

INVESTIGATION PLAN/ April 19, 2018

Official title: Paracetamol And Ibuprofen in closing patent ductus arteriosus (PAI)

Unique Protocol ID: 39/2018

EudraCT ID: 2018–000565-36

Principal Investigators:

Outi Aikio, MD, PhD, Central contact person

Sanna Juujärvi, MB

Antti Härmä, MD

Timo Saarela, MD, PhD

Mikko Hallman, MD, PhD

Paracetamol And Ibuprofen in closing patent ductus arteriosus (PAI)

The purpose of this pilot trial is to study the efficacy and safety of simultaneous intravenous (iv) ibuprofen and paracetamol medications in the closure of patent *ductus arteriosus* (PDA) in preterm infants. Premature infants (born before 37 weeks gestational age) with PDA are the focus of the study since no studies on the additive efficacy of these two medications on the contraction of *ductus arteriosus* is available. It is one center, randomized, placebo-controlled, double-blind, phase 1, clinical trial with an additional open arm.

The primary outcome of this study is ductal closure. The secondary outcomes are the need for ductal therapies, cardiac ultrasound findings, the duration of any ventilation assist, paracetamol serum levels, and paracetamol side effects. Other secondary outcomes during the first hospitalization include the long term complications of prematurity (moderate-to-severe BPD, intraventricular hemorrhage gr 2-4, moderate to severe necrotizing enterocolitis, ROP needing therapy), other long-term morbidity, and mortality.

Hypothesis:

1. Simultaneous iv paracetamol therapy with iv ibuprofen closes PDA more often in preterm infants.
2. Simultaneous iv paracetamol therapy with iv ibuprofen has no detectable adverse effects in preterm infants.
3. The present paracetamol doses do not result in high paracetamol serum levels.
4. Pharmacodynamics of paracetamol is likely to reveal unique features.

Objectives: to study in preterm infants requiring iv ibuprofen for treatment of PDA

1. efficacy of iv paracetamol with iv ibuprofen in randomized, controlled, double-blind clinical trial
2. safety of iv paracetamol with iv ibuprofen in randomized, controlled, double-blind clinical trial
3. pharmacokinetics and pharmacodynamics of iv paracetamol

Sample size:

As no previous trials are available, we plan to recruit at least 10-20 preterm infants.

1 Permissions and practices

The investigation plan has been approved by the following officials:

- Finnish Medical Agency (Fimea)
- Pohjois-Pohjanmaa Health Care District Regional Ethics Board
- Department of Pediatrics, Oulu University Hospital

The trial has been reported in the European Clinical Trials Database (EudraCT 2018-000565-36) and ClinicalTrials.gov registries.

The present trial is conducted by applying the principles of Good Clinical Practice (Fimea directive 2/2012, Clinical trials). The essential changes in the investigation plan will be announced to Fimea according to the Drug act, moment 87a. This will be announced using the European Commission internet form (<http://ec.europa.eu/health/documents/eudralex/vol-10/>).

The study doctor will discuss with all study patients' parents for informed written consent.

2 Methods

Study patients and the exclusion criteria

Preterm infants (born before 37+0 gestation weeks) who are diagnosed to have a hemodynamically significant PDA and who, according to the decision of the attending clinician, need ibuprofen therapy, are eligible to this trial.

If the parents deny the consent for randomization, they are asked for the permission to use the patient data of the child for the research purposes. If this permission is given, these patients form the additional open arm of the study.

If the parents deny the consent, the patient will be treated according to the standard PDA treatment of Oulu University Hospital: three days' iv ibuprofen Pedea® 5mg/ml solution infusion, dosing: 10 mg/kg + 5 mg/kg + 5 mg/kg (q24h). In case of any contraindications for ibuprofen, the treatment would be surgical ligation.

The exclusion criteria include:

- severe malformation or suspected chromosomal defect
- other very severe life-threatening disease (e.g. very severe birth asphyxia or persistent pulmonary hypertension, etc.)

