DOSE RESPONSE RELATIONSHIP OF NEUROMUSCULAR BLOCKADE, INTUBATION CONDITIONS AND CARDIOVASCULAR CHANGES WITH CHANDONIUM IODIDE

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ABSTRACT

One hundred and forty ASA physical status I and II patients undergoing general or gynaecological surgery were the subjects of this study. Patients were randomly assigned into five groups receiving 100, 150, 180, 200 and 250 µg/kg I.V. of chandonium iodide after induction of general anaesthesia with thiopentone. Neuromuscular blockade was assessed clinically, as well as, with twitch response/train of four using myotest nerve stimulator. Increasing dosage of chandonium iodide decreased the time to onset of jaw relaxation and apnoea ($p < 0.01$) and caused linear increase in the duration of neuromuscular blockade from 10.90 ± 5.31 to 25.18 ± 7.15 min ($p < 0.01$) over the dosage range of 100 to 250 µg/kg. Intubation conditions also improved with increasing doses of chandonium iodide, so that, although intubation was possible in all the patients, grading of good intubation conditions were achieved in 64, 80, 88, 100 and 100% of patients in groups I to V respectively. 200 µg/kg of chandonium iodide produced ideal intubation conditions. Recovery to spontaneous ventilation was rapid and smooth, further facilitated with neuromuscular antagonists. Short lasting increase in heart rate and blood pressure was seen which was neither dose dependent nor outlasting the duration of neuromuscular blockade.

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KEY WORDS : Neuromuscular blocking agents; Intubation conditions; Chandonium iodide.

Introduction

Chandonium iodide, a new non-depolarising neuromuscular blocking agent [1] has been under multicentric clinical trials. It has the advantages of short duration of action, rapid onset, cardiovascular stability, no ganglion blockade, no histamine release, no accumulation following repeated doses and ease of reversibility [2]. However, in clinical practice, the time to onset and duration of action may have to be defined so that the use of the drug can be tailored to the variable duration of surgery. Infusion of neuromuscular blocking agents, necessitates neuromuscular monitoring which is unlikely to be available in various surgical centres in underdeveloped countries

like India. Chandonium is highly specific in its action at the neuromuscular junction, free from side effects even in high doses [3]. We have investigated the dose response relationship, the time course of neuro-muscular blocking action, the intubation conditions, haemodynamic stability and recovery time following neuromuscular block induced by the administration of 100, 150, 180, 200 and 250 µg/kg of chandonium iodide in anaesthetised patients.

Material and methods

Study was approved by the Ethics Committee and written informed consent was obtained from each patient. One hundred and forty ASA physical status I and II patients, aged 18-55 years, of either sex, scheduled for

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TABLE 1

Age (Years) Weight (Kg) and Sex

	GROUPS				
	1 (n=25)	2 (n=25)	3 (n=25)	4 (n=40)	5 (n=25)
AGE (Years) (Mean $\pm$ SD)	31.65 $\pm$ 8.25	27.40 $\pm$ 5.50	27.40 $\pm$ 5.50	25.66 $\pm$ 6.82	30.81 $\pm$ 5.77
WEIGHT (kg) (Mean $\pm$ SD)	52.75 $\pm$ 12.30	47.00 $\pm$ 9.11	51.13 $\pm$ 10.50	48.75 $\pm$ 9.65	49.18 $\pm$ 8.57
SEX					
MALES	9	12	4	20	8
FEMALES	16	13	21	20	17

general or gynaecological surgery were the subjects of this study. None of the patients had neuromuscular, hepatic or renal disorders. Those who were taking drugs likely to cause neuromuscular blockade or potentially difficult endotracheal intubation were excluded. Patients were randomly assigned into five groups who received 100, 150, 180, 200 and 250 μ g/kg I.V. of chandonium iodide after induction of general anaesthesia (Table 1). Intubation was done by one of the authors well experienced with more than 10 years standing in the practice of clinical anaesthesia. Patients were premedicated according to their preoperative anxiety status as advised in the anaesthetic assessment clinic (Table 2). Surgical procedure conducted with muscular relaxation of chandonium iodide are shown in Table 3.

