 5-aminolevulinic acid. Phenacemide also gives false positive estimates of serum creatinine but the mechanism of this effect is not clear [2,3].

Improper blood sampling may also cause drug interference. Saenger et al. [13] reported the negative interference by catecholamines in blood samples obtained from indwelling catheters whereas no interference was noted in peripheral blood samples. The reversible adherence of catecholamines to indwelling catheter has been suggested to be the cause of this interference as has been found with cyclosporins [17]. Therefore, blood draws from indwelling catheter should be avoided. Further, the test ordering form should contain the information about the drugs being given to the patient so that the analyst could select the suitable method for creatinine estimation.

Endogenous Substances

Table 1 shows the endogenous substances interfering in creatinine assay. Among the endogenous substances causing positive interference in Jaffe's methods, the most important ones are glucose and acetoacetate. The extent of this positive interference is quite less in enzymatic methods. However, no general conclusions regarding Jaffe's or enzymatic technologies can be drawn [9]. Haemoglobin and lipemia have been shown to interfere positively in Jaffe's method but negatively with enzymatic assays. The haemoglobin interference can be easily avoided by not using haemolysed sera.

Bilirubin is a negative interferent in both enzymatic and Jaffe's methods. This results in underestimation of serum creatinine in icteric sera. Several modifications in the assay systems have been suggested to overcome this negative interference due to bilirubin [8,18]. The manufacturers of reagent kits generally do not mention specifically about the quantitative effect of interferents. Hence it is imperative for the analysts to check every kit for the extent of interference before use [19].

Another source of false estimate of serum creatinine is increased production due to increased intake of cooked meat. The creatine present in meat is converted into creatinine on cooking which is absorbed causing a significant increase in serum creatinine [20]. Therefore, fasting blood should be preferred for creatinine estimation and GFR calculation.

Conclusions

The false estimates of serum creatinine due to endogenous and exogenous substances are well known. Therefore, the awareness about the drug-induced or endogenous substances-induced false estimates of serum creatinine is important to interpret the laboratory results correctly for diagnosis of renal function/disease. Some remedial measures to avoid these interferences are: (i) avoiding blood draws from indwelling catheter, (ii) giving preference to fasting blood specimen and (iii) selecting the suitable analytical method for creatinine estimation (based on the information about the drugs being given to the concerned patient).

Executive summary

Accurate and precise measurement of serum creatinine is very important for assessment of kidney function. However, false estimates of serum creatinine have been found due to interference by both exogenous and endogenous substances which have been attributed to factors such as decreased or inhibited tubular secretion of creatinine, interference with serum creatinine assays and increased production of creatinine.

Several drugs cause positive and negative interference through these mechanisms resulting in false positive and negative estimates of serum creatinine which may affect glomerular filtration rate (GFR) calculation also. Endogenous substances also affect the creatinine assay systems resulting in false estimate of serum creatinine concentration.

Therefore, the awareness about the drug-induced or endogenous substance-induced false estimates of serum creatinine and preanalytical errors in blood sampling is important. Some remedial measures to avoid these interferences are: (i) avoiding blood draws from indwelling catheter, (ii) giving preference to fasting blood specimen and (iii) selecting the suitable analytical method for creatinine estimation (based on the information about the drugs being given to the concerned patient).

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