The patient attending to this trial is allowed to have a ventricular septal defect smaller than 3 mm in caliber, but bigger ones are regarded as the exclusion criteria. An open *foramen ovale* is considered physiological in preterm infants.

Randomization and masking

The computed randomization will be done beforehand by a separately nominated randomization group. Randomization will be done in blocks of four.

As the informed consent is given, the study patient receives a trial number from the list made prior to the entry of the study. The trial number will match with an envelope where has been drawn a leaflet with the patient's study medication group written on it. The study medication will begin immediately.

Placebo, 0.45 % saline, is similar to paracetamol, both being clear liquids, so the staff will remain unaware which drug the patient receives. The study drug will be kept and prepared away from the NICU, at the separate ward 55 office, in a locked cabinet. The study drug will be prepared by the

research nurse, the pharmacist of the ward, or during nighttime, by a nurse who does not participate in the study patients' treatment in any way.

Intervention

The study patients will be recruited as soon as the need for ibuprofen therapy is identified. After the parental consent, the patient is assigned the study code number, and the study drug is started accordingly. It is continued for altogether 3 days, i.e. as long as the ibuprofen treatment period will last. The ductal outcomes are defined by the attending clinicians.

The masked study drug is either paracetamol 10mg/ml infusion solution, or placebo, half-physiological 0.45% saline. The placebo is chosen in order to avoid the risk of hypernatremia. The study drug loading dose 20 mg/kg will be given \pm 6 hours from the first ibuprofen dose, and continued 7.5 mg/kg every 6 hours up to 3 days. If the patient had received any paracetamol preparation within two days (48 h) before the study drug, no loading dose is given. The study drug is administered as 15 minutes infusion.

No other paracetamol preparations are allowed to be given during the study drug. After the trial, the paracetamol administration should be limited if possible throughout the hospital course. Otherwise, two days wash-out period is recommended. All the other medical or other therapies are prescribed by the judgment by the attending physicians. In cases of suspicion of severe side effects or other absolute necessities, the attending physician is allowed to break the study code, and stop the study drug (protocol violation).

The pain therapy needed is accomplished using openly the opioid preparation used normally in the each unit (*e.g.* morphine, fentanyl).

Duration of the drug

The drug treatment continues for three days (12 doses).

Primary outcome

The primary outcome is defined as the ductal closure.

Secondary outcomes

Secondary outcomes include the need for additional PDA therapies, the duration of any ventilation assist, paracetamol serum levels, and possible paracetamol side effects. Other secondary outcomes during the first hospitalization include the long term complications of prematurity (moderate-to-severe BPD, intraventricular hemorrhage gr 2-4, moderate to severe necrotizing enterocolitis, ROP needing therapy), other long-term morbidity, and mortality.

The efficacy of the pain therapy

The pain symptoms are estimated according to the pain scales used in each center. All the given pain medication (opioid) doses are recorded and cumulative doses calculated.

NICU follow-up

The cardiac ultrasound examinations will be carried out at least before and after the study drug, and at the discharge from the NICU. If the patient's state is stable enough, the ductal calibers and LA/Ao-ratios will be measured.

During the study drug, diuresis (ml/kg/h), and near infra-red spectroscopy (NIRS) of the forehead will be measured, and the left-overs of the routine blood samples will be saved for paracetamol serum level measurements. Laboratory values, including hepatic transaminase (P-alat) and renal function (S-cystatin-C) will be measured after the study drug.

3 Safety

Previously, no hepatic or renal failure has been reported using the study drug dosage. In our previous cohort studies and in the trial of preterm infants, no signs of hepatic or renal insufficiency have been detected in any patient (Juujärvi 2018, Härkin 2016, Härmä 2016, Aikio 2014).