In the operation theatre, an I.V. catheter (angiocath 16G) was inserted into a vein on the back of one hand and connected to a continuous infusion of saline or Ringer's lactate. Surface electrodes were placed near the ulnar nerve at the wrist using the arm without I.V. cannula; supramaximal stimuli of 0.2 ms duration at a frequency of 0.1 Hz were delivered from a myotest nerve stimulator (Biometer, Denmark). Once a stable twitch response has been obtained, anaesthesia was induced with thiopentone 5 mg/kg. A bolus dose of chandonium iodide, 100, 150, 180, 200 and 250 μ g/kg, was then administered according to the assigned patient group. Ventilation was controlled manually via a face mask with 60% nitrous oxide in oxygen until tracheal intubation was performed. Follow-

TABLE 2

Premedication

	GROUPS				
	1 (n=25)	2 (n=25)	3 (n=25)	4 (n=40)	5 (n=25)
Atropine(0.6 mg)	1	0	0	2	2
Atropine(0.6 mg)+ morphine(15 mg)	12	18	22	20	15
Atropine(0.6 mg)+ fortwin(30 mg)	7	4	2	8	5
Atropine(0.6 mg)+ morphine(15 mg)+ promethazine (25 mg)	5	3	1	10	3

TABLE 3

Surgical Procedures

	GROUPS				
	1 (n=25)	2 (n=25)	3 (n=25)	4 (n=40)	5 (n=25)
Abdominal tubal ligation	10	13	21	18	15
Caesarean section	1	0	0	1	2
Trauma*	9	8	3	15	5
General surgery	5	4	1	6	3

* Trauma: emergency = 25, Elective = 13.

ing intubation, anaesthesia was maintained with 60% nitrous-oxide in oxygen and halothane (inspired concentration 0.5%). Chandonium supplement, one fourth of the initial intubation dose was administered as and when required. At the completion of surgery, clinical recovery of spontaneous ventilation was assessed, residual neuromuscular blockade was antagonised with I.V. neostigmine 40 and atropine 20 μ g/kg mixture. Recovery time, time to limb movements,

TABLE 4

Neuromuscular blockade, time to onset of jaw relaxation and apnoea and duration of action (mean $\pm$ SD)

	GROUPS				
	1 (n=25)	2 (n=25)	3 (n=25)	4 (n=40)	5 (n=25)
Time to onset of jaw relaxation (secs)	97.75 $\pm$ 15.00	86.37 $\pm$ 13.25	89.40 $\pm$ 9.16	72.33 $\pm$ 10.06	55.20 $\pm$ 9.88
Number of patients showing jaw relaxation in					
< 60 secs	0	5	3	17	16
60-90 secs.	6	8	16	20	4
> 90 secs.	19	12	6	3	5
Time to onset of apnoea (secs)	214.28 $\pm$ 18.30	149.20 $\pm$ 12.50	132.80 $\pm$ 15.66	115.60 $\pm$ 10.55	95.41 $\pm$ 9.15
Number of patients showing onset of apnoea in					
< 90 secs.	0	3	3	12	14
90-120 secs.	0	6	12	18	11
120-180	12	9	4	7	0
> 180 secs.	13	7	6	3	0
Duration of apnoea (min.)	10.91 $\pm$ 5.31	14.18 $\pm$ 5.95	15.53 $\pm$ 7.10	19.68 $\pm$ 5.22	25.18 $\pm$ 7.15

time to return of hand grip and time to head lift for 5 seconds after the extubation, were recorded in the postoperative recovery suite.

Laryngoscopy and endotracheal intubation conditions were assessed according to the criteria of McDowell and Clarke [4] as "Good", when vocal cords were abducted and motionless; "Fair" — some movements of the vocal cords; and "Poor", when the movements of the arytenoids, vocal cords and active laryngeal reflex made the intubation impossible. Reaction to intubation was recorded as Grade 0, no reaction; Grade 1, coughing and bucking on the tube; Grade 2, movements of the limbs or of the whole body. Intubation time was defined as time from mid point administration of chandonium iodide until intubation was complete; Time to onset, as the time from mid-point administration of chandonium iodide until the jaw was completely relaxed (clinically) for laryngoscopy; time to onset of apnoea as the time from the mid-point administration of chandonium until cessation of respiration; and duration of neuromuscular blockade as the time from mid-point administration of chandonium

until initiation of spontaneous ventilation.

Clinical assessment was considered essential alongwith neuromuscular monitoring as the drug will be used in clinical anaesthesia after commercial release where neuromuscular monitoring may not be available. Arterial pressure and heart rate were recorded every two min from induction of anaesthesia, until 10 min after endotracheal intubation and every 5 min thereafter using a 'Dinamap' oscilometric blood pressure monitor applied to the left arm. Electrocardiogram was continuously displayed to monitor the cardiac rhythm. Heat loss was prevented by the use of electric blankets and adequate air conditioning of the theatre.

Analysis of variance was used for comparison of the groups. Fisher's protected test of least significance was used and $p < 0.01$ was considered statistically significant.

