Egyptian Journal of Anaesthesia (2014) **30**, 197–202

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

Cisatracurium dose–response relationship in patients with chronic liver disease

Mohamed Z. Ali [a,*], Reeham S. Ebied [a], Maha A. Atallah [a], Hossam H. El Sabea [a], Amr Abd El Monaem [b], Mounis A. Abo-Sedira [a], Inas Kamel [b]

[a] *Department of Anesthesia, Theodor Bilharz Research Institute, Giza, Egypt*
[b] *Department of Anesthesia, Faculty of Medicine, Cairo University, Cairo, Egypt*

Received 2 August 2013; revised 8 October 2013; accepted 27 October 2013
Available online 23 November 2013

KEYWORDS

Cisatracurium;
Dose–response curve;
Chronic liver disease

Abstract *Objective:* Cisatracurium is approximately 3 times more potent than atracurium, devoid of histamine release and cardiovascular side effects and mainly eliminated by Hofmann degradation. Patients with liver disease exhibit abnormal response to most of muscle relaxants. This study was designed to evaluate the dose–response of cisatracurium in patients with mild–moderate liver impairment in comparison with healthy subjects.

Methods: Eighty ASA physical status I–II patients of both sexes, scheduled for elective surgical procedures under general anesthesia, were divided according to their preoperative hepatic status and laboratory investigations into two groups; Group I (control group with normal liver functions, $n = 40$) and Group II (Liver dysfunction group, Child-Pugh Score A or B, $n = 40$). The dose–response curve was constructed, ED_{50} and ED_{95} were estimated.

Results: The preoperative laboratory parameters showed statistically significant differences between the two groups regarding serum albumin, total bilirubin, ALT, AST, PT, PC and INR. The operative data showed statistically insignificant difference between the two groups regarding the 1st dose response ($p = 0.152$), the estimated ED_{80} ($p = 0.886$) and the calculated 2nd dose ($p = 0.886$) and statistically significant differences between the two groups regarding the 2nd dose response ($p = 0.006$), the measured ED_{50} ($p = 0.010$) and the measured ED_{95} ($p = 0.001$). In conclusion, the measured ED_{50} and ED_{95} through two-dose dose–response curve technique were clinically insignificant from using the single-dose technique. The dose–response curve of cisatracurium in patients with chronic liver disease was clinically insignificant in comparison with healthy subjects.

* Corresponding author. Tel.: +20 1111113115; fax: +20 235408125.
E-mail addresses: zeidanoma@hotmail.com, zeidanoma@yahoo.com (M.Z. Ali).

Peer review under responsibility of Egyptian Society of Anesthesiologists.

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1. Introduction

Introduction of skeletal muscle relaxants into clinical anesthesia practice has not only made general anesthesia (GA) more effective but also allowed sophisticated techniques to be accomplished. The use of muscle relaxants in controlled

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mechanical ventilation and management of respiratory failure extend its use in the intensive care unit. Since the first use of *Curare*, many muscle relaxants have been discovered and studied in an attempt to meet the requirements of an ideal muscle relaxant [1].

Cisatracurium was found to be approximately three times more potent than atracurium, with no histamine release or cardiovascular side effects. The duration of action is about 45–50 min compared to atracurium which is 35–40 min [2]. Hofmann degradation has a greater role in the elimination of cisatracurium than that of atracurium [3].

Patients with chronic liver disease exhibit an abnormal response to the effect of most of muscle relaxants. The expanded extracellular fluid compartment leads to increase in volume of distribution of the highly ionized neuromuscular blockers. Hence an apparent resistance is usually observed in the form of increased dose requirement which when administered may last longer due to the associated delayed elimination in this group of patients [4,5].

The dose–response curves could be used to plot the results of many kinds of experiments. The *X*-axis plots concentration of a drug (dose). The *Y*-axis is the response. The shape of dose–response curves depends on which drug is used and which response is measured as in Fig. 1. The standard dose–response curves is defined by four parameters: the *base response* (Bottom), the *maximum response* (Top), the *Slope* and the Concentration that provokes a response half-way between the baseline and the maximum (EC_{50}) [6].

