Clinical trial results:
High volume haemodiafiltration in treatment of severe sepsis -- impact on pharmacokinetics of doripenem and piperacillin tazobactam and inflammatory response.

Summary

EudraCT number	2011-000644-16
Trial protocol	EE
Global end of trial date	25 June 2014

Results information

Result version number	v1 (current)
This version publication date	02 January 2020
First version publication date	02 January 2020

Trial information

Trial identification

Sponsor protocol code	Dor1.0

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Tartu, Clinic of Anaesthesiology and Intensive Care
Sponsor organisation address	L. Puusepa 8, Tartu, Estonia, 51014
Public contact	Principal Investigator, University of Tartu, Clinic of Anaesthesiology and Intensive Care, kadri.tamme@kliinikum.ee
Scientific contact	Principal Investigator, University of Tartu, Clinic of Anaesthesiology and Intensive Care, kadri.tamme@kliinikum.ee

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2014
Global end of trial reached?	Yes
Global end of trial date	25 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Describe the pharmacokinetics of doripenem and piperacillin-tazobactam during high volume haemofiltration.

Protection of trial subjects:

All patients were treated and monitored in intensive care.
Informed consent was obtained from the patient or legal representative prior to study inclusion.
All blood samples were drawn from indwelling arterial catheter.
Patients with known hypersensitivity to carbapenems, penicillins or other beta-lactams were excluded.

Background therapy:

All patients received high volume haemodiafiltration prescribed by the treating physician.

Evidence for comparator: -

Actual start date of recruitment	01 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Estonia: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	9
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Pharmacokinetics of doripenem during HVHDF - 9 patients recruited from September 1, 2011 till August 31, 2012.
Pharmacokinetics of piperacillin/tazobactam during HVHDF - 10 patients were recruited from September 1, 2012 till June 25, 2014.

Pre-assignment

Screening details:

Patients in severe sepsis or septic shock who were prescribed high volume haemodiafiltration were eligible. Of 36 prescreened patients, 19 were enrolled in the study. The reasons for exclusion were were absence of informed consent from next of kin, life expectancy of < 8 hours, and age <18 years.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Doripenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single dose of 500 mg of doripenem in 50 mL of 0.9% sodium chloride was administered in addition to the ongoing antibacterial therapy as a 1 hour intravenous infusion.

Investigational medicinal product name	Piperacillin/tazobactam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single dose of 4000 mg of piperacillin and 500 mg of tazobactam in 50 mL of 0.9% sodium chloride was administered in addition to the ongoing antibacterial therapy as a 30 minute intravenous infusion.

Number of subjects in period 1	Single arm
Started	19
Completed	19

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
Adults (18-64 years)	9	9	
From 65-84 years	10	10	
Age continuous Units: years			
median	65		
inter-quartile range (Q1-Q3)	56 to 72	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	12	12	
Weight Units: kilogram(s)			
median			
inter-quartile range (Q1-Q3)		-	
Serum C-reactive protein Units: milligram(s)/litre			
median			
inter-quartile range (Q1-Q3)		-	
Serum creatinine Units: micromole(s)/litre			
median			
inter-quartile range (Q1-Q3)		-	
Serum lactate Units: millimole(s)/litre			
median			
inter-quartile range (Q1-Q3)		-	
APACHE II score Units: points			
median			
inter-quartile range (Q1-Q3)		-	
SOFA score Units: points			
median			
inter-quartile range (Q1-Q3)		-	

Subject analysis sets

Subject analysis set title	Doripenem pharmacokinetics
Subject analysis set type	Full analysis

Subject analysis set description:

Patients who received doripenem

Subject analysis set title	Piperacillin/tazobactam pharmacokinetics
Subject analysis set type	Full analysis

Subject analysis set description:

Patients who received piperacillin/tazobactm

Reporting group values	Doripenem pharmacokinetics	Piperacillin/tazobactam pharmacokinetics	
Number of subjects	9	10	
Age categorical Units: Subjects			
Adults (18-64 years)	3	6	
From 65-84 years	6	4	
Age continuous Units: years			
median	66	63	
inter-quartile range (Q1-Q3)	61.5 to 74.5	54.5 to 68.75	
Gender categorical Units: Subjects			
Female	3	4	
Male	6	6	
Weight Units: kilogram(s)			
median	80	87.5	
inter-quartile range (Q1-Q3)	77.5 to 97	68.5 to 98.75	
Serum C-reactive protein Units: milligram(s)/litre			
median	252	243	
inter-quartile range (Q1-Q3)	241 to 331.5	69 to 285	
Serum creatinine Units: micromole(s)/litre			
median	312	163.5	
inter-quartile range (Q1-Q3)	127.5 to 436	135.25 to 209.75	
Serum lactate Units: millimole(s)/litre			
median	1.9	1.65	
inter-quartile range (Q1-Q3)	1.4 to 3.1	1.3 to 1.95	
APACHE II score Units: points			
median	17	18.5	
inter-quartile range (Q1-Q3)	14 to 19	16.25 to 21.75	
SOFA score Units: points			
median	11	10	
inter-quartile range (Q1-Q3)	10 to 13	7 to 11	

