Clinical trial results:
The effects of different vasopressors on the innate immune response during experimental human endotoxemia, a pilot proof-of-principle study

Summary

EudraCT number	2015-002706-36
Trial protocol	NL
Global end of trial date	21 March 2016

Results information

Result version number	v1 (current)
This version publication date	08 May 2021
First version publication date	08 May 2021
Summary attachment (see zip file)	Effect of vasopressors on the macro- and microcirculation during systemic inflammation in humans in vivo (shk.0000000000001357.pdf) Norepinephrine Dysregulates the Immune Response and Compromises Host Defense during Sepsis (rccm.202002-0339oc (1).pdf)

Trial information

Trial identification

Sponsor protocol code	VASOPRESSOR-LPS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CMO: 2015-2079

Notes:

Sponsors

Sponsor organisation name	Radboud University Nijmegen Medical Centre
Sponsor organisation address	Geert Grooteplein 10, Nijmegen, Netherlands, 6500 HB
Public contact	Research IC, office of Roel Stolk, Radboudumc, roeland.stolk@radboudumc.nl
Scientific contact	Research IC, office of Roel Stolk, Radboudumc, roeland.stolk@radboudumc.nl

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	21 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2016
Global end of trial reached?	Yes
Global end of trial date	21 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to investigate whether noradrenaline exerts immunomodulatory effects in humans in vivo during experimental human endotoxemia. (administration of lipopolysaccharide [LPS] in healthy volunteers).

Protection of trial subjects:

All subjects provided written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2016
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	Netherlands: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

40 healthy male volunteers were included.

Pre-assignment

Screening details:

All subjects were screended by physical examination, electrocardiography and routine laboratory exams.

Pre-assignment period milestones

Number of subjects started	40
Number of subjects completed	40

Period 1

Period 1 title	Infusion of study medication (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Norepinephrine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Noradrenaline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

five-hour infusion of 0.05 µg/kg/min norepinephrine

Investigational medicinal product name	lipopolysaccharide (E. coliderived LPS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

intravenous bolus injection with 2 ng/kg lipopolysaccharide

Arm title	Phenylepiphrine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fenylefrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

five hour infusion of 0.5 µg/kg/min phenylephrine

Investigational medicinal product name	lipopolysaccharide (E. coliderived LPS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:
intravenous bolus injection with 2 ng/kg lipopolysaccharide

Arm title	Vasopressin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Agripressin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
five hour infusion of 0.04 IU/min vasopressin

Investigational medicinal product name	lipopolysaccharide (E. coliderived LPS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:
intravenous bolus injection with 2 ng/kg lipopolysaccharide

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	NaCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
five hour infusion of placebo (NaCl 0.9%)

Investigational medicinal product name	lipopolysaccharide (E. coliderived LPS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:
intravenous bolus injection with 2 ng/kg lipopolysaccharide

Number of subjects in period 1	Norepinephrine	Phenylepiphrine	Vasopressin
Started	10	10	10
Completed	10	10	10

Number of subjects in period 1	Placebo
Started	10
Completed	10

Baseline characteristics

Reporting groups	
Reporting group title	Norepinephrine
Reporting group description: -	
Reporting group title	Phenylepiphrine
Reporting group description: -	
Reporting group title	Vasopressin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Norepinephrine	Phenylepiphrine	Vasopressin
Number of subjects	10	10	10
Age categorical Units: Subjects			
Adults (18-64 years)	10	10	10
Gender categorical Units: Subjects			
Male	10	10	10

Reporting group values	Placebo	Total	
Number of subjects	10	40	
Age categorical Units: Subjects			
Adults (18-64 years)	10	40	
Gender categorical Units: Subjects			
Male	10	40	

End points

End points reporting groups	
Reporting group title	Norepinephrine
Reporting group description: -	
Reporting group title	Phenylepiphrine
Reporting group description: -	
Reporting group title	Vasopressin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Mean arterial pressure	
End point title	Mean arterial pressure
End point description:	
End point type	Primary
End point timeframe:	
Before and after LPS administration (t=-90, -30, 0, 90, 210, 270 min)	

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: mmHg				
arithmetic mean (standard error)				
t=-90	92 (± 8)	92 (± 10)	94 (± 8)	95 (± 8)
t=-30	105 (± 6)	102 (± 9)	95 (± 4)	96 (± 6)
t=90	101 (± 8)	95 (± 12)	98 (± 10)	94 (± 7)
t=270	82 (± 5)	77 (± 5)	81 (± 7)	84 (± 7)

Statistical analyses

Statistical analysis title	Two way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

Primary: Heart rate

End point title	Heart rate

End point description:

End point type	Primary

End point timeframe:

Before and after LPS administration (t=-90, -30, 0, 90, 210, 270 min)

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: bpm				
arithmetic mean (standard error)				
t=-90	61 (± 8)	64 (± 8)	67 (± 8)	62 (± 10)
t=-30	57 (± 12)	56 (± 8)	65 (± 10)	61 (± 11)
t=90	70 (± 9)	72 (± 13)	77 (± 8)	78 (± 12)
t=270	87 (± 10)	86 (± 6)	94 (± 11)	82 (± 9)

Statistical analyses

Statistical analysis title	Two way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

Primary: Cardiac output (PCA)