2. Subjects and methods

This study was approved by the Theodor Bilharz Research Institute Ethical Committee. All patients provided written informed consents. This prospective observational study included 80 ASA physical status I–II adult patients of both sexes scheduled for elective general surgical or urological procedures under general anesthesia. Elderly, morbidly obese, pregnant patients and those with malignancies were excluded. Also patients receiving drugs affecting neuromuscular blockers as anticonvulsants, antihistaminics, antibiotics, diuretics and antidepressants were excluded.

Patients were allocated into one of two equal groups according to their preoperative hepatic status and laboratory investigations; Group I (control group, with normal liver functions, $n = 40$) and Group II (Liver dysfunction group, Child-Pugh Score A or B, $n = 40$) (Table 1).

All the patients were assessed preoperatively regarding liver function tests (serum total bilirubin, total proteins, albumin and glubulins, AST, ALT, Alkaline phosphatase, prothrombin time and concentration and INR), kidney function tests (blood urea and serum creatinine), fasting blood glucose and complete blood count.

Standard continuous monitoring including 5-lead ECG, NIBP, S_pO_2, $P_{ET}CO_2$ and anesthesia gas analyzing system (Dräger infinity Kappa, Dräger Medical Corporation, Germany) was attached to all patient. Neuromuscular monitoring using TOF-Guard (INMT Organon Teknika NV-Belgium) was also used.

Without any premedication, preoxygenation with 100% O_2 was administered via face mask before induction of anesthesia for at least five deep breaths. Anesthesia was then induced using I.V. fentanyl 2 μg kg^{-1} and I.V. 2.5% thiopentone sodium 5–7 mg kg^{-1}.

Patients were then ventilated manually via facemask with isoflurane 1% (end-tidal concentration) in O_2: Air mixture ($F_iO_2 = 0.6$) for 3 min. A Laryngeal Mask Airway Classic (LMA™, Intavent Orthofix, Maidenhead, UK) was then inserted (size 3 for females and 4 for males). Ventilation was assisted or controlled to maintain normocapnia ($P_{ET}CO_2$ = 36–40 mmHg). Anesthesia was then maintained with the same gaseous mixture plus fentanyl 50 μg I.V. increments given as clinically indicated.

While hemodynamic stability was achieved, the ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 m s duration; delivered in a train-of-four (TOF) sequence at 2 Hz repeated every 15 s. An acceleration Piezoelectric transducer was fastened to the volar surface of the distal phalanx of the thumb contralateral to the site of I.V. infusion. The arm was immobilized in splint. Free movement during evoked thumb adduction was ensured by fixation of the extended four ulnar fingers by an elastic bandage or adhesive tape. Registration of evoked thumb acceleration, in response to adductor pollicis contractions was carried out using TOF-Guard. After calibration of TOF-Guard device and a stable TOF-response for a minimum of 3–5 min was reached, the study was started and all information were derived from acceleration transducer recorded on a memory card and subsequently a computer print-out was obtained using TOF-Guard reader software.

According to the method recommended by Kopman et al. (to get the dose–response curve from two doses), a small initial dose (10 μg kg^{-1}) of cisatracurium was given and the neuromuscular blockade was monitored and recorded until no further change is observed. This would constitute the 1st dose–response point. This value used to draw the patient's measured dose response curve, from that curve the estimated ED_{80} was identified. The difference between the 1st dose which already given to the patient and the estimated ED_{80} would

