

Nephrotoxicity Testing in Clinical Trials

The incidence of drug-induced nephrotoxicity is unknown but is generally considered to be high. Kleinknecht et al. (1987)¹ suggested that the incidence of kidney damage due to antibiotics has been reported to be up to 36%, much of which is fortunately reversible. The range of pharmaceutical drugs shown to be nephrotoxic in some individuals is extensive. This is hardly a surprise as 25% of the cardiac output passes through the kidney for filtration and reabsorption of biochemical components in controlling metabolic homeostasis. Damage may be the result of pre-renal issues, haemodynamic changes, renal cell injury, inflammation or obstruction. Thus in clinical studies, detection of any renal dysfunction is important.

The range of tests selected in the present day safety profiles in drug studies of haemoglobin, platelets, urinalysis, blood urea (BUN), urate and creatinine only show overt changes, yet in the evaluation of new drug entities early warning of possible toxicity is mandatory for patient safety. Of the individual tests, diagnostic interpretation favours creatinine as the prime measurement, but clinical scientists are well aware of the lack of accuracy and, in particular, the poor sensitivity of this biomarker. No apparent increase in serum creatinine will be noted until the glomerular filtration rate which is normally at a level of about 120 mL/minute, is less than 50 mL/minute, at which time there is significant renal dysfunction. Newer procedures for the evaluation of kidney function such as the Modification of Diet in Renal Disease (MDRD)² equation and Cystatin C are proving invaluable in the assessment of kidney function in non transplant patients.

The National Service Framework for Renal Services recommends that local pathology services include the estimation of Glomerular Filtration Rate (eGFR) on clinical reports and more recently the Department of Health is recommending the implementation of routine eGFR in all NHS laboratories by 1st April, 2006³. Although there is debate on the best and most appropriate formula, the original MDRD offers much greater sensitivity and accuracy over serum creatinine only. The MDRD formula is:

Stages of Chronic Kidney Disease eGFR as mL/min/1.73m²

| | | | |
|------------|---|--------------|-----------------|
| I | = | 90+ | normal |
| II | = | 60-89 | mild |
| III | = | 30-59 | moderate |
| IV | = | 15-29 | severe |

Reference Range for Cystatin C

Less than 50 years = 0.52 - 0.95 mg/L

Over 50 years = 0.58 - 1.05 mg/L

This applies to white males over 18 years of age. For females the result is multiplied by 0.742 and for black ethnic groups by 1.212.

Clinical laboratories may deviate from the original MDRD formula dependent on the instrumentation and reagents employed in creatinine measurement and participation in external quality assessment surveys will help in harmonising data between different laboratories.

Preiss and colleagues (2007)⁴ reported on the influence of cooked-meat meals on serum creatinine and on the estimated glomerular filtration rate. The effect of various meat meals were examined and confirmed the expected increase in serum creatinine and a reduction in the estimated creatinine clearance. The same authors evaluated the changes in the cysteine protease inhibitor – Cystatin C. There was no significant difference in the Cystatin C measurements in subjects after a meat meal. This biomarker also provides greater sensitivity for changes in GFR than serum creatinine.

It is recommended that consideration be given to the inclusion of eGFR and/or Cystatin C in clinical trial protocol design to improve patient safety.

1. Kleinknecht et al. Drug-associated acute renal failure; a prospective collaborative study of 81 biopsied patients. *Adv Exp Med Biol* 1987;212:125-128
 2. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999; 130(6):461-70
 3. <http://www.dh.gov.uk/assetRoot/04/13/30/21/04133021.pdf>
 4. Preiss DJ, Godber IM, Lamb EJ, Dalton RN and Gunn IR The Influence of a cooked-meat meal on estimated glomerular filtration rate. *Ann Clin Biochem* 2007; 44: 35-42
 Example of eGFR calculation <http://www.patient.co.uk/showdoc/40001093>

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