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0-36

A HUMAN PROXIMAL TUBULAR EPITHELIAL CELL MODEL TO EXPLORE A KNOWLEDGE GAP ON NEONATAL DRUG DISPOSITION

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Background Finding the right drug-dosage for neonates is still a medical challenge. Up to now, neonatal doses are extrapolated from adult and children doses. However, there are differences between neonatal and adult kidney physiology that should be put into consideration, especially when it comes to active drug metabolism. Studying renal drug clearances in neonates is limited by the lack of reliable human cell models. Our aim was to illustrate the feasibility to develop an *in vitro* model for neonatal proximal tubule epithelial cells (nPTECs) for studying renal drug clearances at this age.

Method nPTECs were isolated from urine samples of neonates of different gestational age (GA) and conditionally immortalised using a temperature sensitive SV40T anti-gen and human telomerase hTERT. The cell clones were characterised on gene expression level for PTECs markers such as P-glycoprotein (P-gp), aquaporin1 (AQP1), and organic cation transport protein 2 (OCT2). In addition, protein expression and functional assessment were performed for P-gp and OCT2.

Results We established 101 clonal cell lines of cinPTECs derived from neonatal urine. Gene expression analysis confirmed the expression of the PTECs (P-gp, AQP1, and OCT2), similar to the expression in the adult control ciPTECs. P-gp was expressed in cinPTECs from the different gestational ages and exhibited similar functionality as the adult derived ciPTECs. In contrast, OCT2 functionality was significantly lower in the cinPTECs cell lines compared to the adult ciPTECs.

Conclusion We demonstrate the feasibility of culturing cinPTECs expressing mature ciPTECs markers with high efficiency out of the urine samples of neonates. The cell model presented here can serve as a valuable tool to study proximal tubule physiology and pharmacology in new-borns. In addition, we demonstrate the physiological differences between the neonatal and adult kidney, which puts emphasis on the importance of studying drug pharmacokinetics in neonatal models instead of extrapolating from adult models.

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PREVENTING AMINOGLYCOSIDE-INDUCED NEPHROTOXICITY USING STATINS: AN EXAMPLE OF BENCH-TO-BEDSIDE RESEARCH

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Background Megalin-mediated endocytosis is the principal pathway for the accumulation of aminoglycosides in proximal tubule epithelial cells,¹ resulting in kidney toxicity. Activation of this pathway depends on intermediates derived from mevalonate, the product of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reduction, catalysed by HMG-CoA reductase.² We hypothesised that inhibition of HMG-CoA reductase by statins would reduce uptake of aminoglycosides in the proximal tubule, leading to a reduction in toxicity. This has previously been demonstrated *in vitro*.³ We tested this in two *in vivo* models.

Methods Sprague Dawley rats, (n=4/group) received intraperitoneal (IP) dosing with saline (control), gentamicin (200 mg/kg/day), rosuvastatin (40 mg/kg/day), or gentamicin and rosuvastatin for 9 days. Nephrotoxicity was measured using urinary N-Acetyl-β-d-glucosaminidase (NAG) and kidney injury molecule-1 (kim-1) on urine samples collected within 24 hours after the final dose. Male Hartley guinea pigs (n=6/group) received IP dosing with saline (control), gentamicin (100 mg/kg/day), statin, or combined gentamicin and statin (simvastatin or rosuvastatin, 0.4 to 40 mg/kg/day) for 9 days. Nephrotoxicity was measured using serum creatinine and blood urea nitrogen (BUN) on urine samples collected within 24 hours after the final dose.

Results In rats co-administered rosuvastatin and gentamicin, urinary concentrations of NAG and kim-1 were significantly lower than for gentamicin alone (p<0.01). In guinea pigs, rosuvastatin reduced gentamicin-induced nephrotoxicity in a dose-dependent manner: doses of 0.4, 4 and 40mg/kg/day led to 46% (p<0.01), 81% (p<0.0001), and 83% (p<0.0001) reductions, respectively, in serum creatinine compared to animals receiving gentamicin only. Similar results were seen with BUN. The minimum effective dose to prevent toxicity was 0.97mg/kg/day. Using a dose scaling algorithm this equates to a dose of 10mg/day in children. Simvastatin did not protect the kidney from gentamicin-induced nephrotoxicity. The results from the *in vitro* and *in vivo* animal studies led to the design of a phase IIa multi-centre, randomised, controlled clinical trial (RCT) in children with cystic fibrosis receiving clinically indicated treatment with aminoglycosides, where co-treatment with rosuvastatin (10mg) will be compared with current standard of care.

Conclusion Rosuvastatin inhibits gentamicin-induced nephrotoxicity in both rat and guinea pig models; in the latter, at therapeutic doses used in humans. This led to an RCT in children which has just completed recruitment. This bench-to-bedside translational research showcases the exciting area of drug repurposing with potential for significant patient benefit.

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THE INFLUENCE OF BODY COMPOSITION ON PAEDIATRIC DRUG DOSING

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O-37 Preventing aminoglycoside-induced nephrotoxicity using statins: an example of bench-to-bedside research

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