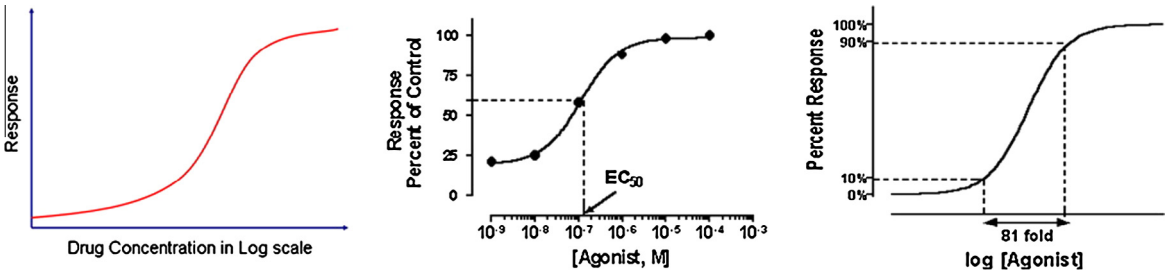

Figure 1 The dose–response curves.

Table 1 Child-Pugh Score.

Measure	1 Point	2 Points	3 Points
Total bilirubin, μmol/l (mg/dl)	< 34 (< 2)	34–50 (2–3)	> 50 (> 3)
Serum albumin, g/l	> 35	28–35	< 28
PT INR	< 1.7	1.7–2.3	> 2.3
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medications)	Grade III–IV (or refractory)
Points	Class	One year survival	Two year survival
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

indicate the supplemental dose of cisatracurium that when administered should produce 80% blockade.

Following the administration of the supplemental dose, the neuromuscular response was observed until maximum block was achieved. This would constitute the second dose–response point. From the two dose–response points the dose–response curve was constructed (knowing that the slopes of all muscle relaxants are nearly identical and equal to 4.75). This formed the two-dose dose–response curve for each individual. From that curve the ED_{50} and ED_{95} for each individual was estimated. The ED_{50} and ED_{95} for each group of subject were calculated and statistically analyzed.

After completing the study, tracheal intubation and controlled mechanical ventilation was achieved. At the end of surgery, reversal of the neuromuscular blockade was established and the patient was extubated.

Preoperative laboratory parameters in addition to 1st dose–response (degree of suppression), estimated ED_{80}, calculated 2nd dose, 2nd dose–response (degree of suppression), measured ED_{50} and measured ED_{95} were recorded in both groups.

2.1. Statistical methods

Data were analyzed using SPSS version 15 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean ± standard deviation (Mean ± SD). Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using independent sample *t*-test. A p-value < 0.05 was considered significant.

3. Results

There was no statistical significant difference between the two study groups regarding demographic data (Table 2). Regarding the preoperative laboratory parameters (Table 3), there was no significant difference between the two groups regarding the levels of hemoglobin concentration ($p = 0.534$), fasting blood glucose ($p = 0.276$), blood urea ($p = 0.525$), serum creatinine ($p = 0.819$) and total plasma proteins ($p = 0.135$). However, there were statistical significant differences between the two groups regarding serum albumin concentration ($p = 0.001$), total bilirubin level ($p = 0.001$), ALT ($p = 0.001$), AST ($p = 0.001$), PT ($p = 0.001$) PC ($p = 0.001$), and INR ($p = 0.001$).

There was no statistical significant difference between the two groups regarding the 1st dose response (degree of suppression) which ranges from 5.75% to 6.65% in the hepatic and control groups, respectively ($p = 0.152$). Similarly, the estimated ED_{80} was comparable in the two groups; 15.13–16.59 μg kg^{-1} in the control group and 15.13–16.98 μg kg^{-1} in the hepatic group ($p = 0.886$). The calculated 2nd dose in the control group (5.13–6.59 μg kg^{-1}) was not significantly different from that of the hepatic group (5.13–6.98 μg kg^{-1}) ($p = 0.886$).

However, the measured response to the calculated 2nd dose was significantly higher in the control group (32.00–46.00 μg kg^{-1}) than the hepatic group (32.00–42.00 μg kg^{-1}) ($p = 0.006$). The measured ED_{50} (15.13–21.39 μg kg^{-1}) in the hepatic group was significantly higher than the corresponding values in the control group (16.59–21.37 μg kg^{-1}) ($p = 0.010$). The measured ED_{95} (57.54–100 μg kg^{-1}) in the hepatic group was significantly higher than the corresponding values in the control group (31.62–79.43 μg kg^{-1}) ($p = 0.001^{*}$). Table 4 and Figs. 2–4 show the operative variables in the study groups.

