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Pathophysiological central nervous system changes in a porcine model of acetaminophen-induced acute liver failure

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ABSTRACT

Background: Critical care management of patients suffering from acute liver failure (ALF) continues to be challenging. Animal models studying the pathophysiological central nervous system alterations during the course of ALF provide an opportunity to improve diagnostic and therapeutic strategies. The aim of this study was to analyse the course of cerebral oxygenation in addition to conventional neuromonitoring during the course of acetaminophen-induced ALF.

Methods: ALF was induced by intrajejunal acetaminophen administration in 20 German landrace pigs. All animals underwent invasive hemodynamic and neuromonitoring and were maintained under standardized intensive care support. Neuromonitoring consisted of continuous intraparenchymatous recording of intracranial pressure and brain partial oxygen pressure. Hemodynamic and ventilation parameters were continuously recorded; laboratory parameters were analysed every eight hours. Mean values were compared using the Wilcoxon test.

Results: Acute liver failure occurred in all intoxicated animals after 23 ± 2 h, resulting in death due to ALF after further 15 ± 2 h. Continuous neuromonitoring was performed in all animals during the whole experiment without observing signs of intracranial haemorrhage. Two hours after manifestation of ALF an increase in brain tissue oxygen (PtiO2) was observed. Brain oxygenation stayed stable until nine hours before death. Intracranial pressure (ICP) remained basically at a plateau level until manifestation of ALF. In the following ten hours a linear and slow increase was observed until five hours before death, followed by a fast and continuous rise in ICP to a final level of 35 ± 1 mmHg. Cerebral perfusion pressure (CPP) began to decrease 25 h prior to exitus, further decreasing to 18 ± 2 mmHg at the end of the experiment. A strong negative linear correlation was found between PtiO2 and ICP (R = 0.97). Arterial partial pressure of oxygen (PaO2) below 100 mmHg was associated with lower PtiO2 levels. Changes in arterial partial pressure of carbon dioxide (PaC02) did not influence PtiO2 values. Hemoglobin values below 7 g/dl were associated with lower PtiO2 values.

Conclusions: The results of our experiments demonstrate that ICP and PtiO2 measurements indicate impending damage well before serious complications occur and their use should be considered in order to protect endangered brain function in the presence of acetaminophen-induced ALF.

Abbreviations: ALF, acute liver failure; CPP, cranial perfusion pressure; CVP, central venous pressure; ICP, intracranial pressure; MAP, mean arterial pressure; PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide; PT, prothrombin time; PtiO2, brain tissue oxygen; SEM, standard error of mean

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1. Background

Hepatic encephalopathy, cerebral edema and intracranial hypertension are severe complications of acute liver failure (ALF) and a leading cause of mortality in ALF (Bernal et al., 2010). This is especially the case in acetaminophen (Paracetamol®) −induced ALF, the major cause of ALF in Europe and the United States (Bernal and Wendon, 2013; Lee and Seremba, 2008). Paracetamol® is a popular, widely used analgesic with few side-effects when taken in therapeutic doses. However, an overdose consumed either inadvertently or deliberately induces hepatotoxicity, which may result in acute liver failure.

Acetaminophen-induced hepatotoxicity shows the characteristic hyperacute form of acute liver failure, in which encephalopathy occurs within seven days of the onset of jaundice (Bernal and Wendon, 1999; O'Grady et al., 1993). The clinical course is often rapidly progressive and therefore the desease may be misjudged, underdiagnosed or diagnosed in an advanced state. To make matters worse, ALF is a multisystem disease including the unspecific symptoms jaundice, coagulopathy and encephalopathy (Trey and Davidson, 1970).

Despite advances in diagnosis and therapy of ALF, critical care management continues to be very challenging to the physician. Ambiguous clinical courses and unpredictable complications in combination with severe multiorgan failure impede standardized therapy. Especially hepatic encephalopathy plays a crucial role in this multisystem disease and requires extensive critical care management (Bernal et al., 2015).

Standard critical care monitoring in patients suffering from ALF consists of hemodynamic parameters, and not yet routinely of ICP monitoring. But even when neuromonitoring is performed, new monitoring techniques such as direct measurement of cerebral oxygenation by means of brain tissue oxygen (PtiO2) probes are currently not used for ALF.

To address this issue, animal models analysing the pathophysiological central nervous system alterations during the course of ALF provide an opportunity to improve diagnostic and therapeutic strategies. Recently, we established a reproducible, intensively monitored and clinically relevant porcine model of acetaminophen intoxication with standardized intensive care management (Thiel et al., 2011).

The purpose of the following study was to analyse the course of cerebral oxygenation in addition to conventional neuromonitoring during the development, onset and further course of acetaminophen-induced ALF without specific neurological therapy or neuroprotective interventions.