Drug-induced liver damage (hepatotoxicity) results not from paracetamol itself, but from one of its metabolites, N-acetyl-p-benzoquinoneimine (NAPQI). Therefore, in the case of intoxication, the possible symptoms would not manifest immediately after administration, but after a period of time. The hepatic injury can be prevented by using the available antidote, acetyl cysteine. Even the suspicion of paracetamol overdose should be taken seriously, the situation clarified and acetyl cysteine therapy started promptly.

Typical symptoms and signs of the paracetamol intoxication would be:

- During the first 24 hours after the drug administration, nausea, vomiting, weariness, lack of appetite, and sweating may occur
- 24 – 48 hours after the administration, serum bilirubin and liver aminotransferase levels and prothrombin time increase. Diuresis may decrease due to dehydration (vomiting) or renal injury
- 2 to 5 days after the administration the hepatic and renal failure is manifested, usually with metabolic acidosis

Using early acetyl cysteine therapy, started earlier than 16h after administration, the hepatic failure can be prevented, but if started later, the possible injury may be diminished as well. The intoxication treatment includes effective intravenous fluid therapy in order to attenuate the metabolic acidosis, and the diuresis should be aimed to be more than 1.5 ml/kg/h.

The intravenously administered study drug can cause no harm to study patients' families, nursing staff, or the ward milieu.

Reporting and follow-up of the possible adverse events or adverse effects

All study infants will be observed for any clinical signs of adverse effects of paracetamol, especially hepatic or renal insufficiency. The serum or skin bilirubin levels and diuresis are detected during the

study period. In case of exceptionally severe hyperbilirubinemia, an abdominal ultrasound scan will be done. Any suspicion of hepatic or renal failure would be a reason to immediately stop the study drug and examine the serum transaminase levels. Symptoms of hepatic or renal failure are considered as an emergency.

In case of suspicion of severe safety issues associated with the trial, separately nominated safety group will be able to break the study code and interrupt the trial, if necessary.

All adverse events and suspected adverse effects are classified by the possible association to the study drug. The classification scale is: clear – likely – unlikely – not possible. Sudden unexpected severe adverse reactions (SUSAR) are recorded into a special file maintained by the responsible investigator. Of them, death or danger of life are reported to Fimea within 7 days after the incident, others within 15 days. This file is reported to Fimea every year.

Pharmacokinetics and pharmacodynamics

From all study patients, the left-overs of the routine blood samples will be recovered.

4 Research data

From all study infants, an internet-based study file will be filled out. It contains following information:

- Gestational parameters: maternal age and diagnoses, parity, medications during the pregnancy, possible complications, the amount of amnion fluid, cause of premature birth
- Infants: gestational age, gender, birth measurements (weight, length, head circumference), PDA therapies, blood pressures, cerebral and abdominal ultrasound scan reports, pain medication doses, diuresis.
- Laboratory values: transaminase, bilirubin and creatinine values if taken
- Diagnoses: PDA, BPD, ICH, NEC, ROP

All the research data is confidential. The whole study personnel are bound to secrecy. The data will be collected to specified files stored into the hospital datasets of the responsible investigator's affiliation. The study registry has been reported to Finnish Data Protection Ombudsman's Office. The study results will be published in international medical series and theses.

Quality control

A separate monitoring group will be nominated to follow the quality and justification of the methods used, and fulfillment of the study patients' rights and their well-being. We propose that no interim analysis is planned unless excess of adverse effects are observed.

5 Long-term follow-up

The long-term follow-up trial is planned to be accomplished at the 2 to 3 years age, and at 7 years age, including developmental and cardiac examinations as well as parental questionnaire.

6 Statistical analyses

Clinical trial data will be analyzed based on the intention-to-treat principles. The data analysis software will be SPSS. Student's t-test, Chi squared test, and regression analyses will be used as appropriate.

7 Timetable estimation

2017-2018: permissions

2018-2020: recruitment of the patients

2020-2021: data analysis and reporting.