ASCEPT-AUPS-HBPRCA JOINT MEETING
4 – 9 DECEMBER 2011, PERTH, AUSTRALIA

# INHIBITION OF CYSTATHIONINE-GAMMA-LYASE AND THE BIOSYNTHESIS OF ENDOGENOUS HYDROGEN SULPHIDE AMERIOLATES GENTAMICIN-INDUCED NEPHROTOXICITY

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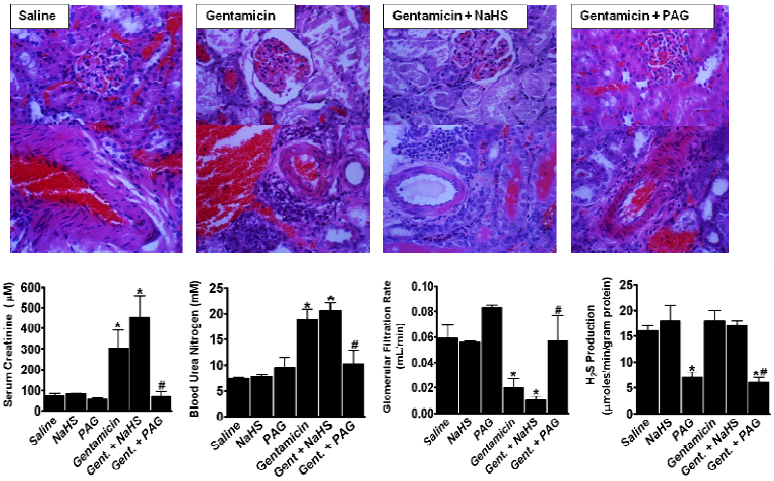
**Introduction:** Gentamicin is a commonly used antibiotic against infectious Gram negative bacteria. However, the clinical use of gentamicin over prolonged periods is limited because of dose- and time-dependent nephrotoxicity. Primarily, lysosomal phospholipidosis, generation of intracellular reactive oxygen species and heightened inflammation have been implicated. Hydrogen sulphide ($H_2S$) is a small gaseous, endogenously produced signal transduction molecule with antioxidant, anti-inflammatory, antiapoptotic and cytoprotective properties. In kidneys for example, the production of endogenous $H_2S$ by cystathionine-γ-lyase was found to limit oxidative stress, renal ischemic-reperfusion injury and dysfunction. We hypothesized that $H_2S$ ameliorates gentamicin-induced toxicity, preventing nephron necrosis and renal dysfunction.

**Methods:** Adult female Sprague-Dawley rats were divided into six groups (n = 4–8 animals) and then treated for 10 days with; physiological saline only, sodium hydrosulphide (NaHS; an exogenous $H_2S$-donor, 50 µmoles/Kg/day, i.p) only, DL-propargyl glycine (PAG; an irreversible inhibitor of cystathionine-γ-lyase, 25 mg/Kg/day, i.p) only, gentamicin (100 mg/Kg/day, i.p) only, a combination of getamicin and NaHS, or gentamicin and PAG respectively. Blood samples and kidneys were collected for biochemical, histological and morphometric analysis.

**Results & Discussion:** Nephrotoxic effects of gentamicin were not altered by administering NaHS but PAG significantly attenuated the toxic effects of gentamicin thus improving renal function (* $P < 0.001$ compared to saline controls and $^{\#}$ $P < 0.001$ compared to gentamicin only).




Gentamicin-induced histopathological changes including tubular necrosis, oedema and infiltration of the interstitium by inflammatory cells were attenuated by co-administering gentamicin with PAG. These data show that inhibition of the endogenous biosynthesis of $H_2S$ reduces gentamicin-induced renal damage. This effect might be related, at least in part, to the reduced inflammatory responses observed in animals treated with both gentamicin and PAG. Endogenous $H_2S$ and enzyme systems involved in its biosynthesis may offer a viable therapeutic target in alleviating the nephrotoxic effects of gentamicin.