NEUROMUSCULAR EFFECTS OF CISATRACURIUM IN MORBIDLY OBESE PATIENTS

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Summary

Obesity is associated with significant changes in body composition and function that may alter the pharmacodynamics and pharmacokinetics of various drugs.

In this study, we investigated the neuromuscular effects of cisatracurium in morbidly obese as compared to control group of normal body weight patients. In the morbidly obese group (n = 20), corrected weight was used to calculate the drug doses. In the control group (n = 20), the dose was calculated on ideal body weight (IBW). 0.15 mg/kg^{-1} cisatracurium was administered as the neuromuscular blocker.

Neuromuscular effects were recorded at T_0 (onset time), T_1 (appearance of first stimulus of TOF), T_{25} (25% recovery of T_1) and T_{25-75} (time of T_{25} to T_{75}, recovery time). T_0 was determined as 177 ± 23 s and

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168 ± 19 s in the morbidly obese, and control group, respectively. T_{25} was determined as 46 ± 7 min and 56 ± 8 min, in the morbidly obese and control group, respectively ($p<0.05$). T_{25-75} was determined as 11 ± 5 min and 14 ± 6 min in the morbidly obese and control group, respectively ($p<0.05$). Intubation conditions were determined as good in 13, excellent in 7 patients in the morbidly obese group, and as good in 4 and excellent in 16 patients in the control group ($p<0.05$).

As different neuromuscular effects of cisatracurium were detected, we conclude that neuromuscular agents must be monitored in the morbidly obese patients.

Key words: Neuromuscular monitoring, neuromuscular block, cisatracurium in morbidly obese.

Introduction

Obesity is one of the major health problems of this century. Morbid obesity is described as an excess of the ideal body weight (more than 160%), or BMI over 35 or 40. This condition leads to major health problems[1,2]. In our country, obesity is common, involving 26.4% of females and 38.5% of males.

Obesity is associated with changes in body composition and functions which may alter the pharmacodynamics and pharmacokinetics of various drugs. In that regard, increased fat masses, reduced proportion of muscle mass and body water, altered liver function, protein binding capacity and tissue distribution, have been documented[3].

The number of studies that have investigated the actions of neuromuscular blocking (NMB) agents in the obese patient, is limited. In obese patients, NMB agents had different effects on neuromuscular transmission. The effects of succinylcholine, pancuronium, dimethyl tubocurarine, vecuronium and atracurium on neuromuscular junction have been reported in obese patients[4-12]. Distribution volume, clearance and elimination half life were changed in obese individuals[11].

Cisatracurium is a relatively new NMB. Approximately 76.9% of the cisatracurium undergo Hoffman elimination which in turn depend on pH and body temperature. Cisatracurium also has other metabolisation pathways such as hepatic and renal elimination[13,14].

The purpose of our study was to compare the onset and the duration time of cisatracurium-induced neuromuscular blockade in morbidly obese patients to a control group.

Materials and Methods

Approval of the hospital Ethical Committee, and the informed consent of the patients were procured. 40 patients ASA II-III to undergo elective general surgical procedures (laparascopic gastric banding in the morbidly obese, and laparascopic cholecyctectomy in normal or control patients), were included in our study. All patients displayed normal clinical features. Patients who manifested possibility of difficult airway, were excluded from this study.

Before the study was started, power analyses were done to determine the minimum patient number; 16 with α: 0.05 and β: 80%.

Patients were divided into two groups, morbidly obese group (n = 20) with BMI of 55±5, and the normal or control group (n = 20) with BMI of 22±4. Patients in the morbidly obese group underwent laparoscopic gastric banding while patients in control group underwent laparoscopic cholecyctectomy (Table I).

In the morbidly obese group, drugs were administered according to the corrected body weight calculation, in the following manner:

First, the ideal body weight of patients were calculated:

Females = Length (cm)-105] Males = Length (cm)-100][15].

Second, using the ideal body weight, the corrected body weights were calculated according to the following formula:

(Corrected body weight = [0.4 x excess weight] + ideal body weight)[16].

