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Original Article

Age and the neuromuscular blockading effects of cisatracurium

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Abstract: Purpose: To investigate the influence of age on the neuromuscular blocking effect of cisatracurium. Methods: 90 patients with ASA I and II were assigned to the following groups according to their age: adults, children, and infants. Each group was subdivided into three subgroups according to the first dose of cisatracurium. Patients were administrated at a first dose of cisatracurium randomly, and their responses to train-of-four (TOF) stimulation were observed. When the same degree of the first response (T_1) continuously repeats three times, the percentage of T_1 inhibition was recorded, and the curve of dose-effect relationship and ED_{95} were calculated. A second dose of cisatracurium was then administrated (total volume 100 μg/kg). The recovery phase in each patient was observed upon T_1 reaching the maximum blocking effect (100%). Results: Once the maximum blocking effect was reached, patients were intubated. There were 83 cases (92.2%) of patients with grade 1 and 7 (7.8%) patients with grade 2 intubating conditions. ED_{95} was 59.29, 55.88 and 45.39 μg/kg in adults, children, and infants, respectively. ED_{95} positively correlated with age. The clinical duration of neuromuscular blockade, effective action duration of neuromuscular blockade, and *in vivo* action duration of neuromuscular blockade in adults was longer than that in children ($P<0.05$), but shorter than in infants ($P<0.05$). However, there were no significant differences in the recovery index among groups ($P>0.05$). Conclusion: Age influences the neuromuscular blocking effects of cisatracurium to a certain extent.

Keywords: Cisatracurium, dose-effect relationship, recovery phase, age

Introduction

Cisatracurium is one of ten isomers constituting the racemic mixture of atracurium, as well as its cis- and optical isomer. Similar to atracurium, it is a non-depolarizing muscular relaxant with an intermediate duration of action, which competitive binds with cholinergic receptors at motor end-plates. Cisatracurium has several advantages over other agents, such as it is rapid in action and recovery, does not release histamine [1], has minimal effects on the cardiovascular system, has no accumulative effects, has no metabolite toxicity, and its metabolic product has no neuromuscular blocking effects [2]. Consequently, it is extensively used [3], especially in pediatric patients [4, 5]. However, the effects of age on the pharmacodynamics of cisatracurium remain poorly reported. Thus, the present study characterized the dose-effect relationship and recovery phase of cisatracurium in patients of different ages to provide theoretical basis for its clinical application.

Methods

Ethical approval

Ethical approval for this study was provided by the Ethical Committee of Gongli Hospital, Clinical Medicine of the Second Military Medical University, Pudong New Area, Shanghai (Chairperson Jiu Cheng). All study participants themselves or their families had signed the written informed consent.

Patient characteristics

A total of 90 patients, aged 1 month to 59 years, with an American Society of Anesthesiologists (ASA) pre-operative physical status grade of I and II were selected. They had normal

Table 1. Baseline patient characteristics of various groups (n = 10, $\bar{x} \pm s$)

Group	n	Male/ Female	Age (year/month)	BMI (kg/M^2)	Temperature (°C)
I_{30}	10	7/3	32.10±15.32 (y)	20.67±3.33	36.69±0.28
I_{40}	10	6/4	31.90±16.33 (y)	21.54±2.31	36.67±0.22
I_{50}	10	4/6	31.40±13.40 (y)	21.39±2.85	36.54±0.33
II_{30}	10	7/3	7.55±2.24 (y)	20.24±2.13	36.65±0.26
II_{40}	10	6/4	7.20±2.53 (y)	20.56±2.0	36.55±0.37
II_{50}	10	7/3	6.65±3.04 (y)	20.15±2.49	36.55±0.37
III_{30}	10	4/6	11.10±8.77 (m)	20.66±2.40	36.89±0.28
III_{40}	10	5/5	10.87±8.75 (m)	20.42±2.23	36.56±0.39
III_{50}	10	5/5	9.83±7.82 (m)	20.51±2.40	36.84±0.42

heart, lung, liver and kidney function, no neuromuscular system diseases, no disturbance in electrolyte or acid-base balance, no malnutrition or obesity, and no history of drugs affecting nerve or muscular function prior to operation. Patients were assigned to three groups according to age: adult (n = 30; 16-59 years), child (n = 30; 2-12 years), and infant (n = 30; 1 month-2 years) groups. Each group was then further subdivided into three subgroups by table of random number, administrated respective initial dose of cisatracurium (i.e. 30 μg/kg, 40 μg/kg, and 50 μg/kg). Both participants and experimenters were blind to the grouping. Baseline patient characteristics are presented in **Table 1**.

