Clinical trial results:
The Impact of Target Temperature Management on Drug Metabolism
Summary

EudraCT number	2018-002226-22
Trial protocol	AT
Global end of trial date	17 June 2020

Results information

Result version number	v1 (current)
This version publication date	17 June 2022
First version publication date	17 June 2022
Summary attachment (see zip file)	Publicaiton (1-s2.0-S0753332221013603-main-2.pdf)

Trial information

Trial identification

Sponsor protocol code	2.0

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Währinger Gürtel 18-20, Vienna, Austria, 1090
Public contact	Department of Emergency Medicine, Medical University of Vienna, +43 14040019640, post_akh_ls_6d@akhwien.at
Scientific contact	Department of Emergency Medicine, Medical University of Vienna, +43 14040019640, post_akh_ls_6d@akhwien.at

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	01 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2020
Global end of trial reached?	Yes
Global end of trial date	17 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To compare the half-life of pantoprazole during cooling and after rewarming

Protection of trial subjects:

The study was of an observational nature and only patients, who received pantoprazole as part of their standard treatment, were included. Thus, no patient received a drug other than their standard treatment. Blood sampling was performed using existing central or peripheral venous or arterial catheters.

Background therapy:

Patients received standard of care after cardiac arrest. The study did not interfere with standard of care at any time.

Evidence for comparator:

We compared the pharmacokinetics of pantoprazole during three periods after cardiac arrest within the same patient:
1) mild therapeutic hypothermia
2) after rewarming, at ICU
3) after recovery, at normal ward.

No comparator substance (e.g. placebo) was used within the study.

Actual start date of recruitment	25 May 2019
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	Austria: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	13
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening depended mainly on in- and exclusion criteria, but also on availability of the study team.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Target Temperature Management

Arm description:

all patients received a 40mg bolus infusion of pantoprazole as soon as target temperature (32-34 degrees Celsius) was reached

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

Dosage and administration details:

40mg intravenous bolus infusion

Arm title	Rewarming

Arm description:

40mg bolus infusion as soon as normal body temperature was reached

Arm type	Active comparator
Investigational medicinal product name	pantoprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

40mg intravenous bolus infusion

Arm title	Recovered

Arm description:

After patients have almost completely recovered and were treated at the normal ward, the third study period was conducted. Patients received a 40mg intravenous bolus of pantoprazole.

Arm type	Active comparator
Investigational medicinal product name	pantoprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

40mg intravenous bolus infusion

Number of subjects in period 1	Target Temperature Management	Rewarming	Recovered
Started	16	16	10
Completed	16	16	10

Baseline characteristics

Reporting groups

Reporting group title	Main

Reporting group description:

16 patients were eligible for inclusion and completed the TTM period (=target temperature management), the rewarming period (=after rewarming at the ICU) and 10 of these 16 patients entered the recovered period (=at normal ward). Six patients either died or had poor neurologic outcome and couldn't provide informed consent for participation in period 3. For period 1 and 2 the EC waived informed consent.

Reporting group values	Main	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	13	13	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous Units: years			
median	53		
inter-quartile range (Q1-Q3)	46 to 62	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	13	13	

Subject analysis sets

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who completed the three trials (each patient took part in up to three periods, that were compared with each other)

Reporting group values	Per Protocol		
Number of subjects	10		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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 65-84 years	1		
85 years and over	0		
Age continuous			
Units: years			
median	53		
inter-quartile range (Q1-Q3)	46,25 to 60,5		
Gender categorical			
Units: Subjects			
Female	3		
Male	7		

End points

End points reporting groups

Reporting group title	Target Temperature Management
Reporting group description:	
all patients received a 40mg bolus infusion of pantoprazole as soon as target temperature (32-34 degrees Celsius) was reached	
Reporting group title	Rewarming
Reporting group description:	
40mg bolus infusion as soon as normal body temperature was reached	
Reporting group title	Recovered
Reporting group description:	
After patients have almost completely recovered and were treated at the normal ward, the third study period was conducted. Patients received a 40mg intravenous bolus of pantoprazole.	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who completed the three trials (each patient took part in up to three periods, that were compared with each other)	

Primary: terminal elimination half-life

End point title	terminal elimination half-life
End point description:	
End point type	Primary
End point timeframe:	
24h per period	

End point values	Target Temperature Management	Rewarming	Recovered	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[1]	10	10	
Units: h				
median (inter-quartile range (Q1-Q3))	2.4 (1.8 to 4.8)	2.8 (2.1 to 6.8)	1.2 (0.9 to 2.3)	

Notes:

[1] - only patients who completed all three periods were included in the final analysis

Statistical analyses

Statistical analysis title	Friedman ANOVA
Statistical analysis description:	
comparing the three periods, including 10 patients who completed the three periods.	
Comparison groups	Target Temperature Management v Rewarming v Recovered

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001 [3]
Method	ANOVA

Notes:

[2] - included n=10 who completed all three study periods

[3] - a significant difference was found

Secondary: Area under the time-concentration curve

End point title	Area under the time-concentration curve

End point description:

