INFUSION OF RECOMBINANT IL-6 IN HEALTHY HUMANS ELEVATES PLASMA NGAL CONCENTRATIONS WITHOUT A REDUCTION IN RENAL FUNCTION.

Naushad A Junglee[1,3], Catrin R Searell[2], Mahdi M Jibani[1] and Jamie H Macdonald[3].
Departments of Nephrology[1] and Biochemistry[2], Ysbyty Gwynedd Hospital, Bangor, Wales, UK.
College of Health and Behavioural Sciences[3], Bangor University, Bangor, Wales, UK.

Introduction

- Interleukin-6 (IL-6) is believed to be an important pro-inflammatory cytokine in acute kidney injury (AKI).[1]
- In instances of severe sepsis with AKI, high plasma concentrations of IL-6 are positively correlated with poor renal outcomes.[2]
- Thus, IL-6 could be viewed as both a mediator and biomarker of AKI.
- We determined whether IL-6 *per se* was able to influence plasma biomarkers of AKI (NGAL) and kidney function (creatinine, cystatin C) in healthy humans.

Methodology

- A three-hour rhIL-6 infusion (Sandoz, Basle, Switzerland) was administered to six healthy, males (age 25 ± 5 years) at a rate of 5 µg/h.
- Similar infusion protocols have been used in previous human studies and a peak plasma IL-6 concentration above 100 pg/ml can be achieved without significant side-effects.[3]
- Plasma IL-6, NGAL, creatinine, and cystatin C concentrations were measured at 0h, 0.5h, 3h and post-infusion at 24h and 48h.
- Tympanic temperature was recorded at 0h and 3h.
- To determine if AKI had occurred during or after the infusion, AKIN criteria were applied based upon any rise in plasma creatinine of ≥ 0.3 mg/dl or 1.5 or 2 times higher from baseline.[4]

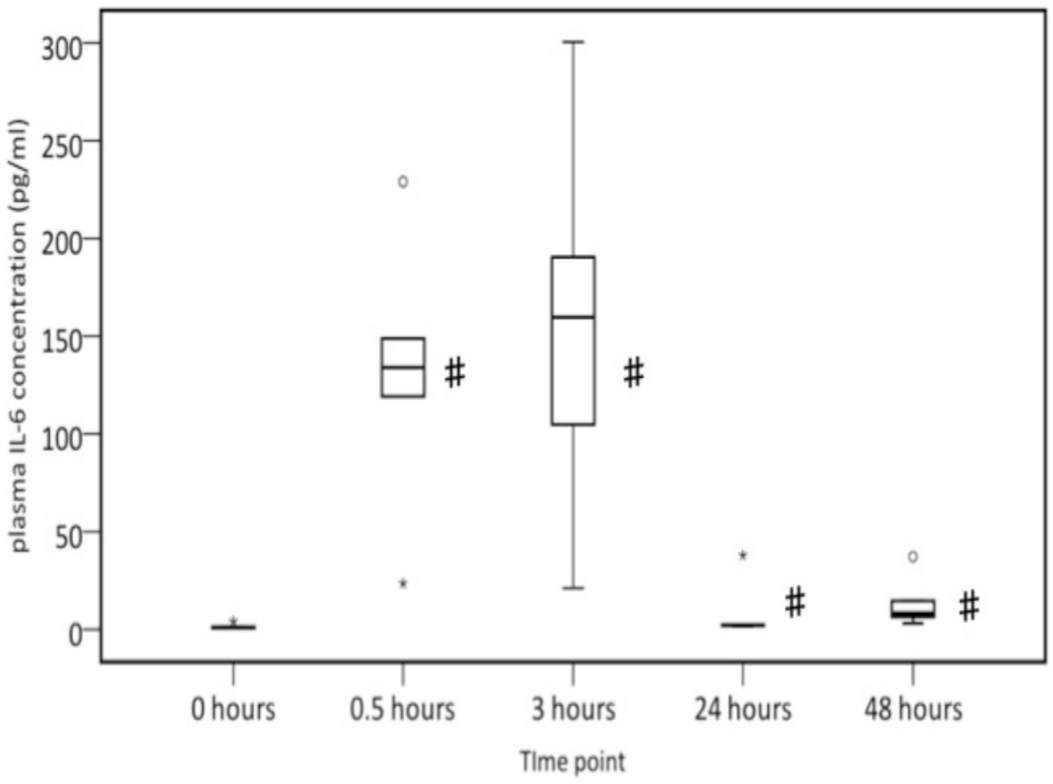

Figure 1. Effect of rhIL-6 infusion upon plasma IL-6 concentrations. Data are medians (thick lines) and ranges. Open circles and asterixes are outliers. There was a significant effect of time (P = 0.007). #, difference compared to 0 hours sample point.

