Reviewer's report

Title: Development of an invasively monitored porcine model of acetaminophen-induced acute liver failure

Version: 1 Date: 3 February 2010

Reviewer: Humphrey Hodgson

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This study contains worthwhile data, which should help other researchers intending to develop a large animal model for acute liver failure. It has some important messages, but there are also some significant omissions and areas of discussion need attention.

A key approach in this porcine model was to monitor acetaminophen levels and thus (more-or-less) avoid methaemoglobinaemia (an event which if it occurs confounds comparison with human acetaminophen toxicity acute liver failure problem).

An important omission in the clinical detail is an account of the anaesthetic strategy used to maintain the animals. In particular what fluids were infused? The increased pulmonary resistance and dyspnoea observed in many of the pigs would be unsurprising if these hypoproteinaemic animals received large volumes of saline and died of pulmonary oedema. (Incidentally fig 4 appears to be mislabeled as the rising pulmonary pressure terminally is seen in the control group). The authors speculate on the nature of the lung pathophysiology, but provide no histological evidence.

The authors maintain that these animals developed encephalopathy on the basis of a reversal of Fisher’s ratio. While this ratio is correlated with the development of encephalopathy in some studies, it is certainly not evidence of encephalopathy. This short-coming should be at least discussed.

There was a failure to develop increased intracranial pressure in this model which is a significant deviation from human analogue. Many other models of acute liver failure in pigs e.g. ischaemic, do achieve this within this time frame. This discrepancy should be discussed further.

The authors state that this model would be useful for the assessment of artificial liver devices, but they should discuss this further. Although ‘reproducible’ the survival of the animals varied enormously from 8 - >28hrs, and a significant number of animals with euthanased. The criteria for ‘death under anaesthesia’ are not defined. In view of this group’s experience it would be very helpful for them to address this issue – would they aim to improve survival – and if so how would they measure survival – or do they have another criterion for failure or for parameters to be improved.
These are immensely complicated as well as costly experiments to do; although there are obvious short-comings as outlined, it would be unreasonable to ask the group to reassemble (many of them no longer work in the initial centre) to do further experimental work, however, the discussion could usefully address the issues raised.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'