Area under the time concentration curve from 0-24h of pantoprazole after 40mg bolus infusion

End point type	Secondary

End point timeframe:

24 hours per period

End point values	Target Temperature Management	Rewarming	Recovered	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[4]	10[5]	10[6]	
Units: ng/mL*h				
median (inter-quartile range (Q1-Q3))	12.7 (9.6 to 22.6)	9.8 (7.6 to 18.6)	7.2 (5.9 to 9.5)	

Notes:

[4] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

[5] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

[6] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

Statistical analyses

Statistical analysis title	Friedman ANOVA

Statistical analysis description:

comparison of all three groups in one analysis

Comparison groups	Target Temperature Management v Rewarming v Recovered
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.027 [8]
Method	ANOVA

Notes:

[7] - n=10 because the same ten subjects completed all three periods

[8] - there was a significant difference between the three study periods

Secondary: Volume of Distribution

End point title	Volume of Distribution

End point description:

three study periods were compared with each other. 10 patients completed the three periods and were therefore eligible for comparison. The Volume of distribution is presented in the unit L (Liters).

End point type	Secondary
End point timeframe: 24h per period	

End point values	Target Temperature Management	Rewarming	Recovered	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[9]	10[10]	10[11]	
Units: Liters				
median (inter-quartile range (Q1-Q3))	11.4 (10.2 to 12.7)	16.5 (14.3 to 21.2)	12.5 (8 to 15.6)	

Notes:

[9] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

[10] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

[11] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

Statistical analyses

Statistical analysis title	Friedman ANOVA
Statistical analysis description: all three periods were compared with each other using a Friedman ANOVA	
Comparison groups	Target Temperature Management v Rewarming v Recovered
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [12]
Method	ANOVA

Notes:

[12] - there was a significant difference between the three study periods.

Secondary: Clearance

End point title	Clearance
End point description: The main comparison was performed in 10 patients, who completed all three study periods.	
End point type	Secondary
End point timeframe: 0-24h after each dose,	

End point values	Target Temperature Management	Rewarming	Recovered	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[13]	10[14]	10[15]	
Units: L/h				
median (inter-quartile range (Q1-Q3))	2.9 (1.7 to 4.0)	3.9 (2.0 to 4.9)	5.5 (3.9 to 6.5)	

Notes:
[13] - Ten patients completed the three study periods and were included in the final analysis
[14] - Ten patients completed the three study periods and were included in the final analysis
[15] - Ten patients completed the three study periods and were included in the final analysis

Statistical analyses

Statistical analysis title	Friedman Anova

Statistical analysis description:
all three periods were compares in one statistical test - a Friedman ANOVA

Comparison groups	Target Temperature Management v Rewarming v Recovered
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 [16]
Method	ANOVA

Notes:
[16] - There was a significant difference between the three study periods.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

First visit of each patient to last visit of each individual patient. This was depending on the clinical course of the patients and lasted up to 19 days until all three study periods were completed.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	3.0

Reporting groups

Reporting group title	Full Analysis Set

Reporting group description:

Due to the observational nature of the study and the critical illness of the patients, only serious adverse events were documented.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: This was a non-interventional, observational study in patients who have undergone a successful cardiopulmonary resuscitation. Pantoprazole was part of their standard of care and we quantified pharmacokinetics. Thus, we have only recorded serious adverse events, but no non-serious adverse events.

Serious adverse events	Full Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Hypoxic brain damage	Additional description: In five subjects treating physicians diagnosed a hypoxic brain damage after initial cardiac arrest. Because of poor prognosis treatment was withdrawn. There was no causal relationship with the study. Of note, pantoprazole was part of standard of care		
subjects affected / exposed	5 / 16 (31.25%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 5		
Hepatobiliary disorders			
Hypoxic hepatitis	Additional description: In one patient a hypoxic hepatitis was diagnosed after initial cardiac arrest. There was no causal relationship with the study or the study drug. Pantoprazole was part of standard of care.		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury	Additional description: Two patients developed an acute kidney failure after initial cardiac arrest. There was no causal relationship with the study or the study drug. Of note, pantoprazole was part of the standard of care.		

subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Full Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 February 2019	The study was initially submitted as an interventional trial in patients undergoing cardiopulmonary resuscitation. The IMPs included paracetamol, erythromycin and pantoprazole. However, as we couldn't provide sufficient evidence for the individual benefit of the participating subjects, we were only able to conduct a non-interventional study investigating the pharmacokinetics of pantoprazole. Hence, due to the non-interventional nature of the study, the Ethics Committee did not demand a EudraCT entry. However, since the current EudraCT entry was still opened, we decided to enter study data as far as possible. The Amendment date relates to the last change of the study protocol, which in its final version describes a non-interventional study focusing on the pharmacokinetics of pantoprazole.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

16 patients were included in total. However, six couldn't participate in the last period due to death or poor neurologic outcome. Hence, the final population consists of 10 patients.

Notes: