PTU-008  
A REPRODUCIBLE, CLINICALLY-RELEVANT, INTENSIVELY-MANAGED, PIG MODEL OF ACUTE LIVER FAILURE FOR TESTING OF THERAPIES AIMED TO PROLONG SURVIVAL

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Introduction Hospitalisations from acetaminophen poisoning are increasing (1999, n=39,045; 2010, n=52,707. UK, NHS admissions). For the most serious cases there are no effective therapies to assist recovery or prolong survival apart from liver transplantation, which remains a limited resource. We report a clinically-relevant, intensively-managed, model of ALF, which mimics the human condition and has a predictable survival time, for testing of new potential therapies.

Methods Nine, 30–40 kg, female pigs were anaesthetised and instrumented for continuous monitoring and management of respiratory and cardiovascular systems and acid-base and electrolyte status, using standardised intensive care protocols and intermittent positive pressure ventilation. Intracranial pressure (ICP) was monitored but not treated. Six animals were induced to ALF with acetaminophen administered via an oroduodenal tube: a loading dose of 0.25 g/kg was followed by hourly doses of 0.5–4.0 g, adjusted according to serum acetaminophen concentrations. At irreversible ALF (defined as prothrombin time >3 times normal), continuous renal replacement therapy (CRRT) was initiated. Three animals acted as controls with initiation of CRRT at 20 h and termination at 40 h.

Results Following onset of acetaminophen dosing, peak serum acetaminophen concentrations of 367±30 mg/l were achieved at 12 h and irreversible ALF at 19±1.8 h. Death occurred predictably 12.6±2.7 h after irreversible ALF. Development of ALF was associated with progressive hypotension (p<0.001) and metabolic acidosis (p=0.001), not observed in controls. Mean arterial pressure (MAP) was maintained with aggressive fluid therapy, noradrenaline and terlipressin. Metabolic acidosis was corrected successfully with bicarbonate and CRRT. In ALF, there was significant (p<0.001) rise in ICP compared to controls with sudden marked increase prior to death: at study end, ICP in ALF and controls was 41.2±8.6 mm Hg and 22.7±2.5 mm Hg respectively. Death was preceded by abrupt increase in central venous pressure, fall in MAP and bradycardia. Histopathology confirmed moderate to marked acute centrilobular and midzonal hepatocyte degeneration and necrosis in ALF.

Conclusion A predictable model of ALF, with death due to multi-organ failure, has been successfully validated for testing of new potential therapies for ALF.

Competing interests None declared.

PTU-010  
COMPUTATIONAL MODEL PREDICTS THAT PORTOSYSTEMIC SHUNTING IS KEY TO THE DEVELOPMENT OF HYPERAMMONAEMIA IN LIVER CIRRHOSIS

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Introduction Hyperammonaemia occurs in patients with advanced cirrhosis, which is also associated with a major redistribution of blood flow (hyperdynamic circulation). Previous investigations have sought to explain hyperammonaemia on the basis of metabolic adaptation (enzymatic derangements). We hypothesised that hyperammonaemia is centrally linked to the haemodynamic disturbances caused by portal hypertension. To test this hypothesis, we developed a theoretical model, which predicted arterial ammonia levels when organ blood flow is modulated.

Methods Assumptions on individual organ fluxes of ammonia (across the gut, liver, muscle, brain and kidney) were based on published arterio-venous differences and tracer kinetic data. In order to study the role of organ blood flow in isolation, we assumed that hepatic detoxification function and ammonia production were normal. A wide range of conditions was investigated (increased cardiac output, splanchic vasodilation, low to high porto-systemic shunt fraction). In addition, we used scenarios of organ blood flow corresponding to Child Pugh A, B and C. Finally, we considered the effect of lowering ammonia release in the renal vein.

Results Hyperammonaemia developed when the fraction of gastrointestinal blood shunted was more than 65%. The influence of