Table I
Patients and operation characteristics (Mean ± SD)

	Morbidly Obese (Lap. gastric banding) Group (n = 20)	Control Group (Lap. cholecyctect.) (n = 20)
ASA (I-II)	8/12	11/9
Age (year)	43.8 ± 9	41.8 ± 11
Weight (kg)	167 ± 19*	167 ± 11
Height (cm)	162 ± 15	165 ± 14
Body mass index (BMI)	55 ± 5*	22 ± 4
Mallampati Classification (I-II-III-IV)	9/11/0/0	18/2/0/0*
Sex (Femal/Male)	12/8	14/6
Operation duration (min)	78 ± 39	69 ± 17

* $p<0.05$, between two group

Before the operation was commenced, low molecular weight heparin (enoxiparine 20 mg/day), and H_2 receptor antagonist (100 mg iv ranitidine) were administered to the morbidly obese group.

After applying Allen test, 20 G cannula was inserted into the radial artery under local anesthesia. The heart rate, invasive blood pressure, peripheral oxygen saturation (SpO_2), and end expiratory carbondioxide pressure ($EtCO_2$) by Millenia (Millenia, Orlando, USA) were monitored perioperatively.

Same anesthesia technic was given to both groups. In the morbidly obese patients, however, all medications were administered with doses according to corrected body weights.

Anesthesia was induced with 2 mg/kg^{-1} propofol and 2 $\mu g/kg^{-1}$ fentanyl. After the administration of 0.15 mg/kg^{-1} cisatracurium, trachea was intubated and patient mechanically ventilated with 40% FiO_2, 10 ml/kg^{-1} tidal volume, 12 min^{-1} frequency by Draeger Sulla 808 V (Lübeck, Germany). Anesthesia was maintained with 1% isoflurane and oxygen-air mixture (3/5 l/dk^{-1}). 1 $\mu g/kg^{-1}$ fentanyl and 0.03 mg/kg^{-1} and cisatracurium was administered intravenously when necessary. After induction, nasogastric tube was placed in to all patients. CO_2 was insufflated with a 2

l/min^{-1} flow rate via laparoscopic insufflation apparatus to fascilitate pneumoperitoneum.

The NMB was monitored with Paragraph (Utah, USA) neuromuscular monitor. Adductor pollicis muscle and ulnar nerve were chosen for neuromuscular monitorisation. In every 10 second, train-of-four (TOF) stimuli were performed with 2 hertz submaximal frequency and 0.2 msec time interval. T_0 (onset time = time interval between drug administration and the time that T_1 reaches 0), T_{25} (time of the T_1 recovered 25%), T_{25-75} (after last drug administration T_{25} reaching time to T_{75}), were recorded. The temperature of the monitored hand was kept over 33°C. When maximum block (T_0) was attained, trachea was intubated. For every patient intubation, quality was evaluated either as perfect, good, poor or imposible[17]. During the operation, TOF stimuli were performed every one second. When TOF had three answers, cisatracurium was repeated at 0.03 mg/kg^{-1} doses. At the end of the operation, neuromuscular blockade was antagonized with 0.01 mg/kg^{-1} atropine and 0.02 mg/kg^{-1} neostigmine intravenously.

For statistical analysis of the collected data, Student's *t* and chi square tests were used. Data was given as mean ± standard deviation. Values of $p<0.05$ were accepted as statistically significant

Results

Characteristics of patients and perioperative data are shown in Table 1.

We have not found any significant difference between the two groups in terms of operation duration, age, sex, height and ASA score. In terms of BMI, weight and mallampaty scores, the morbidly obese group had significant difference from normal or control patients ($p<0.05$) (Table I).

T_0 interval was not significantly different between two groups ($p>0.05$), but T_{25} and T_{25-75} intervals were significantly shorter in the morbidly obese group ($p<0.05$) (Table II).