Anesthesia

All patients older than 12 years of age were injected with atropine (0.01 mg/kg) and phenobarbital sodium (2 mg/kg) intramuscularly 30 minutes prior to surgery. Patients that were younger than 12 years of age were injected with ketamine (5 mg/kg). Anesthesia was induced with midazolam (0.1 mg/kg), fentanyl (5 μg/kg), propofol (1-2 mg/kg), cisatracurium (100 μg/kg), and lidocaine (2%). Remaining dose of cisatracurium was administered once T_1 inhibition was stable after administration of the first dose of cisatracurium for a total of 100 μg/kg. Patients were tracheally intubated, and oxygen was inspired at a rate of 2 L/min and $P_{ET}CO_2$ was maintained between 35-45 mmHg. Anesthesia was maintained with propofol administered through a venous pump, and if necessary, midazolam and fentanyl were also injected. Bis value was maintained between 45 and 60. Skin surface temperature was kept at >32°C.

Monitoring of neuromuscular blockade

Muscle function was monitored using a TOF-Watch monitor system. A sensor was attached to the palmar thumb to measure the contraction velocity of the thumb adductor. A stimulating electrode was placed on the wrist surface, where the ulnar nerve is present. TOF stimulation at 2 Hz, with a 0.2 ms wave width, and a 15-second interval, was used to stimulate the ulnar nerve on the forearm. The amplitude of myopalmus at T_1 was adjusted. Patients were administered 10 minutes after T_1 was stable at 100%.

Dose-effect relationship

The dose-effect relationship curve and recovery phase of cisatracurium were determined via the single administration method. All patients were administrated cisatracurium twice, where each patient was randomly subjected to a dose of either 30 μg/kg, 40 μg/kg or 50 μg/kg. The response to TOF stimulation was determined, when T_1 of the same magnitude was consecutively repeated three times, and the percentage of T_1 inhibition was recorded. Then, the dose-effect relationship curve and effective dose for 95% inhibition (ED_{95}) were calculated.

Recovery phase

Following administration of the first dose of cisatracurium, each patient was injected with cisatracurium intravenously once T_1 inhibition was stable. The total injection volume was 100 μg/kg for each patient. The recovery phase following cisatracurium administration was determined at 100% T_1 inhibition. Specifically, the clinical duration of neuromuscular blockade (i.e. time from administration to T_1 restoration to 5%), effective action duration of neuromuscular blockade (i.e. time of T_1 restoration to 25%), *in vivo* action duration of neuromuscular blockade (i.e. time of T_1 restoration to 90%), and recovery index (i.e. time from T_1 restoration at 25% to 75%) were recorded.

Table 2. Comparison of hemodynamic variables following anesthesia induction

Parameter	Group	n	Baseline	T_1 reaching the maximum block effect
Heart rate (beats·min^{-1})	Adult	30	79.70±9.30	76.17±6.76
	Child	30	104.33±12.76	100.50±10.25
	Infant	30	120.57±11.38	116.27±7.45
	F value		2.315	1.826
	P value		0.117	0.179
MAP (mm Hg)	Adult	30	82.60±10.21	78.37±4.80
	Child	30	63.43±2.64	62.13±2.76
	Infant	30	59.63±2.63	58.07±2.61
	F value		1.643	0.733
	P value		0.211	0.489

Footnotes: Data were expressed as Means ± SD.

Tracheal intubating conditions

Tracheal intubation was characterized on a grade scale of 1 through 4 [6]. Grade 1 indicated a successful glottis exposure and tracheal intubation, with no cough or limb movement. Grade 2 indicated a successful glottis exposure and tracheal intubation, occasionally accompanied by cough or limb movement. Grade 3 indicated difficult glottis exposure and tracheal intubation, accompanied by cough or limb movement. Lastly, grade 4 indicated unable to perform tracheal intubation. Grade 1 or 2 was regarded to as good intubating conditions. Moreover, patients were monitored for the presence of symptoms such as redness and bronchial spasms.

Statistical analysis

Data were analyzed using SPSS13.0 software. Normally distributed data were expressed as Means ± standard deviation (SD). Comparison of hemodynamic variables at baseline and following anesthesia induction was conducted using paired Student's t-test, and comparison of BMI, temperature and medicine using interval of various groups and comparison of monitoring parameters of muscle relaxation effect of various groups were conducted using one-way analysis of variance. The first dose of cisatracurium was logarithmic transformed. Percent of T_1 inhibition underwent probability unit transformation (Probit). Dose-effect curves were plotted using the linear regression method, and ED_{95} values were calculated from these curves. Categorical data were tested using the χ^2-test. $P<0.05$ was considered statistically significant.

