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

Short running title: Cisatracurium generic vs original brand-name

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Introduction

Generic drugs are made to be chemically and therapeutically equivalent to the original brand name but they have the advantage of being significantly cheaper because they are allowed to enter the market after the original brand's patent has expired[1]. To control costs, many payers/providers have encouraged substitution of inexpensive bioequivalent generic versions of these drugs[2]. In the last 30 years, several controversies concerning

the generic drug legislation have arisen. Recent literature reviews demonstrated that physicians, pharmacists and people hold negative perceptions and knowledge of generic medicines[3-7].

Neuromuscular Blocking Agents (NMBAs) are some of the drugs usually used in intensive care and are represented by a variety of products administered in patients with altered respiratory system mechanical properties such as Acute Respiratory Distress Syndrome (ARDS), status asthmaticus or severe acute exacerbation of COPD (AE/COPD)[8]. Only several products exhibit the criteria of the so called ideal NMB which are influenced by required speed of onset and offset, cardiovascular stability, possible accumulation of the NMBA metabolites, elimination routes, and cost [9, 10]. One of these products is cisatracurium which is a nondepolarizing NMBA, a benzylisoquinolinium like atracurium, cisatracurium, doxacurium, and mivacurium)[11]. Cisatracurium is the R-cis-R-cis isomer of atracurium, one of ten stereoisomers that constitute the drug[12, 13].

Since its introduction in the early 2000, cisatracurium was widely used in the ICUs (Intensive Care Units) in developed countries. However, it generated a relatively high cost[14]. Here and there several cisatracurium generics have been developed to respond to this need. Cisatracurium became of relatively frequent use in critical care, taking advantage of its higher potency and less side effects[15]. Payen et al.[16], in an observational study of 1381 patients throughout their first six days in 44 ICUs, demonstrated that NMBAs were used in 9% of patients on day two, 7% on day four and 5% on day six. The exact distribution of cisatracurium use was not detailed. However, cisatracurium was reported as accounting for 70% of NMBA use. In developing countries, such as North-African ones, cisatracurium use remained rather sporadic[4]. 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 involving generic drugs legislation especially the approval process, issues of bioequivalence and corruption that have arisen at that time, 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 intensivist while using Cisatrex®.

The aim of the present study was to compare efficacy and tolerance of two marketed forms, original brand-name (Nimbex®) and generic (Cisatrex®) of continuous cisatracurium-induced paralysis in hypoxemic ventilated patients.

Material and methods

It was a crossover randomized double-blind physiological study conducted in an 8-bed Medical ICU in Farhat Hached Hospital in Sousse, Tunisia, from February 2015 to March 2016, which compared neuromuscular blockade efficacy and tolerance induced respectively by brand-name (Nimbex®) and generic (Cisatrex®) of continuous cisatracurium infusion during two successive periods.

Following the approval of the Local Medical Ethics' and Research Committee of Farhat Hached University Hospital in Sousse, Tunisia, and written informed consent from family members or surrogates, patients admitted to the ICU with severe acute respiratory failure with severe hypoxemia (ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) < 200), put under invasive mechanical ventilation with important patient-ventilator asynchrony and requiring paralysis despite deep analgo-sedation as assessed by RSS[17] were enrolled. Patients with history of allergy to cisatracurium, malignant hyperthermia, pregnancy or neuromuscular disorders, were not included in the present study.

Sample size

It was assessed as the number of patients needed to demonstrate a difference of 10min in the mean delay to reach a defined objective of paralysis assessed by a Train-Of-Four (TOF) ≤ 2.

Given: μ1= mean delay for Nimbex® to reach TOF=2/4, assessed at 70mn after a trial on a pre-protocol patient. μ2= mean delay for Cisatrex® set as 60mn as approximately reported in literature[18]. $d=\mu_1-\mu_2=70-60=10mn$. σ=10mn=Standard deviation. Thus, variance is $s^2=100mn^2$ (variable distribution was normal and variances were equal). β=0.1 (Thus power of the study is 90%).

According to normal distribution: $\alpha = 5\%$; $Z_{(1-\sigma)} = 1.96$; $\beta = 10\%$; $Z_{(1-\beta)} = 1.28$

The sample size of each group was estimated according to the following formula[19]:

$N= [(Z_{(1-\sigma)} + Z_{(1-\beta)})^2 (\sigma^2+ \sigma^2)]/d^2 = [((1.96+1,28)^2)(10^2+10^2)] / 10^2 = 22$ patients in each group.