Results

Demographic intergroup differences as regards age, weight and sex were not significant (Table 1). Surgical procedures and premedication administered to the patients

TABLE 5

Intubation conditions at 120 seconds

	1 (n=25)	2 (n=25)	Groups 3 (n=25)	4 (n=40)	5 (n=25)
Apnoea					
complete	0	9	15	30	25
incomplete	25	16	10	10	0
Jaw relaxation					
relaxed	25	25	25	40	25
not relaxed	0	0	0	0	0
Laryngoscopy					
easy	25	25	25	40	25
difficult	0	0	0	0	0
impossible	0	0	0	0	0
Pharyngeal wall					
moving	0	0	0	0	0
not moving	25	25	25	40	25
Glottis					
visible	25	25	25	40	25
not visible	0	0	0	0	0
Vocal cords					
paralysed	10	18	21	40	25
moving	15	7	4	0	0
closed	0	0	0	0	0
Intubation					
easy	25	25	25	40	25
difficult	0	0	0	0	0
impossible	0	0	0	0	0

were comparable (Table 2 and 3). All patients had good sedative and anxiolytic effect of premedication.

Increasing the dose of chandonium iodide decreased time to onset of jaw relaxation and apnoea; 97.75 ± 15.00 to 55.20 ± 9.88 and 214.28 ± 18.30 to 95.41 ± 9.15 seconds respectively in 100 to 250 $\mu\text{g}/\text{kg}$ groups ($p < 0.01$) (Table 4). Time to onset was significantly different in all the groups except 150 and 180 $\mu\text{g}/\text{kg}$ groups. There has been a linear increase in the duration of action ($p < 0.01$) of the neuromuscular blockade from 10.90 ± 5.31 min in 100 $\mu\text{g}/\text{kg}$ group to 25.18 ± 7.15 min in 250 $\mu\text{g}/\text{kg}$ group as the dose of chandonium iodide was increased. Difference was minimal between 150 vs 180 $\mu\text{g}/\text{kg}$ groups. Premedicant drugs neither influenced the onset nor duration of the neuromuscular blockade of chandonium iodide.

Intubation conditions also improved with increasing doses of chandonium iodide. Jaw

and laryngeal muscles were relaxed earlier than the complete abolition of twitch response of abductor pollicis longus. Intubation attempted at 120 secs (Table 5) showed incomplete apnoea with moving vocal cords in 60, 28 and 16% of patients administered 100, 150 and 180 $\mu\text{g}/\text{kg}$ doses of chandonium iodide. Higher doses 200-250 $\mu\text{g}/\text{kg}$ produced complete apnoea and paralysis of the vocal cords in all the patients. Mild reaction to intubation was seen in 36, 20 and 12% of patients in 100, 150, 180 $\mu\text{g}/\text{kg}$ chandonium iodide groups. Intubation was easy as complete jaw and laryngeal muscle paralysis was achieved, however, good intubation conditions were seen in 64, 80, 88, 100 and 100% of patients with increased doses, 100-250 $\mu\text{g}/\text{kg}$ of chandonium iodide. Intubation was possible in all the patients (Table 6). Post-operative recovery to spontaneous ventilation was rapid and smooth (Table 7). Those patients where neuromuscular blockade out-

TABLE 6

Intubation conditions : reaction to intubation and overall assessment at 120 seconds

	GROUPS				
	1 (n=25)	2 (n=25)	3 (n=25)	4 (n=40)	5 (n=25)
Reaction to intubation					
Grade 0	16	20	22	40	25
Grade 1	9	5	3	0	0
Grade 2	0	0	0	0	0
Assessment					
Good	16	20	22	40	25
Fair	9	5	3	0	0
Poor	0	0	0	0	0

Overall assessment done according to McDowell and Clarke (1969), otherwise good intubation conditions were seen in all the groups. Mild vocal cord movement or reaction to intubation did not interfere with the surgical procedure and settled within 1-2 min with halothane supplement.

lasted the short duration of surgery, were administered neostigmine 60 µg/kg and atropine 20 µg/kg mixture with rapid, smooth and complete recovery to spontaneous ventilation. There was no evidence of clinical or twitch response of residual neuromuscular blockade after single I.V. bolus dose administration of neuromuscular antagonist.

Heart rates and arterial pressure(s) before and after the administration of chandonium iodide 100-200 µg/kg has been shown in Table 8. Increased heart rate 20-25% ($p < 0.01$) with insignificant rise in blood pressure was seen at 1 min interval after chandonium administration which subsided to normal basal level within 5-10 min. Increase in heart rate was neither dose dependent nor outlasted the duration of neuromuscular blockade.

Discussion

This study has clearly demonstrated that over a dosage range 100-250 µg/kg, dose dependent decrease in time to onset of neuromuscular relaxation, better intubation conditions and increase in duration of action could be achieved without compromising the cardiovascular stability and post operative recovery. Muscular relaxation could be tailored to the needs of the individual patients as suggested by Savarese and Kitz [5]. Minimum effective dose, of chandonium iodide in man is 80 µg/kg [2]. This study has confirmed that ideal intubation conditions

could be achieved with 150-250 µg/kg and we have recommended 200 µg/kg of chandonium iodide as the standard intubation dose in man [6].

