EudraCT number2012-002836-97

Sponsor protocol number 1703

Authorization of Research Ethics Committee of Tartu University of Tartu number 188T-2 issued at 14.12.2012

Authorization of Estonian Agency of Medicines number RKU-4/13 issued at 19.03.2010

Full title of trial: **Pharmacokinetics of Meropenem in Very Low Birth Weight Neonates**

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This trial was not part of an agreed pediatric investigation plan

To this trial does not apply article 45 of Regulation No 1901/2006

To this trial does not apply article 46 of Regulation No 1901/2006

Analysis stage is final

Primary completion date 3.12.2010

Global end of trial 1.02.2011

Actual start date of recruitement 7.04.2010

Main objective of trail: We aimed to compare the steady state PK and safety of meropenem given via bolus or prolonged infusion to very low birth weight neonates with the ultimate goal to define the most appropriate dosing regimen for a phase 3 study comparing meropenem with standard of care in treatment of late onset neonatal sepsis

Long term follow up was not planned

No involment of Independent data monitoring committee

Protection of subjects: study group consisted of premature newborns to who meropenem was clinically indicated. We used the dose in line with the current dose recommendation for meropenem. We collected additional blood only for PK samples. Blood collection was limited according to instructions of Committee for Medicinal Products for Human Use and Paediatric

Committee of European Medicines Agency. Invasive monitoring and cannulas were used only when clinically indicated.

Planned number of subjects 20

Screened number of subjects 21. Actual number of subjects enrolled 19, all preterm neonates <37 weeks with postnatal age 0-27 days; males 12, females 7.

Recruitement details: 1.Gestational age of ≤ 32 weeks and birth weight below 1500 grams;

2. Postnatal age of ≤ 56 days; 3. Written consent signed by parents or legal representatives;

4. Required hospitalisation into intensive care unit; 5. Arterial or venous cannula settled for clinical reasons; 6. Need for meropenem treatment on following clinical indications:

a. Proven or suspected sepsis, lower respiratory tract infection, complicated intraabdominal infection; b. Clinical deterioration with symptoms suggesting worsening of infection during antibacterial treatment used for empiric treatment of EOS; c. Isolation of bacteria from normally sterile sites known to be or suspected to be resistant to presently used antibiotics but susceptible to meropenem; d. Suspected infection with multi-resistant bacteria, that is in-ward at same time patient with multiresistant bacteria; 7. Expected not to die within 24 hours; 8. No major uncorrected congenital malformations.

Period title: overeall trial

Allocation method: not applicable

Blinding was not used

Arms:

The bolus injection group (group 1). Meropenem administration at a dose of 20 mg/kg Q 12h over 30 minutes

Number of subjects started 9. Number of subjects completed 9.

The continuous infusion group (Group 2). Meropenem administration at a dose of 20 mg/kg Q 12h as a four hour infusioon

Number of subjects started 10. Number of subjects completed 10.

Study endpoints:

Pharmacokinetic endpoints

Primary endpoint. Timeframe: steady state. Description mean (SD): area under the time-concentration curve (AUClast); volume of distibution (Vss); dug clearance (Clss), maximum concentration (Cmax); minimum concentration (Cmin); time to Cmax in seerum (Tmax)

Group I, bolus injection: Vss (ml/kg) 270.6 (83.3); AUClast (hxμg/ml) 369.2 (66.1); CLss (ml/h/kg) 52.4 (15.5) T1/2 3.4(0.9); Cmax (mg/L) 89.3 (32.7); Cmin (mg/L) 6.5 (3.7); Tmax (h) 0.7 (0.4)

Group II, prolonged infusion: Vss (ml/kg) 342.9 (174.3); AUClast (hxμg/ml) 338.6 (121.6); CLss (ml/h/kg) 62.7 (31.6) T1/2 3.3(1.7); Cmax (mg/L) 54.5 (19.0); Cmin (mg/L) 7.2 (6.1); Tmax (h) 4.0 (1.9)

Goup I and II were compared by Mann-Whitney test. Significant diference between groupd ($p<0.05$) was found only for Cmax and Tmax.

Safety endpoints

Description of all adverse events experienced by premature neonates received study drug.

Adverse events information:

Timeframe for averse event reporting: starting from the day when study drug was administered. Finishing on the day after the end of treatment with study drug.

Adverse events assessment type was systematic. Frequency threshold for reporting non-serious averse events was 0.1.

Adverse events registration: no serious adverse events were registered, no non-serious adverse events were registered.

There were no global substantial amendments made to the protocol.

There were no global interruprions made to the trial.

Online reference: https://pubmed.ncbi.nlm.nih.gov/22733063/