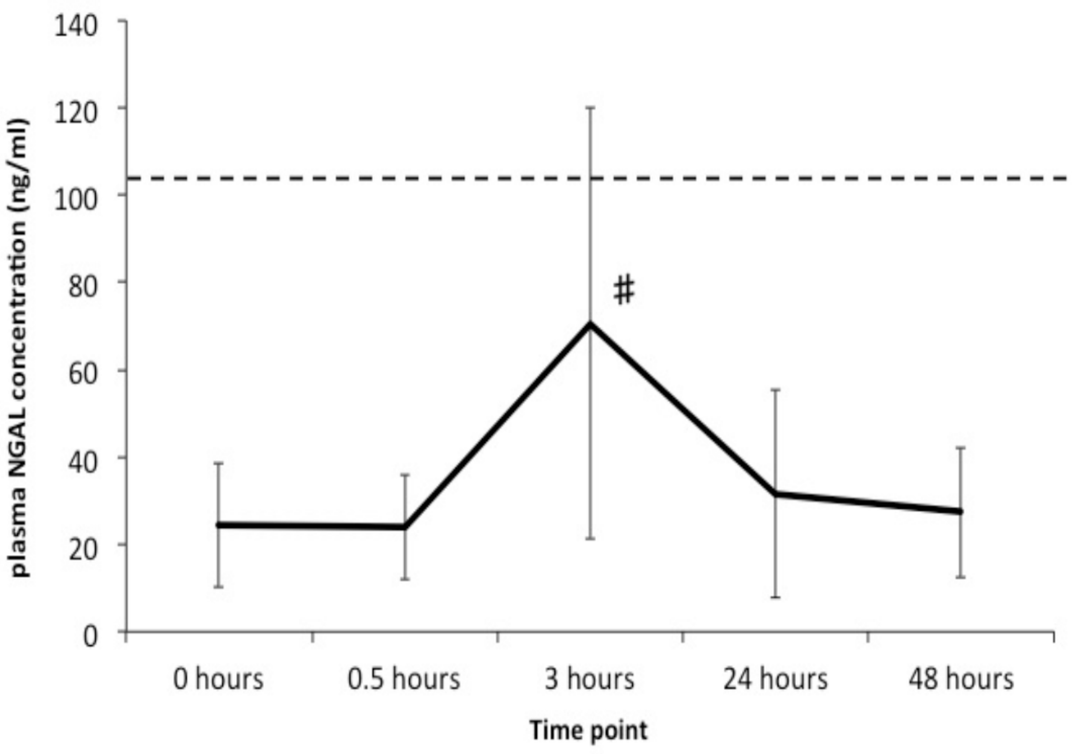

Figure 2. Effect of rhIL-6 infusion upon plasma NGAL concentrations. Data are means and standard deviations. Dotted line indicates upper limit of normal range for plasma NGAL (106 ng/ml). There was a significant effect of time (P = 0.025). #, difference compared to 0 h sample point.

References

1. Lee DW, Faubel S, Edelstein CL (2011). Cytokines in acute kidney injury (AKI). *Clin Nephrol* **76**, 165-173.
2. Zarjou A, Agarwal A (2011). Sepsis and acute kidney injury. *J Am Soc Nephrol* **22**, 999-1006.
3. Nemet D, Eliakim A, Zaldivar F *et al.* (2006). Effect of rhIL-6 infusion on GH-->IGF-I axis mediators in humans. *Am J Physiol Regul Integr Comp Physiol* **291**, R1663-1668.
4. Ricci Z, Cruz DN, Ronco C (2011). Classification and staging of acute kidney injury: beyond the RIFLE and AKIN criteria. *Nat Rev Nephrol* **7**, 201-208.
5. Bonventre JV, Zuk A (2004). Ischemic acute renal failure: an inflammatory disease? *Kidney Int* **66**, 480-485.
6. Simmons EM, Himmelfarb J, Sezer MT *et al.* (2004) Plasma cytokine levels predict mortality in patients with acute renal failure. *Kidney Int* **65**,1357-1365.
7. Sosman JA, Aronson FR, Sznol M *et al.* (1997). Concurrent phase I trials of intravenous interleukin 6 in solid tumor patients: reversible dose-limiting neurological toxicity. *Clin Cancer Res* **3**, 39-46.

Results

- All subjects completed the experiment without side-effects.
- Plasma IL-6 concentrations were 0.7 {0.6, 1.2} {interquartile range} pg/ml at 0h and peaked at 3h to 159.7 {114.6, 186.7} pg/ml (figure 1). By 48 hours this fell to 8.2 {6.8, 13.0} pg/ml (main effect of time, p = 0.007).
- Plasma NGAL concentrations were 24.3 (13.2) ng/ml at 0h and peaked at the end of the infusion at 3h to 70.6 (49.3) ng/ml (figure 2). At 48 hours, this fell to 31.7 (16.5) ng/ml (main effect of time, p = 0.025).
- Plasma creatinine and cystatin C concentrations were unchanged throughout.
- Tympanic temperature rose from 36.9 (0.2) °C to 37.5 (0.6) °C at 0h and 3h, respectively (p = 0.046). Plasma NGAL was positively correlated with tympanic temperature (r = 0.945, p = 0.004).

Discussion

- We achieved plasma IL-6 concentrations found in clinical models of AKI, but plasma NGAL elevations were typically below the range associated with AKI and there were no changes to renal function measures.
- This suggests: 1. IL-6 *per se* is not responsible for AKI and other physiological aberrations are needed; or 2. higher IL-6 concentrations are required to induce kidney dysfunction.[5-7]
- Further studies are required to determine the impact of IL-6 *per se* upon urinary biomarkers of kidney injury and function.

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