End points

End points reporting groups

Reporting group title	Single arm
Reporting group description: -	
Subject analysis set title	Doripenem pharmacokinetics
Subject analysis set type	Full analysis
Subject analysis set description: Patients who received doripenem	
Subject analysis set title	Piperacillin/tazobactam pharmacokinetics
Subject analysis set type	Full analysis
Subject analysis set description: Patients who received piperacillin/tazobactm	

Primary: Pharmacokinetic parameter total body clearance

End point title	Pharmacokinetic parameter total body clearance
End point description: Non-linear mixed effects modelling was used to estiamte the total body clearance of the study drug.	
End point type	Primary
End point timeframe: Blood samples were collected before and immediately after the end of study drug infusion, every half hour for 4 hours and then every hour till 8 hours after the study drug administration.	

End point values	Doripenem pharmacokinetics	Piperacillin/tazobactam pharmacokinetics		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	10		
Units: Litres per hour				
arithmetic mean (confidence interval 95%)	6.82 (6.80 to 7.19)	6.9 (6.1 to 7.9)		

Statistical analyses

Statistical analysis title	Non-linear mixed effects modelling
Statistical analysis description: PK data were analysed by non-linear mixed effect modelling.	
Comparison groups	Piperacillin/tazobactam pharmacokinetics v Doripenem pharmacokinetics
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.01 [2]
Method	Mixed models analysis

Notes:

[1] - Non-linear mixed effects modelling. No comparisons between analysis groups were performed

[2] - Covariates that reduced the objective function value (OFV) by at least 6.635 points ($p<0.01$) were considered statistically significant and included in the subsequent covariate analysis.

Secondary: Pharmacokinetic parameter volume of distribution of central compartment

End point title	Pharmacokinetic parameter volume of distribution of central compartment

End point description:

Non-linear mixed effects modelling was used to estimate volume of distribution of central compartment.

End point type	Secondary

End point timeframe:

Blood samples were collected before and immediately after the end of study drug infusion, every half hour for 4 hours and then every hour till 8 hours after the study drug administration.

End point values	Doripenem pharmacokinetics	Piperacillin/tazobactam pharmacokinetics		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	10		
Units: litre(s)				
arithmetic mean (confidence interval 95%)	10.8 (10.54 to 10.82)	9.0 (7.4 to 11.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter volume of distribution of peripheral compartment

End point title	Pharmacokinetic parameter volume of distribution of peripheral compartment

End point description:

Non-linear mixed effects modelling was used to estimate volume of distribution of peripheral compartment

End point type	Secondary

End point timeframe:

Blood samples were collected before and immediately after the end of study drug infusion, every half hour for 4 hours and then every hour till 8 hours after the study drug administration.

End point values	Doripenem pharmacokinetics	Piperacillin/tazobactam pharmacokinetics		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	10		
Units: litre(s)				
arithmetic mean (confidence interval 95%)	12.1 (12.01 to 13.64)	11.2 (8.9 to 14.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All patients were monitored for adverse events for at least 7 days after study drug administration.

Adverse event reporting additional description:

All patients were monitored for adverse events for at least 7 days after study drug administration. Monitoring included clinical evaluation for occurrence of allergic reactions and seizures, laboratory and vital parameters and microbiological cultures. Concomitant medications were recorded during the whole ICU stay.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Doripenem group
Reporting group description: -	
Reporting group title	Piperacillin/tazobactam group

Reporting group description: -

Serious adverse events	Doripenem group	Piperacillin/tazobactam group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Doripenem group	Piperacillin/tazobactam group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	
Cardiac disorders			
Atrial fibrillation	Additional description: One patient developed temporary atrial fibrillation.		
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hypotension	Additional description: One patient developed hypotension at the beginning of high volume haemodiafiltration, stabilized with infusion therapy and temporary increase in norepinephrine dose		
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25408310

http://www.ncbi.nlm.nih.gov/pubmed/26830215

http://www.ncbi.nlm.nih.gov/pubmed/26064875