The total sample size (two groups) was estimated at 44 patients.

Taking into account the crossover design of the present study the number needed to treat was assessed at 22 patients.

Data collection

All data regarding patients' characteristics at ICU admission (demographic characteristics, underlying diseases, diagnosis at admission, severity of illness, therapeutic characteristics) were collected from the charts. Chart abstractors were well trained residents. Clinical, physiological, therapeutic and outcome characteristics were collected at baseline after a short period of respiratory and hemodynamic stabilization. An explicit protocol was used to precise all needed definitions and to ensure uniform handling of the collected and the measured data. A data form was designed for this purpose.

Studied medications

Cisatracurium is a non-depolarizing agent that acts as a competitive antagonist of nicotinic receptors, blocking the action of acetylcholine[13]. It's a benzylisoquinolinium that has effect as a neuromuscular-blocking drug (or skeletal muscle relaxant) like atracurium, doxacurium and mivacurium[11, 13].

Nimbex®, the brand name of cisatracurium 2mg/ml, is a trademark of the Glaxo group of companies, AbbVie Corporation licensed use.

Cisatrex®, producted by MédiS, 10mg/5ml, was first-to-market the generic of cisatracurium in Tunisia.

TOF application device

TOF monitor (Innervator NS252FBB, Fisher-Paykel Health Care, New Zealand) was applied to test the changes of the contraction of the thumb (number and height) in response to a peripheral neuro-stimulator of the ulnar nerve with a stimulus intensity set at 60mA. The target of neuromuscular block depth induced by neuromuscular blockade drugs was set at two responses to the TOF in order to obtain the desired clinical effect[20-22].

Protocol description

A pre-protocol test patient was 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 stabilization period and referring to the current state-of-the-art targeting respiratory and hemodynamic stability, patients were 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.

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

Paralysis depth was monitored by TOF[23].

A short period of stabilization under effective analgosedation 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[22, 24].

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 was chosen based on the pharmacodynamic properties of the product which suggest that its elimination would be rapid due to its metabolism by Hofmann elimination[25] and as suggested by several studies which assessed a recovery time ranging from 45min to 68min[18, 21, 26-28]. The wash-out period was 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.

Definitions

Efficacy

Paralysis delay: It is the time needed from intravenous infusion of cisatracurium onset to reach a TOF of 2/4. It was also assessed the respective differences at each time intervals from the cisatracurium intravenous infusion onset until 120min.

Recovery time: The time needed to reach a TOF of 4/4 after stopping the cisatracurium intravenous infusion. For commodity reasons, authors rather assessed the respective differences at each time intervals from the cisatracurium intravenous infusion cessation until 60min, especially the between-two studied drugs' TOF difference at 60min of the recovery period.

TOF variability: It was defined by the changes in the TOF responses between the different interval times within the paralysis period and recovery time. This would appreciate the stability of the paralysis or decurarization over time[9].

Tolerance

Hemodynamic tolerance was defined by a significant 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.

Drug interactions mainly with antibiotics was also used to evaluate tolerance.

Used scales

SAPS II (Simplified AcutePhysiology Score): was used to measure the severity of disease for patients admitted to the intensive care unit[29].

Ramsay sedation scale (RSS): The RSS was the first scale to be defined to monitor the depth of sedation in the critically ill patients[17].

Statistical analysis

Variable distribution analysis was tested using the Kolmogrov-Smirnov test. Results were expressed as mean±standard deviation (SD) (95%CI, confidence intervals) when the distribution was normal and variances were

equal. If not, results were expressed by their medians (IQR, interquartile range). Qualitative data were expressed by their relative proportions.

Time delays were compared between the two studied drugs and at each time intervals by applying repeated measures analysis of variance (ANOVA). Differences were tested meaning two-tailed "t" paired test.

Statistical seizure and analyses were performed using the statistical software package SPSS20.0. The p values less than 0.05 were considered as statistically significant.

Declarations

- **Ethics approval and consent to participate**

The the Local Medical Ethics' and Research Committee of Farhat Hached University Hospital in Sousse, Tunisia, issued a favorable opinion and approved the study protocol under the reference number, 0107/2016. (see ethics approval and consent to participate form as supplementary material)

All family members or surrogates of each participant gave a written informed consent to participate to the study.

- **Consent for publication**

Not applicable

- **Availability of data and material**

Not applicable

- **Competing interests**

None

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- **Authors' contributions**

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data
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