4. Discussion

Results of the present study demonstrates no significant difference in the degree of suppression produced by the first dose of cisatracurium in liver disease patients compared to control

Table 2 Patients' characteristics in the two groups of the study.

Variables	Control group ($n = 40$)	Patient group ($n = 40$)	p Value
Age (yrs)	43.9 ± 11.3	48.3 ± 11.3	0.226^{NS}
Weight (kg)	81.7 ± 16.6	87.9 ± 14.1	0.210^{NS}
Gender (male/female)	24/16	21/19	0.327^{NS}
ASA physical status (I/II)	21/19	23/17	0.519^{NS}

Data are expressed as mean ± SD, numbers NS = not significant.

Table 3 Preoperative laboratory parameters in the two groups of the study.

Variables	Control group (n = 40)	Patient group (n = 40)	p Value
Hb (g/dl)	12.5 ± 2.0	12.1 ± 1.3	0.534^{NS}
Fasting blood glucose (mg/dl)	88.7 ± 15.7	84.4 ± 7.1	0.276^{NS}
Blood urea (mg/dl)	25.4 ± 6.2	26.6 ± 6.2	0.525^{NS}
Serum creatinine (mg/dl)	1.3 ± 0.2	1.2 ± 0.2	0.819^{NS}
Serum total bilirubin (mg/dl)	1.2 ± 0.2	2.0 ± 0.5	0.001^{*}
Serum total proteins (g/dl)	7.5 ± 0.5	7.3 ± 0.4	0.135^{NS}
Serum albumin (g/dl)	4.5 ± 0.6	3.4 ± 0.4	0.001^{*}
SGOT (AST) (IU/L)	29.5 ± 6.1	75.2 ± 13.5	0.001^{*}
SGPT (ALT) (IU/L)	34.0 ± 6.3	84.1 ± 14.7	0.001^{*}
Prothrombin time (s)	12.3 ± 0.9	18.0 ± 1.3	0.001^{*}
Prothrombin concentration (%)	88.0 ± 5.0	57.5 ± 7.6	0.001^{*}
International normalized ratio	1.1 ± 0.1	1.7 ± 0.3	0.001^{*}

Data expressed as mean ± SD. NS = not significant; * = significant.

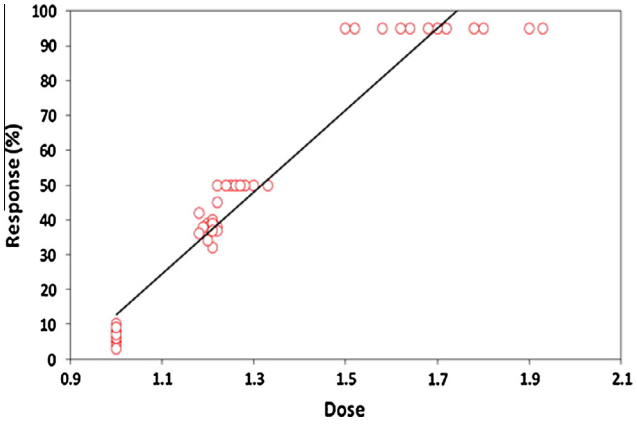

Figure 2 The measured dose response curve of the control group.

