MECHANISM-SPECIFIC RENAL BIOMARKERS PREDICT NEPHROTOXICITY EARLY FOLLOWING GLYPHOSATE SURFACTANT HERBICIDE (GPSH) POISONING.

Mohamed F.[1,2,3]; Endre Z.H.[2, 4]; Pickering J.W. [4]; Gawarammana I.[1]; Buckley N.A.[1, 3]

[(1)] *South Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Peradeniya, Sri Lanka*

[(2)] *Department of Nephrology, Prince Of Wales Hospital and Clinical School, University of New South Wales, Sydney, Australia*

[(3)] *Department of Pharmacology, SOMS, Sydney Medical School, University of Sydney, NSW, Australia*

[(4)] *Department of Medicine, University of Otago, Christchurch, New Zealand*

Objectives: Acute kidney injury (AKI) is common following deliberate ingestion of glyphosate surfactant herbicide (GPSH) and an important risk factor for mortality. Serum creatinine (sCr) is the most widely used renal biomarker for diagnosis of AKI although a recent study in rats suggested that urinary kidney injury molecule-1 might better predict AKI earlier after GPSH-induced nephrotoxicity. We aimed to explore the utility of panel of biomarkers to diagnose GPSH-induced nephrotoxicity in humans.

Methods: In a prospective observational study in 5 centres, urine and blood samples were collected at 4, 8, 16, and 24 hours post-ingestion and then daily until discharge and at follow-up at one and three months. Biomarker levels at different time points were quantified and diagnostic performance of each biomarkers was assessed by the area under the receiver-operating characteristic (AUC-ROC) using the Acute Kidney Injury Network (AKIN) definition. Added value of each biomarker to sCr to diagnose AKI was assessed by the integrated discrimination improvement (IDI) metric.

Results: Of 90 symptomatic but previously healthy patients, half (51%) developed AKI [AKIN stage 1(n=30), 2 (n=6) and 3 (n=10)]. Five patients who developed AKIN≥2 died. Increased sCr at 8 and 16 hours predicted moderate to severe AKI and death. None of the 10 urinary biomarkers tested increased above normal range in patients who did not develop AKI or had mild AKI (AKIN1); and most of these patients revealed only mild clinical toxicity (nausea, vomiting, abdominal pains, eosophagitis). In contrast, absolute concentrations of serum and urinary cystatin C (CysC), urinary interleukin-18 (IL-18), Cytochrome C (CytoC) and Neutrophil Gelatinase-Associated Lipocalin (NGAL) increased many fold within 8 hours in patients who developed AKIN≥2 (n=16). These biomarkers also displayed significant positive correlation between each other ($r \geq 0.5$, $p < 0.0001$). Maximum 8 and 16 hour concentrations of these biomarkers showed an excellent diagnostic performance (AUC-ROC ≥0.8) to diagnose AKIN≥2. However, none of these biomarkers added value to sCr to diagnose AKI when assessed by the IDI metrics but uCytoC.

Conclusions: GPSH-induced nephrotoxicity can be diagnosed within 24 hours by sCr. Serum CysC may be a useful alternative functional marker to serum creatinine following GPSH toxicity. Increase in structural injury biomarkers (uCytoC and uIL-18) confirm GPSH-induced apoptosis and mitochondrial toxicity. Use of these biomarkers may help to identify mechanism specific targeted therapies for GPSH nephrotoxicity in clinical trials.