Clinical trial results:
Ensayo clínico aleatorizado y controlado con paracetamol de la seguridad renal de metamizol en el tratamiento de pacientes cirróticos con y sin ascitis
(Randomized Controlled Clinical Trial to study the renal safety of acetaminophen vs metamizol in the treatment of cirrotic patients with or without ascitic decompensation)

Summary

EudraCT number	2007-006232-58
Trial protocol	ES
Global end of trial date	29 October 2010

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	UFC-08/01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Instituto de Salud Carlos III
Sponsor organisation address	C/ Sinesio Delgado, 4 (entrada por Avda. Monforte de Lemos, 5), Madrid, Spain, 28029
Public contact	Pedro Zapater – Hospital General Universitario de Alicante , Hospital General Universitario de Alicante, 34 965913868, zapater_ped@gva.es
Scientific contact	Pedro Zapater – Hospital General Universitario de Alicante , Hospital General Universitario de Alicante, 34 965913868, zapater_ped@gva.es

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	15 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 October 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of therapeutic doses of dipyrone and acetaminophen used for short periods of time (72 hours) on renal function (glomerular filtration rate evaluated by serum cystatin c) of patients with cirrhosis with or without ascites

Protection of trial subjects:

Patients requiring additional analgesic treatment, those developing a serious adverse event or suffering an intercurrent disease that in the opinion of the investigator would compromise patient safety were withdrawn from the study.

Background therapy:

Beta-blockers (40% of patients) and diuretics (50% of patients)

Evidence for comparator:

Acetaminophen and dipyrone are among the most commonly used analgesic and antipyretic drugs worldwide, either on prescription or on over-the-counter. Case–control studies have shown that acetaminophen was the most common analgesic used by patients with cirrhosis, and this use at therapeutic doses was not associated with an increased risk of being hospitalized for liver-associated events. While acetaminophen is a very weak inhibitor of COX activity, dipyrone may cause a more pronounced decline in prostaglandin synthesis and therefore could be associated with a greater risk of renal damage in patients with cirrhosis in which renal blood flow is dependent on prostaglandin production.

Actual start date of recruitment	12 May 2008
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	Spain: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	23
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed in patients with cirrhosis without renal injury followed in the Liver Unit of the University General Hospital of Alicante (Spain) that required analgesic or antipyretic treatment from May 2008 to October 2010

Pre-assignment

Screening details:

Patients with mild to moderate ascites (ascites grade 1 or 2) were included if they could be treated effectively with medical management. Seven patients were included during an episode of AF decompensation. The 80% of patients in both groups received the study treatment for mild–moderate pain and 20% as antipyretic.

Period 1

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

Blinding implementation details:

This was an observer-blind study

Arms

Are arms mutually exclusive?	Yes
Arm title	Acetaminophen

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Acetaminophen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500 mg t.i.d.

Arm title	Metamizole

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Metamizole
Investigational medicinal product code	
Other name	Dipyrone
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

575 mg t.i.d.

Number of subjects in period 1	Acetaminophen	Metamizole
Started	15	15
Completed	15	14
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Acetaminophen
Reporting group description: -	
Reporting group title	Metamizole
Reporting group description: -	

Reporting group values	Acetaminophen	Metamizole	Total
Number of subjects	15	15	30
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	12	23
From 65-84 years	4	3	7
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	51.8	56.5	
standard deviation	± 9.8	± 13.5	-
Gender categorical Units: Subjects			
Female	2	3	5
Male	13	12	25
Cause of cirrhosis Units: Subjects			
alcohol	12	13	25
viral	3	2	5
Child-Pugh score Units: arbitrary units			
arithmetic mean	6.7	7.0	
standard deviation	± 1.7	± 1.5	-
Estimated glomerular filtration rate (eGFR)			
calculated from cystatin C values using the Grubb cystatin C equation.			
Units: ml/min/(1.73 m2)			
arithmetic mean	77.22	79.88	
standard deviation	± 33.39	± 51.95	-
Serum Cystatin C Units: mg/L			
arithmetic mean	1.2	1.2	
standard deviation	± 0.5	± 0.6	-

End points

End points reporting groups	
Reporting group title	Acetaminophen
Reporting group description: -	
Reporting group title	Metamizole
Reporting group description: -	

Primary: Serum cystatin C at 72 hours

End point title	Serum cystatin C at 72 hours
End point description:	
End point type	Primary
End point timeframe: 72 hr	

End point values	Acetaminophen	Metamizole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: mg/L				
arithmetic mean (standard deviation)	1.2 (± 0.4)	1.3 (± 0.5)		

Statistical analyses

Statistical analysis title	Differences mean serum cystatin C values at 72 hr
Comparison groups	Acetaminophen v Metamizole
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	Wilcoxon (Mann-Whitney)

Secondary: Serum cystatin C at 48 hours

End point title	Serum cystatin C at 48 hours
End point description:	
End point type	Secondary
End point timeframe: 48 hr	

End point values	Acetaminophen	Metamizole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: mg/l				
arithmetic mean (standard deviation)	1.3 (± 0.6)	1.3 (± 0.6)		

Statistical analyses

Statistical analysis title	Differences mean serum cystatin C values at 48 hr
Comparison groups	Acetaminophen v Metamizole
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	Wilcoxon (Mann-Whitney)

Secondary: Serum PGE2 at 72 hours

End point title	Serum PGE2 at 72 hours

End point description:

End point type	Secondary

End point timeframe:

72 hr

End point values	Acetaminophen	Metamizole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	450 (400 to 500)	700 (550 to 850)		

Statistical analyses

Statistical analysis title	Differences serum PGE2 at 72 hr
Comparison groups	Acetaminophen v Metamizole

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: PGE2 urine levels at 72 hr

End point title	PGE2 urine levels at 72 hr

End point description:

End point type	Secondary

End point timeframe:

72 hr

End point values	Acetaminophen	Metamizole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	500 (200 to 530)	1000 (600 to 1100)		

Statistical analyses

Statistical analysis title	Differences Urine PGE2 at 72 hr
Comparison groups	Acetaminophen v Metamizole
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Serum 6-keto-PGF1 at 72 hr

End point title	Serum 6-keto-PGF1 at 72 hr

End point description:

End point type	Secondary

End point timeframe:

72 hr

End point values	Acetaminophen	Metamizole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	150 (125 to 160)	300 (250 to 450)		

Statistical analyses

Statistical analysis title	Differences serum 6-keto-PGF1 at 72 hr
Comparison groups	Acetaminophen v Metamizole
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Urine 6-keto-PGF1 at 72 hr

End point title	Urine 6-keto-PGF1 at 72 hr

End point description:

End point type	Secondary

End point timeframe:

72 hr

End point values	Acetaminophen	Metamizole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	750 (550 to 900)	1350 (1150 to 1400)		

Statistical analyses

Statistical analysis title	Differences urine 6-keto-PGF1 at 72 hr
Comparison groups	Acetaminophen v Metamizole

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

adverse events were recorded during the 72 hours of oral administration treatment and until 7 days after end drug administration

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	2019AB

Reporting groups

Reporting group title	Acetaminophen
Reporting group description: -	
Reporting group title	Metamizole

Reporting group description: -

Serious adverse events	Acetaminophen	Metamizole	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
Ascites	Additional description: One patient treated with dipyrone required a large-volume paracentesis (6.5 l) 24 hr after inclusion		
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Acetaminophen	Metamizole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	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.

Finally, it was not possible to recruit the number of patients initially expected of 40 necessary to analyze differences based on the presence or absence of ascites between the two treatments.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25154757