Table II
Neuromuscular effects (Mean ± SD)

	Morbidly Obese Group (Lap. gastric banding) (n = 20)	**Control Group (Lap. cholecyctect.) (n = 20)**
T_0	177 ± 23	168 ± 19
T_{25} (min)	46 ± 7*	56 ± 8
T_{25-75} (min)	11 ± 5	14 ± 6

* $p<0.05$, between groups

T_0: Onset time

T_{25}: Time to 25% recovery of T_1

T_{25-75}:Time of T_{25} to T_{75}

In the morbidly obese group, intubation quality was found to be good in 13, perfect in 7 patients, the control group, it was found good in 4 and perfect in 16 patients. These datas show significant differences between the two groups ($p<0.05$).

Discussion

In the present study we investigated the pharmacodynamic effects of cisatracurium, the onset time and duration of action, in morbidly obese patients.

There are conflicting reports concerning the effects of obesity on the pharmacodynamics of nondepolarizing neuromuscular blocking drugs. Neuromuscular blockers are polar and hydrophilic drugs, thus their distribution between fat and lean tissues may further influence their pharmacokinetics in obese individuals[3].

In obese patients, drug pharmacokinetics and biotransformations show changes. In obesity there is an abnormal elevation in fat tissue. While total body water in normal patients is about 65%, it is decreased to 40% in the morbidly obese patients, thus affecting drug distribution volumes. When a highly lipid soluble drug like fentanyl is given to obese patients, lipid solubility becomes of importance. Elevated storage in fatty tissue, increase in distribution volume and in elimination period, have

influences on drug effect intervals.

Changed effects of NMB action in obese patients may contribute to the pathologies that accompany obesity and the relative decrease in the splanchnic blood flow. Changed effects of NMB agents in obese patients may attribute to increased pseudocholinesterase activity, increased extracelluler liquid volume, drugs variable lipid solubility, changed renal and liver clearances[5,10,12].

Cisatracurium is one of the 10 stereoisomers of atracurium. The main advantage of cisatracurium is the clinical absence of nonimmunological histamine release. The pharmacokinetics of cisatracurium are similar to those of atracurium. However, the plasma clearance of cisatracurium is negatively influenced by renal failure[14].

In 10 morbidly obese patients Alvarez et al.[18] used cisatracurium as a NMB, and then during the operation they used rocuronium with propofol, remifentanyl, and midazolam in order to perform total intravenous anesthesia. The TOF stimulus was used. They titrated the cisatracurium concentration to achieve the 1 TOF response. They determined that cisatracurium was suitable for the induction of anesthesia, observed comfortable intubation condition and stable hemodynamic status in perioperatory period and found it is cost effective in the morbidly obese patients.

In other different studies, verocurium's NMB action was found to be prolonged and suxamethonium's NMB action was shortened. When administered according to the corrected body weight, pancuronium and dimetyl tubocurarine's NMB action were found to be unchanged[5-12]. They concluded, that the shortened suxamethonium NMB action contributed to the elevated pseudocholinesterase activity and extracellular liquid volume, and that unchanged pancuronium action contributed to the low lipid solubility and verocurium's elevated effect contributed to the wide distribution volume and changed liver elemination.

In our study, we measured the maximal block interval (T_0) to be 9 seconds longer in the morbidly obese patients, but this difference was of no statistical importance ($p>0.05$). Other neuromuscular effects were

shortened in morbidly obese patients ($p<0.05$). In contrast of the possibility of the sevoflourane's NMB action potantialising effect, we found all the intervals shortened (Table II).

It is commonly believed that tracheal intubation is more difficult in obese than in normal body weight patients. The airway of obese individuals may be narrowed by fleshycheeks, a large tongue, and copious flaps of palatal, pharyngeal, and supralaryngeal soft tissue. We found that the worst intubation quality was in the morbidly obese patients. This finding conforms to the Mallampaty scores and carry statistical importance ($p<0.05$).

In this study, we found that NMB effect of cisatracurium is changed in the morbidly obese patients as compared to the normal control patients. We conclude, that the monitorisation of cisatracurium's NMB action is useful in the morbidly obese group of patients.

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