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Cisatracurium generic vs original brand-name

Submission date 08/10/2017	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 30/10/2017	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 21/11/2023	**Condition category** Respiratory	[_] Individual participant data

Plain English summary of protocol

Background and study aims
Several diseases may induce severe acute respiratory failure. This life-threatening condition may be stabilised with mechanical ventilation (a machine that inserts a tube in provide air to the lungs). In some patients with complicated breathing problems require sedation and paralysis (being put to sleep). This is usually done by being given neuromuscular blocking agents (NMBAS) a type of anaesthesia that puts the patients under sedation and paralysis. Recently the introduction of Cisatrex®, the generic of the brand name Nimbex®, provided an opportunity to substitute cisatracurium to other NMBAs. Because of the physicians' reluctance to prescribe generics and all the controversies surrounding, authors hypothesized that a proof of safety and efficacy of Cisatrex® compared to its original brand-name could be of an invaluable support to reassure the physician while using Cisatrex®. The aim of this study is to compare the efficacy and tolerance of the two different paralysis agents Nimbex® and Cisatrex®.

Who can participate?
Adults aged 18 and older who are admitted to the ICU with severe acute respiratory failure with severe hypoxemia.

What does the study involve?
After a short period of stabilization under optimal analog-sedation. Patients are assigned randomly to receive one of the two drugs intravenously. They are subsequently monitored for the efficacy by a neurostimulator each 5 minutes for 3 hours period each drug.

What are the possible benefits and risks of participating?
There are no direct benefits with participation. There are risks with many medical procedures, however the present study deals with rottenly recommended drugs that are efficient and well tolerated. In several cases this may induce reversible cardiocirculatory disorder such as bradycardia or hypotension.

Where is the study run from?
Farhat Hached University Hospital (Tunisia)

When is the study starting and how long is it expected to run for?
July 2016 to March 2017

Who is funding the study?
Farhat Hached University Hospital (Tunisia)

Who is the main contact?
Professor Mohamed Boussarsar

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
01072016

Study information

Scientific Title
Compared efficacy and tolerance of the neuromuscular blockade induced by original brand-name (Nimbex®) and generic (Cisatrex®) of cisatracurium in mechanically ventilated critically ill patients: A crossover double-blind randomized study

Study objectives
Cisatracurium original brand-name (Nimbex®) is better than his generic (Cisatrex®).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Medical Ethics' and Research Committee of Farhat Hached University Hospital in Sousse, 01/07/2016, ref: IRB registration number assigned by OHRP: IRB00008931

Primary study design
Interventional

Study design
Crossover double-blind randomised trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Patients admitted to ICU, under optimized sedation and ventilation, for hypoxemic acute respiratory failure with a PaO2/FIO2 < 200 and requiring paralysis to improve gas exanges and offset patient-ventilator asynchronies.

Interventions
Participants admitted to the ICU under optimised sedation and ventilation for hypoxemic acute respiratory failure a PaO2/FIO2 < 200 and requiring paralysis to improve gas exanges and offset patient-ventilator asynchronies.

Neuromuscular blockade is induced respectively by the two cisatracurium forms during two successive periods, separated by a one-hour washout period. Neuromuscular function was monitored by a calibrated train-of-four (TOF) stimulation.

A pre-protocol test patient is performed in order to define the minimum delay for paralysis, recovery time, better intervals for monitoring and to train the co-investigator residents (NF, JA & SR) to monitor the different parameters and to get familiar with the form designed to collect these parameters. The same co-investigators monitored all the included patients to ensure the maximal consistency and homogeneity of the collected data.

After a one hour of the stabilisation period and referring to the current state-of-the-art targeting respiratory and hemodynamic stability, participants arre randomized to a double-blind inclusion for the order of infusion of the two products under study, based on the random table. The principal investigator (MB) implemented the random allocation sequence, enrolled and assigned participants to interventions. He pre-prepared the assigned drug and concealed the sequence until all interventions were performed. Co-investigators (NF, JA & SR), participants and care providers were blinded after assignment to interventions. Participants are randomised to receiving either one of two paralysis agents, either Nimbex® and Cisatrex®.

In all studied patients it was ensured within the study period that the patients displayed no significant patient-ventilator asynchrony.

Paralysis depth is monitored by TOF.

A short period of stabilization under effective analgo-sedation as assessed by RSS was performed.

The neuromuscular blockade drug is initiated, a continuous infusion of cisatracurium is started at a dose of 0.06mg.kg-1.h-1 and increased in increments of 0.03mg.kg-1.h-1 every 30min to reach and sustain a TOF at 2/4, with a maximum study time limited to two hours and a maximum dose of 0.18mg.kg-1.h-1 as assessed by the pre-protocol test patient and The 2002 “Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient” updated in 2016.

During this same period, the following parameters were measured at the same intervals every five minutes (TOF, heart rate, systolic and diastolic blood pressures, and ventilatory parameters). The infusion of the first product is stopped after two hours to allow the elimination of the first active paralysis agent before the infusion of the second (wash-out period).

The one-hour wash-out period is chosen based on the pharmacodynamic properties of the product which suggest that its elimination would be rapid due to its metabolism by Hofmann elimination and as suggested by several studies which assessed a recovery time ranging from 45min to 68min. The wash-out period is checked to be quite sufficient to recover a TOF of 4/4 as demonstrated in the pre-protocol test patient. This same period would serve to monitor the recovery kinetics (recovery time) of the first product. At the end of the wash-out period, the second product was then introduced. Its effect and tolerance (hemodynamic tolerance and drug interaction) were monitored according to the same protocol.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Cisatracurium original brand-name (Nimbex®) Cisatracurium generic (Cisatrex®)

Primary outcome(s)
1. Paralysis delay is measured using the train of four (TOF) at baseline and each 5 minutes time interval till 2 hours
2. Recovery time is measured using the TOF after stopping paralysis agent and each 5 minutes time interval till 1 hour

Key secondary outcome(s)
1. TOF variability is measured using the changes of TOF responses at each interval time within the paralysis period and recovery time
2. Hemodynamic tolerance is measured using the variation in heart rate above 30% of the baseline value and/or a significant drop of systolic and/or diastolic blood pressures above 30% of the baseline values at each 5 minutes
3. Tolerance is measured using Drug interactions mainly with antibiotics, monitored within the 6 hours protocol period

Completion date
31/03/2017

Eligibility

Key inclusion criteria
1. Patients admitted to the ICU with severe acute respiratory failure with severe hypoxemia (ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) < 200),
2. Put under invasive mechanical ventilation with important patient-ventilator asynchrony and requiring paralysis despite deep analgo-sedation as assessed by RSS
3. Aged 18 and older

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
22

Key exclusion criteria
1. Patients with history of allergy to cisatracurium
2. Malignant hyperthermia
3. Pregnancy
4. Neuromuscular disorders

Date of first enrolment
01/07/2016

Date of final enrolment
31/03/2017

Locations

Countries of recruitment
Tunisia

Study participating centre
Farhat Hached University Hospital
Medical Intensive Care Unit
1st, Rue Ibn Al Jazzar
Sousse
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4000

Sponsor information

Organisation

Farhat Hached University Hospital

ROR
https://ror.org/0059hys23

Funder(s)

Funder type
University/education

Funder Name
Farhat Hached University Hospital

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		15/12/2020	21/11/2023	Yes	No
Participant information sheet		13/10/2017	01/04/2019	No	Yes
Protocol file			02/04/2019	No	No