Chandonium iodide produced rapid clinical onset of muscular relaxation (jaw and laryngeal muscles relaxation) facilitating ease to laryngoscopy before maximum neuromuscular block of the abductor pollicis longus muscle. Similar findings have been reported by Donati et al with Vecuronium [7]. Depth of anaesthesia may influence the intubation conditions but under comparable anaesthetic conditions, intubation after placebo may be either very difficult or impossible.

Cardiovascular effects over the dosage range 100-250 µg/kg of chandonium demonstrated a 20-25% increase in heart rate, which is comparable to changes in heart rate after an intubation dose of pancuronium [8]. This represents vagolytic effect. Opinion of many anaesthesiologists indicate that an increase in heart rate might be useful to compensate for the decrease in heart rate often seen after the administration of opioid drugs [9], during surgical stimulation [10] or during preoperative cardioactive drug therapy [11]. A relaxant producing a slight increase in heart rate could have clinical advantages, and might be preferred to the available vagolytic drugs, which may produce unpredictable action and unwanted side effects.

TABLE 7

Mean recovery time (mins after extubation) after chandonium iodide : N₂O:O₂ Halothane anaesthesia (mean $\pm$ SD)

	GROUPS				
	1 (n=25)	2 (n=25)	3 (n=25)	4 (n=40)	5 (n=25)
First limb movement	3.30 $\pm$ 1.05	6.00 $\pm$ 2.75	4.80 $\pm$ 1.72	5.10 $\pm$ 1.38	5.60 $\pm$ 2.01
Return of hand grip	8.00 $\pm$ 2.35	6.37 $\pm$ 1.88	5.13 $\pm$ 1.09	6.41 $\pm$ 2.11	6.40 $\pm$ 1.96
Head lift for 5 sec	13.80 $\pm$ 4.17	13.39 $\pm$ 5.19	11.80 $\pm$ 3.65	16.68 $\pm$ 5.80	14.59 $\pm$ 7.30
Postoperative complications	0	0	0	0	0

TABLE 8

Mean pulse rate min⁻¹ and systolic blood pressure (mmHg) before and after administration of chandonium iodide. (mean $\pm$ SD)

	GROUPS				
	1 (n=25)	2 (n=25)	3 (n=25)	4 (n=40)	5 (n=25)
Pulse rate min ⁻¹					
Preoperative	86.19 $\pm$ 16.05	82.16 $\pm$ 12.53	82.53 $\pm$ 15.10	84.65 $\pm$ 13.00	90.00 $\pm$ 12.75
After chandonium iodide					
1 min.	105.80 $\pm$ 12.33	102.15 $\pm$ 9.25	106.13 $\pm$ 15.25	104.16 $\pm$ 9.45	120.00 $\pm$ 75.17
5 min.	94.45 $\pm$ 9.68	91.80 $\pm$ 12.11	93.06 $\pm$ 9.82	92.83 $\pm$ 11.51	105.00 $\pm$ 12.38
10 min.	103.44 $\pm$ 11.07	87.30 $\pm$ 10.55	86.93 $\pm$ 11.31	88.33 $\pm$ 12.22	100.20 $\pm$ 11.37
Systolic Blood Pressure					
Preoperative	117.40 $\pm$ 12.15	119.33 $\pm$ 15.80	119.30 $\pm$ 16.15	117.16 $\pm$ 13.72	122.80 $\pm$ 18.00
After chandonium iodide					
1 min	121.12 $\pm$ 16.20	121.90 $\pm$ 11.65	131.60 $\pm$ 16.13	131.00 $\pm$ 9.60	133.20 $\pm$ 15.44
5 min	116.00 $\pm$ 12.36	114.30 $\pm$ 12.55	122.10 $\pm$ 12.38	121.16 $\pm$ 12.75	120.80 $\pm$ 12.38
10 min	113.30 $\pm$ 10.77	110.15 $\pm$ 9.25	119.33 $\pm$ 15.00	115.83 $\pm$ 12.11	118.00 $\pm$ 12.11

It is clear from our findings, that one can predict a dose of chandonium to produce a short or medium acting degree of neuromuscular blockade. The duration of action may be more predictable than with existing agents and with a more rapid spontaneous recovery [2] than after d-tubocurarine or pancuronium [10]. Clinical recovery, as limb movements, hand grip and head lift for 5 secs after extubation was not affected over dosage range 100-250 μ g/kg of chandonium iodide.

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