Results

Patient characteristics

Pulse and blood pressure were normal in all patients, and there were no significant differences ($P>0.05$; **Table 2**). There were also no significant differences in body mass index and body temperature among groups, as well as the duration between two administrations of cisatracurium (**Table 3**).

Tracheal intubating conditions

Tracheal intubation was conducted following 100% neuromuscular blockade with cisatracurium. There were 83 cases (92.2%) of patients with grade 1 and 7 (7.8%) patients with grade 2 intubating conditions. Redness and bronchial spasm were not detected.

Analysis of the dose-effect relationship curve

It was found that the dose-effect relationship curve of cisatracurium had an excellent goodness-of-fit (i.e. $\chi^2 = 138.047$, $P = 0.000$). A parallel test demonstrated that the linear models of the three groups were parallel and had a common slope of 3.4674 ($\chi^2 = 0.964$, $P = 0.618$). Specifically, the dose-effect relationship curves of the three groups were, as follows: adult group Probit (P) = -4.5026 + 3.4674 × (Lg dose); child group Probit (P) = -4.4134 + 3.4674 × (Lg dose); and infant group Probit (P) = -4.1003 + 3.4674 × (Lg dose). According to these curves, ED_{95} was 59.29 μg/kg in the adult group, 55.88 μg/kg in the child group, and 45.39 μg/kg in the infant group. While the ED_{95} of child group was lower than that of the adult group, there were no significant differences (95% CI = 0.99201-1.13786). However, the ED_{95} of the infant group was significantly lower than both the child and adult groups (95% CI = 1.20762-1.42948 or 0.74560-0.87699).

Analysis of recovery phase

Following the administration of cisatracurium (100 μg/kg), T_1 reached 100% inhibition. The clinical duration of neuromuscular blockade, effective action duration of neuromuscular blockade, and *in vivo* action duration of neuro-

Table 3. Comparison of BMI, temperature and medicine using interval of various groups (n = 30, $\bar{x} \pm s$)

Parameters	Adult group	Enfant group	Infant group	*F* value	*P* value
BMI (kg/m^2)	21.20±2.79	20.32±2.15	20.53±2.27	1.102	0.337
Temperature (°C)	36.64±0.27	36.65±0.33	36.76±0.38	1.305	0.276
Using medicine interval (min)	9.47±1.69	9.05±1.45	9.30±1.58	0.523	0.595

Table 4. Comparison of monitoring parameters of muscle relaxation effect of various groups (n = 30, $\bar{x} \pm s$)

Parameters (min)	Adult group	Enfant group	Infant group	*F* value	*P* value
Clinical acting duration of muscle relaxation	26.50±4.51$^{*,\Delta}$	20.03±3.31	34.63±5.13	83.60	0.000
Effective acting duration of muscle relaxation	34.88±4.43$^{*,\Delta}$	26.05±3.41	44.68±5.79	120.79	0.000
Acting duration of Muscle relaxation in body	52.47±4.75$^{*,\Delta}$	44.37±3.33	62.82±5.43	121.86	0.000
Recovery index	11.47±1.97	11.16±1.63	12.02±1.94	1.63	0.203

Footnotes: Compared with Enfant group $^{*}P<0.05$; Compared with Infant group $^{\Delta}P<0.05$.

muscular blockade was significantly longer in the adult group than in the child group ($P<0.05$), but shorter than in the infant group ($P<0.05$). However, there were no significant differences in the recovery index among the three groups ($P>0.05$; **Table 4**).

Discussion

Cisatracurium has several advantages over other agents, such as it does not release histamine, has minimal effects on the cardiovascular system, has no accumulative effects, has no metabolite toxicity, and has no neuromuscular blocking effect [7]. Therefore, it has been extensively used in the clinic. The present study utilized TOF stimulation generated with a TOF-Watch monitor system to determine the neuromuscular blocking effects of cisatracurium, and to investigate the dose-effect relationship and recovery phase of cisatracurium in different age groups. All of the patients studied had normal liver and kidney function, and blood pressure and heart rates were similar to routine clinical induction values following administration of cisatracurium, indicating that cisatracurium did not have an effect on hemodynamics. Additionally, consistent with a previous study [1], there was no evidence of redness, skin rashes, lowering of blood pressure, or tracheospasm in any patients.