End point title	Cardiac output (PCA)

End point description:

End point type	Primary

End point timeframe:

Before and after LPS administration (t=-90, -30, 0, 90, 210, 270 min)

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: Flow (unit)				
arithmetic mean (standard error)				
t=-90	6.95 (± 2.80)	7.58 (± 4.33)	6.57 (± 3.30)	8.11 (± 3.22)
t=-30	5.75 (± 2.38)	6.97 (± 2.32)	5.54 (± 1.88)	7.89 (± 2.66)
t=90	6.09 (± 2.79)	10.01 (± 5.01)	5.25 (± 2.97)	9.80 (± 2.89)
t=270	12.38 (± 3.35)	15.55 (± 3.19)	11.79 (± 3.18)	13.24 (± 6.23)

Statistical analyses

Statistical analysis title	Two- way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)

Primary: Systemic vascular resistance (PCA

End point title	Systemic vascular resistance (PCA

End point description:

End point type	Primary

End point timeframe:

Before and after LPS administration (t=-90, -30, 0, 90, 210, 270 min)

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: Resistance (unit)				
arithmetic mean (standard error)				
t=-90	15.57 (± 6.94)	14.76 (± 5.95)	17.59 (± 7.88)	13.98 (± 6.99)
t=-30	21.38 (± 10.2)	15.73 (± 3.96)	18.70 (± 5.7)	13.45 (± 4.38)
t=90	19.50 (± 7.99)	11.84 (± 5.61)	23.03 (± 10.96)	10.71 (± 4.75)
t=270	7.09 (± 2.09)	5.12 (± 1.12)	7.62 (± 3.41)	7.72 (± 4.03)

Statistical analyses

Statistical analysis title	Two way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

Primary: TNF-a AUC

End point title	TNF-a AUC
End point description:	
End point type	Primary
End point timeframe:	
Study period	

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: AUC				
arithmetic mean (standard deviation)	37526 (± 16717)	41009 (± 15641)	54772 (± 33812)	38151 (± 19731)

Statistical analyses

Statistical analysis title	Two way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

Primary: IL-6 AUC

End point title	IL-6 AUC
End point description:	
IL-6 Area Under the Curve	
End point type	Primary

End point timeframe: Study period

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: AUC				
arithmetic mean (standard deviation)	76582 (± 34609)	63212 (± 24427)	132229 (± 73580)	89017 (± 32579)

Statistical analyses

Statistical analysis title	Two way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

Primary: IL-8 AUC	
End point title	IL-8 AUC
End point description:	
End point type	Primary
End point timeframe: Study period	

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: AUC				
arithmetic mean (standard deviation)	47912 (± 15395)	49282 (± 12597)	61667 (± 20259)	57342 (± 22089)

Statistical analyses

Statistical analysis title	two way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

Primary: IL-10 AUC

End point title	IL-10 AUC

End point description:

End point type	Primary

End point timeframe:

Study period

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: AUC				
arithmetic mean (standard deviation)	19970 (± 16423)	19068 (± 9330)	14479 (± 8151)	11566 (± 4530)

Statistical analyses

Statistical analysis title	Two way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

Primary: MCP-1 AUC

End point title	MCP-1 AUC

End point description:

End point type	Primary

End point timeframe:

Study period

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: AUC				
arithmetic mean (standard deviation)	310530 (± 126410)	314506 (± 55854)	437264 (± 155595)	433810 (± 149740)

Statistical analyses

Statistical analysis title	two way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

Primary: IP10 AUC

End point title	IP10 AUC

End point description:

End point type	Primary

End point timeframe:

Study period

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: AUC				
arithmetic mean (standard deviation)	2072000 (± 873679)	2731000 (± 1072000)	3397000 (± 1707000)	4640000 (± 3920000)

Statistical analyses

Statistical analysis title	Two way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

Primary: G-CSF AUC

End point title	G-CSF AUC

End point description:

End point type	Primary

End point timeframe:

Study period

End point values	Norepinephrine	Phenylepiphrine	Vasopressin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: AUC				
arithmetic mean (standard deviation)	23828 (± 14986)	28077 (± 15249)	47197 (± 27734)	33041 (± 26548)

Statistical analyses

Statistical analysis title	Two way analysis of variance
Comparison groups	Norepinephrine v Phenylepiphrine v Vasopressin v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout complete study period	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE guidelines
Dictionary version	4.0

Reporting groups	
Reporting group title	Norepinephrine
Reporting group description: -	
Reporting group title	Phenylepiphrine
Reporting group description: -	
Reporting group title	Vasopressin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Norepinephrine	Phenylepiphrine	Vasopressin
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Norepinephrine	Phenylepiphrine	Vasopressin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	10 / 10 (100.00%)	10 / 10 (100.00%)
General disorders and administration site conditions			

Flu-like symptoms subjects affected / exposed occurrences (all)	10 / 10 (100.00%) 10	10 / 10 (100.00%) 10	10 / 10 (100.00%) 10

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events subjects affected / exposed	10 / 10 (100.00%)		
General disorders and administration site conditions Flu-like symptoms subjects affected / exposed occurrences (all)	10 / 10 (100.00%) 10		

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

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

1) Low dosages of norepinephrine and phenylephrine were administered to healthy subjects

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32520577