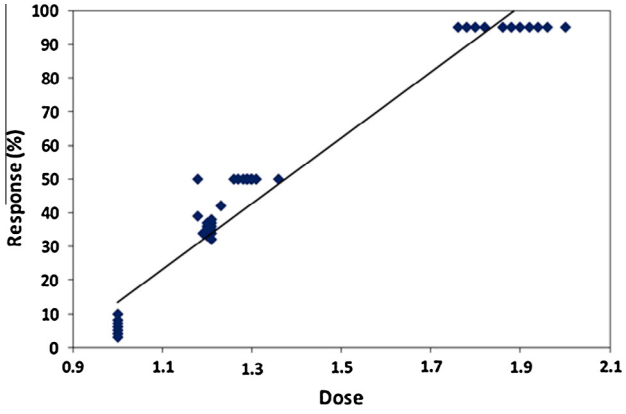

Figure 3 The measured dose response curve of the hepatic group.

cases (p = 0.152). However, degree of suppression of the second dose was significantly lower in liver disease patients (p = 0.006). The dose response curve showed minor difference in the estimated ED_{80} between patients and controls, and significantly higher ED_{50} and ED_{95} in liver disease patients (p = 0.010 and p = 0.001, respectively).

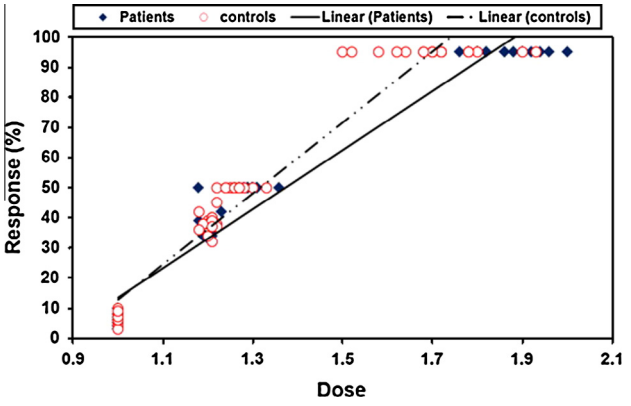

Figure 4 Comparison between the measured dose response curve of the group versus the hepatic group.

The liver plays an important role in the pharmacokinetics of neuromuscular blocking drugs regarding the offset of the block. Patients with liver disease show prolonged duration of action which depends on the character and severity of liver disease and is attributed to prolonged elimination half-life resulting from reduced plasma clearance and increased volume of distribution due to increase extracellular fluid [7]. Atracurium and cisatracurium seem to be favorable exceptions because of their unique breakdown mechanism. However, the elimination half-life of their potentially toxic metabolites in patients with severe liver disease is decelerated [8].

Cisatracurium undergoes spontaneous degradation in the body at physiological pH and temperature by organ-independent Hofmann elimination to form laudanosine and a mono quaternary acrylate metabolite that undergoes hydrolysis by non-specific plasma esterases to form a mono quaternary alcohol. Hydrolysis of cisatracurium by plasma esterases is not an important pathway for elimination of cisatracurium [3]. In contrast, atracurium is eliminated by Hofmann degradation and hydrolysis by non-specific esterases [9,10].

Although the liver seems to play only a minor part in the elimination of cisatracurium, it is a primary pathway for the elimination of its metabolites [10]. These metabolites, however, do not possess neuromuscular blocking activity, but laudanosine can be harmful [11].

Table 4 Operative data in the two groups of the study.

Variables	Control group (n = 40)	Patient group (n = 40)	p Value
1st Dose response (degree of suppression) (%)	6.7 ± 1.8	5.8 ± 2.1	0.152^{NS}
Estimated ED_{80} (μg kg^{-1})	16.0 ± 0.4	16.0 ± 0.4	0.886^{NS}
Calculated 2nd dose (μg kg^{-1})	6.0 ± 0.4	6.0 ± 0.4	0.886^{NS}
2nd Dose response (degree of suppression) (%)	38.0 ± 2.9	35.5 ± 2.5	0.006^{*}
Measured ED_{50} (μg kg^{-1})	18.4 ± 1.0	19.4 ± 1.3	0.010^{*}
Measured ED_{95} (μg kg^{-1})	51.0 ± 0.9	73.6 ± 11.4	0.001^{*}

Data expressed as mean ± SD. NS = not significant; * = significant.

As cisatracurium is more potent than atracurium its dose requirements and subsequently laudanosine concentration are less, therefore the safety margin of the drug is greater especially if given by infusion [12].

