Clinical trial results:
Renal and cardiac effects of terlipressin and dobutamin in cirrhosis and ascites. A randomised study.

Summary

EudraCT number	2012-002275-33
Trial protocol	DK
Global end of trial date	24 May 2018

Results information

Result version number	v1 (current)
This version publication date	24 June 2021
First version publication date	24 June 2021

Trial information

Trial identification

Sponsor protocol code	0805-2012-1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Center for Leverforskning Odense
Sponsor organisation address	Kløvervænget 12, Odense, Denmark, 2100
Public contact	Aleksander Krag, Dept. Gastroenterology, Universityhospital Odense, 0045 29647719, mads.egerod.israelsen@rsyd.dk
Scientific contact	Aleksander Krag, Dept. Gastroenterology, Universityhospital Odense, 20681060 29647719, mads.egerod.israelsen@rsyd.dk

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 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 May 2018
Global end of trial reached?	Yes
Global end of trial date	24 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Many patients with cirrhosis will die of renal failure - the hepatorenal syndrome, which has a median survival of less than 1 month. Hepatorenal syndrome is treated with terlipressin, which increases blood pressure and improves renal function. However, terlipressin also causes a decline in cardiac function, which is unfortunate, since the renal function relies on a sufficient cardiac output. This may explain why only half of the patients respond to this treatment.
We aim to investigate if renal function in patients with cirrhosis and ascites can be improved by combining terlipressin with dobutamin - a drug that increases cardiac function. Dobutamin increases cardiac output primarily by increasing heart rate.

Protection of trial subjects:

This study was performed according to International Council for Harmonisation: Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki and approved by the Committee of Health Research Ethics in the Region of Southern Denmark.
External monitoring was performed by Good Clinical Practice Unit at Odense University Hospital.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2013
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	Denmark: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	25
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From June 2014 to May 2018 we screened patients with cirrhosis and ascites in the outpatient clinic at Odense University Hospital, 46 of which were eligible for the study.

Pre-assignment

Screening details:

We screened 245 patients with cirrhosis and ascites in the outpatient clinic at Odense University Hospital, 46 of which were eligible for the study. Twenty-seven agreed to participate and were included and randomised. Two participants experienced an adverse event between inclusion and the investigation, and they did not receive any study drugs

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dobutamine + Terlipressin

Arm description:

Dobutamine followed by terlipressin

Arm type	Experimental
Investigational medicinal product name	Dobutamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Dobutamine was infused continuously starting at 10 µg/kg body weight/min and increased every 3 minutes by 10 µg/kg body weight/min until reaching the targeted heart rate or a max dose of 40 µg/kg body weight/min. Target heart rate was a 50% increase of resting heart rate or a maximum heart rate of 120 beats per minute.

Arm title	Terlipressin + Dobutamin

Arm description:

terlipressin followed by dobutamine

Arm type	Experimental
Investigational medicinal product name	Terlipressin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Terlipressin 2 mg in 10 mL (9 mg/mL) NaCl solution was administrated as a bolus injection over 2 min.

Dobutamine was infused continuously starting at 10 µg/kg body weight/min and increased every 3 minutes by 10 µg/kg body weight/min until reaching the targeted heart rate or a max dose of 40 µg/kg body weight/min. Target heart rate was a 50% increase of resting heart rate or a maximum heart rate of 120 beats per minute.

Arm title	Placebo

Arm description:

Placebo

Arm type	Experimental
Investigational medicinal product name	Terlipressin + Dobutamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous bolus use , Intravenous drip use

Dosage and administration details:

Terlipressin 2 mg in 10 mL (9 mg/mL) NaCl solution was administrated as a bolus injection over 2 min.

Dobutamine was infused continuously starting at 10 µg/kg body weight/min and increased every 3 minutes by 10 µg/kg body weight/min until reaching the targeted heart rate or a max dose of 40 µg/kg body weight/min. Target heart rate was a 50% increase of resting heart rate or a maximum heart rate of 120 beats per minute.

Number of subjects in period 1	Dobutamine + Terlipressin	Terlipressin + Dobutamin	Placebo
Started	10	10	5
Completed	10	10	5

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	25	25	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
58.8 (9.9)			
Units: years			
arithmetic mean	59		
standard deviation	± 10	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	17	17	

End points

End points reporting groups

Reporting group title	Dobutamine + Terlipressin
Reporting group description: Dobutamine followed by terlipressin	
Reporting group title	Terlipressin + Dobutamin
Reporting group description: terlipressin followed by dobutamine	
Reporting group title	Placebo
Reporting group description: Placebo	
Subject analysis set title	Glomerular filtration rate
Subject analysis set type	Full analysis
Subject analysis set description: Cr-EDTA measurement	

Primary: Glomerular filtration rate

End point title	Glomerular filtration rate
End point description:	
End point type	Primary
End point timeframe: 240 minutes	

End point values	Dobutamine + Terlipressin	Terlipressin + Dobutamin	Placebo	Glomerular filtration rate
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	10	5	25[1]
Units: ml				
arithmetic mean (confidence interval 95%)	-10.4 (-25.5 to 4.8)	18.8 (5.7 to 32.0)	9.0 (-11.1 to 29.2)	0.0 (-1.0 to 1.0)

Notes:

[1] - --

Attachments (see zip file)	Screenshot 2021-02-06 at 02.27.54.png

Statistical analyses

Statistical analysis title	mixed model
Comparison groups	Dobutamine + Terlipressin v Terlipressin + Dobutamin v Placebo v Glomerular filtration rate

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1 day

Adverse event reporting additional description:

We observed two SAEs that developed after signing the informed consent but in both cases the participants were excluded before receiving the study drugs. These are not included in following report

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Dobutamine
Reporting group description: -	
Reporting group title	Terlipressin
Reporting group description: -	
Reporting group title	Terlipressin and Dobutamine
Reporting group description: -	

Serious adverse events	Dobutamine	Terlipressin	Terlipressin and Dobutamine
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 20 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Dobutamine	Terlipressin	Terlipressin and Dobutamine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	15 / 20 (75.00%)	7 / 10 (70.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 20 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
hypotension			
subjects affected / exposed	2 / 10 (20.00%)	0 / 20 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Palpitations			

subjects affected / exposed	2 / 10 (20.00%)	0 / 20 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
Dyspnoea			
subjects affected / exposed	2 / 10 (20.00%)	0 / 20 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Head discomfort			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	2 / 10 (20.00%)	0 / 20 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	15 / 20 (75.00%)	0 / 10 (0.00%)
occurrences (all)	0	15	0
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	5 / 20 (25.00%)	5 / 10 (50.00%)
occurrences (all)	1	5	5
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	2 / 20 (10.00%)	2 / 10 (20.00%)
occurrences (all)	0	2	2

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.

The treatment duration was relative short compared with treatment of AKI-HRS in clinical practice. Based on the results from present study, we cannot conclude that changes in vasoactive substances and their subsequent effects on renal perfusion were

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31841026