2. Methods

2.1. Animal model

Following approval by the institutional review board for animal experiments, all experiments were performed according to the international principles governing research on animals and under the supervision of a veterinarian, who set the guidelines for minimizing suffering.

The study was performed in 20 female German landrace pigs weighing 38 ± 1 kg.

All procedures including premedication, intubation of the trachea, ventilation and anesthesia during surgery have been described previously in detail (Thiel et al., 2011). Intramuscular premedication was administered using atropine 0.1% (0.05 mg/kg), ketamine (7 mg/kg), azaperone (10 mg/kg) and diazepam (1 mg/kg).

2.2. Surgical procedures

The jugular and femoral veins (Dolphin GamCath Double Lumen Central Venous Catheter, Gambro, Hechingen, Germany) as well as the femoral artery (Pulsiocath 5F Thermodilutions Catheter, PULSION Medical Systems AG, Munich, Germany) were instrumented to measure central venous (CVP) and mean arterial pressure (MAP).

Afterward the pigs were turned to prone position in order to place the probes for neuromonitoring. A parietofrontal cranial trepanation 2 cm above the right orbit and 1 cm lateral to the midline was performed with a hand drill and a probe was inserted in the frontal brain parenchyma to a depth of 15 mm below the dura (Neurovent–PTO, Raumedic AG, Münchberg, Germany) for continuous intraparenchymatous recording of ICP and brain partial oxygen pressure (PtiO2). All burr holes were instrumented with the introducer kit provided by the manufacturer to assure a stable position of the probes.

The pigs were subsequently turned to supine position, where they remained during the whole observation period. The abdomen was then entered through a median laparotomy. A jejunal catheter (Gentle-Flo™, Tyco Healthcare, Tullamore, Ireland) was inserted into the upper jejunum for subsequent acetaminophen administration and a 14F urinary catheter (Ruesch Care, Kernen, Germany) was placed by cystostomy. The abdominal wall was closed with a running suture. Liver biopsies were sampled every 24 h following intoxication and upon autopsy. Clear ascites (500–1500 mL) was removed during liver biopsy procedures, which were performed surgically by reopening the abdominal wound.

2.3. Acetaminophen intoxication and ALF

Dosage, administration and acetaminophen plasma level monitoring for a reproducible onset of acute liver failure after intrajejunal acetaminophen intoxication have been previously described in detail (Thiel et al., 2011). In brief, 20 pigs received an initial enteric acetaminophen bolus of 250 mg/kg body weight via the implanted jejunal catheter. Intoxication was continued initially by administering an enteric maintenance dose of 2000 mg acetaminophen every hour. This maintenance dose was fixed 2000 mg per hour and not accounted for body weight.

Acetaminophen plasma levels were recorded every four hours to direct the acetaminophen maintenance dose (1000–3000 mg) to targeted plasma levels between 300 and 450 mg/L. As soon as ALF occurred, acetaminophen administration was discontinued.

The onset of ALF syndrome was defined by the presence of coagulopathy with a decline in prothrombin time (PT) value < 30% and an increase in international normalised ratio (INR) > 2.5.

2.4. Standardized intensive care management

Intensive care medication and algorithms for standardized fluid management that were used to ensure hemodynamic stability have been previously reported in detail (Thiel et al., 2011, 2010).

In brief, all pigs remained in deep general anesthesia, undergoing pressure-controlled ventilation until conclusion of the study protocol (12–30 breaths/minute, tidal volume (TV) of 6–12 mL/kg and oxygen concentration (FiO2) 0.3–1.0 depending on oxygenation). Continuous infusion of ketamine (15 mg/kg/h), fentanyl 0.02 mg/kg/h and midazolam 0.9 mg/kg/h was administered to maintain anesthesia during the study.

Norepinephrine, in combination with hydroxyethyl starch 6% (Voluven® HES 130/0.4, Fresenius, Bad Homburg, Germany) and sodium chloride solution 0.9% was used to ensure hemodynamic stability. After the onset of ALF, fresh-frozen plasma units were given (4 units (1200 mL)/24 h) to avoid spontaneous bleeding complications. Packed erythrocyte units (300 mL) were given if hemoglobin levels were < 6 g/dL. Blood glucose levels were maintained at > 100 mg/dL with glucose 20% solution. Sodium bicarbonate 8.4% solution was used to compensate metabolic acidosis. Pigs received furosemide (maximal 50 mg/h) when diuresis dropped below 40 mL/h to avoid early respiratory complications due to the unphysiological suspine position combined with massive fluid substitution. Further antibiotic prophylaxis of 2 g ceftriaxon was given daily. At the onset of ALF continuous