In a study of 14 patients with end-stage liver disease scheduled for liver transplantation, after a single bolus of cisatracurium, small increases in volume of distribution (21%) and clearance (16%) have been found with no difference in its elimination half-life or change in its recovery profile and no apparent effect of liver disease on its urinary excretion [13].

A pharmacokinetic single-dose study comparing children with normal hepatic function with those awaiting liver transplantation showed no differences in atracurium pharmacokinetics [14].

Bergeron et al. [15] reported that the clinical duration (time to 25% twitch recovery) of the 0.15 mg kg^{-1} dose of cisatracurium was 59 min. This figure was comparable to the 55 min reported by Bluestein et al. [16] at the same dose and under similar anesthetic conditions.

From continuous infusions of atracurium used during liver transplantation, it appeared that the rate of atracurium infusion required during liver transplantation was not different from that in patients with normal hepatic function [17]. Conversely, Cammu et al. [18] reported that cisatracurium dose requirements during liver transplantation tended to be higher than reported infusion rates of cisatracurium in healthy subjects (1.4 μg kg^{-1} min^{-1}).

In most pharmakokinetic–pharmakodynamic studies for cisatracurium, isoflurane was used as the anesthetic agent. During these conditions, administration of a 0.1 mg kg^{-1} bolus dose of cisatracurium resulted in a mean EC_{50} value of 98 ng ml^{-1} [13,19]. This low EC_{50} value is in agreement with the known potentiating effect of isoflurane. When propofol was used as the anesthetic agent the mean EC_{50} value derived after a 5-min infusion of a 0.1-mg kg^{-1} dose of cisatracurium was 153 ng ml^{-1} [15,20].

In the current study, after a total dose of 0.119 mg kg^{-1}, the ED_{50} was 18.4 μg kg^{-1} in control group and 19.4 μg kg^{-1} in liver disease group. The difference was clinically insignificant. Using the single-dose method, Dahaba et al. [21] reported an ED_{50} of 28 μg kg^{-1}. Others reported ED_{50} of 29 μg kg^{-1} [22], 30 μg kg^{-1} [23], and 31.1 μg kg^{-1} [24].

Similarly, we found that ED_{95} of the control group 50.9 μg kg^{-1} which is comparable to 55.3 μg kg^{-1} reported by Dahaba et al., [21] and 48 μg kg^{-1}, 53 μg kg^{-1}, and 57.6 μg kg^{-1} reported by previously mentioned authors, respectively [22–24].

Bergeron et al. [15] proved the dose dependency of the EC_{50} of cisatracurium through pharmacokinetics and pharmacodynamics study. As cisatracurium pharmacokinetics proved to be linear, the dose-related changes observed in the pharmacodynamic parameters cannot be of pharmacokinetic origin. A 15% decrease in the dose-normalized EC_{max} and a 30% increase in tEC_{max} were observed at the highest dose.

Cammu et al. [18] proposed that in continuous infusion of cisatracurium during liver transplantation, the tendency toward higher dose requirements, the protracted duration of infusion, the non-Hofmann elimination and/or other pharmacokinetic changes during transplantation might influence recovery from the neuromuscular block.

In this study, it was found that there was no effect on liver disease on dose response to cisatracurium apart from a statistically and clinically significant higher ED_{95} (73.6 μg kg^{-1} versus 50.99 μg kg^{-1} in the control group).

Liver disease does not appear to have an effect on the urinary excretion of cisatracurium [13]. Similar findings have been published for atracurium. In fact, renal clearance and renal elimination of unchanged drug may be slightly greater for cisatracurium than for atracurium [25–27]. This may be related to the fact that atracurium contains short-acting isomers that are less likely to appear in the urine [13].

5. Conclusion

Use of cisatracurium as a neuromuscular blocking agent in patients with chronic liver disease seems to be favorable and safe. Liver disease does not appear to have an effect on dose response to cisatracurium through study of dose response curve.

Conflict of interest

No conflict of interest to be declared.

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