Creatinine Estimation and Interference

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Sir,

Creatinine is one of the most common analyte used as the indicator of glomerular filtration rate (GFR) and kidney function. In 1886, Jaffe reported a reaction of creatinine and picric acid in an alkaline medium forming complex having absorbance maxima at 520 nm. The reaction has been brought to use for the measurement of creatinine by Folin and Wu in 1919. Since then, Jaffe's reaction has been used for estimation of creatinine in serum and urine sample. For more than 90 years, this method is in use for the measurement of creatinine concentration due to its simplicity and low cost. Creatinine is produced as the byproduct of creatine metabolism and is transported through bloodstream to the kidneys for excretion. Mal-functioning of kidney is reflected by lowering of the amount of creatinine in urine and rise of its level in blood. Creatinine levels in blood and urine also indicate the creatinine clearance, accounting for GFR. Creatinine readings indicate the total kidney GFR which is the sum of filtration rates of all functional nephrons. Early structural damage to the renal cells involving reduction in functional nephron number may not affect an individual's total GFR as

remaining renal units may perform compensatory function, enabling the kidneys to maintain kidney function temporarily even after the loss of functional tissue. Thus, creatinine/GFR may not indicate the early damage to kidney tissue. Jaffe also elaborated the interference in alkaline picrate reaction by number of organic compounds (e.g. acetone, glucose) which has been described as pseudo-chromogens. Still, creatinine remains the gold standard for measuring the glomerular filtration rate and kidney functioning. And Jaffe method remains the default method for estimation of creatinine. In last century, many caveats in this method were reported which we have indicated in brief in this article. Recently we have reported an interference by streptomycin (an aminoglycoside) in high doses which act as false positive in Jaffe reaction [1]. It is known from literature that aminoglycosides can be nephrotoxic and may potentially affect kidney function. If it is so, then, nephrotoxicity due to high dose of aminoglycosides (say streptomycin) can never be correctly estimated as defect in excreting out creatinine would be masked by the false positive Jaffe reaction given by streptomycin.

Antibiotics like cephalixin, cefazolin, cefamandole, cephalothin, and cefoxitin have been shown to interfere with creatinine determination at various concentrations [1, 2]. Phenacemide and cephalothin may interfere either positively or negatively with the determination of creatinine by the Jaffé reaction [3]. Cephalosporin antibiotics have been shown to form non-creatinine chromogen with alkaline picrate reagent and produce false positive results for creatinine. Serum creatinine and creatinine clearance values are positively interfered by cefoxitin in the Jaffé reaction, the routine laboratory method of creatinine measurement. Both invitro and invivo analysis suggest the same [4].

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Many biomolecules like bilirubin, glucose, acetone etc. are also known to interfere with the Jaffe method of creatinine estimation and therefore the method has gone through modifications [5]. To overcome the effect of interference specific enzymatic method of creatinine estimation has been also developed [6]. But in spite of various modification of the Jaffe method and development of the specific enzymatic method for creatinine estimation, the classical alkaline picrate method remains popular in India.

Aminoglycosides and Interference

Aminoglycosides are commonly used antibiotics that are well recognized as nephrotoxic agents. If, it interferes with Jaffe reaction then there may be a false positive elevation of creatinine that may wrongly suggest the clinician to stop the life saving medicine even in a valid indication. But recently it is observed that aminoglycoside antibiotics does not produce false chromogen with Jaffe reagents at therapeutic dosage but streptomycin in high doses interferes positively with Jaffe method of creatinine estimation [1]. So, in higher dose exposure of streptomycin to human subjects' serum/urine creatinine estimation by Jaffe method has to be interpreted in terms of available streptomycin concentration. So if, actual concentration of creatinine is 53 micromoles/litre, then in presence of 10 mg/ml streptomycin in serum, the apparent concentration would be nearly doubled i.e. around 106 micromoles/liter.

Other Drugs

We have checked many other antibiotics and drug molecules which we have found not to significantly interfere with the Jaffe reaction. This includes cisplatin, deriphylline, levofloxacin and phenytoin. They have been checked for interference up to concentration of 10 mg/ml. We are reporting the interference study of these drugs via this letter

and confirming that they do not interact with Jaffe reagent to produce false chromogen. Left over serum and urine samples have been collected randomly for use and the protocol given in reference has been followed [7].

Today, we have a long list of interfering substances of Jaffe method that affects creatinine estimation but the method is popular perhaps for its inherent simplicity but in the clinical context of drugs like aminoglycosides, cisplatin, phenytoin, deriphyllin or levofloxacin, alkaline picrate method may not be made redundant due to false chromogen formation. We, hereby, stress on the need of innovation in field of diagnosis of kidney damage, improvement in methods of creatinine estimation and recommend a boost in research to study potential interfering agents of alkaline picrate method used for creatinine estimation in the scenario of rapidly developing new drug molecules.

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