Under balanced anesthesia with N_2O, the ED_{95} of cisatracurium was 0.047-0.053 mg/kg in adults [8], 0.047±0.007 mg/kg in children (3-10 years old), and 0.043±0.009 mg/kg in infants (4 months to 1 year old) [9]. Under halothane anesthesia, the ED_{95} of cisatracurium was 0.041 mg/kg in children [10]. Under total intravenous anesthesia, the ED_{95} of cisatracurium was 0.56 mg/kg in adults [11]. Very little is known regarding the ED_{95} of cisatracurium in Chinese children. In the present study, it was found that under anesthesia with midazolam, propofol and fentanyl, the ED_{95} of cisatracurium was 0.5929 mg/kg in adults, 0.5588 mg/kg in children, and 0.4539 mg/kg in infants, indicating an age-dependent increase in ED_{95}. There were no significant differences between children and adults in ED_{95}, but there were significant differences among infants, and children and adults.

A previous study reported that adults aged 15-59 years required a lower amount of atracurium for the same degree of muscle relaxation with increasing age [12]. One reason for this may be that younger individuals have a greater muscle to body mass ratio, and thereby a greater amount of body fluid and extracellular fluid, which in turn requires a greater amount of atracurium to induce muscle relaxation to the same degree. However, these findings were not consistent with the findings of the present study. This may be because, in addition to studying adults, we included infants and children in our study (i.e. from 1 month up to 59 years). In comparison to adults, infants have a relative higher cardiac output and shorter circulation time [13], which results in more blood flow through the muscle and motor end-plate, and simultaneously shortens the time available for a muscle relaxant to induce neuromuscular blockade. Therefore, the younger the patient, the lower

the dose of cisatracurium required. Also, in comparison to children and adults, differences in growth and development are significantly different in infants, who are likely more sensitive to cisatracurium due to hypoplasia of the motor end-plates. They display proportionately longer action times [14] and therefore require smaller doses [15]. Additionally, it should be noted that infants and children were injected with ketamine (5 mg/kg) intramuscularly. Although the influence of ketamine on cisatracurium remains unclear [16], both groups were injected with the same dose of ketamine, which theoretically should induce similar effects. Furthermore, given that there were no significant differences detected in ED_{95} among the three groups, there are no influences of preoperative ketamine on the study results.

In the present study, it was found that the clinical duration of neuromuscular blockade, effective action duration of neuromuscular blockade, and *in vivo* action duration of neuromuscular blockade were prolonged with increasing age; an observation that is consistent with previous findings [17]. Specifically, the action duration of cisatracurium was positively correlated with age. One reason for this finding may be that the volume of distribution in infants is greater than that of adults. That is, because of differences in the dose to body mass ratio, the concentration of cisatracurium is relative low, which results in a shortened recovery duration. However, consistent with previous studies [18, 19], the clinical duration of neuromuscular blockade, effective action duration of neuromuscular blockade, and *in vivo* action duration of neuromuscular blockade were longer in infants than in both children and adults. It is likely that approximately 23% of cisatracurium is metabolized by various organs, and 16% is excreted by the kidneys [20]. Drug metabolism in infants is suppressed since their development is incomplete that results in a slower recovery of muscle relaxation. Additionally, non-depolarizing muscular relaxants bind acetylcholine receptors at neuromuscular junction, which thereby inhibits neuromuscular conduction-produced muscle relaxation. Given that neuromuscular junctions in infants are not fully matured, there may be a limited amount of available receptors for cisatracurium to bind to at the motor end-plates. Consequently, cisatracurium could accumulate at the motor end-plates and slow down the drug metabolism process. The recovery duration of muscle relaxation (i.e. T_1 recovery from 25% to 75%) was similar among all groups. This indicates that there is no relationship between recovery speed of neuromuscular blockade and age. This finding provides theoretical evidence for the clinical application of cisatracurium in children. Approximately 77% of cisatracurium is degraded through the Hofmann effect, and 16% through the kidneys [21].

In the present study, it was found that age influences muscle relaxation induced by cisatracurium. However, there are some limitations in the study that need to be addressed. First, infants and children were preoperatively injected with ketamine, resulting in unbalanced experimental conditions. Furthermore, seniors (i.e. >59 years of age) were not included in the study. Lastly, the present study was conducted under total intravenous anesthesia, therefore, future clinical studies need to assess the influence of inhalation anesthesia or intravenous-inhalation combined anesthesia on the pharmacokinetic and pharmacodynamic properties of cisatracurium.

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Disclosure of conflict of interest

None.

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