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Effect of Aminophylline on Atracurium Induced Neuromuscular Block

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ABSTRACT

Background: theophylline is a naturally occurring methylxanthine that plays a role in various body functions through different mechanisms which include: phosphodiesterase enzyme inhibition, adenosine receptor antagonism etc. Its action on skeletal muscles to counteract fatigue and /or paralysis is through increasing acetylcholine release from motor nerve ending and increasing calcium concentrations within the muscle fiber itself. These combined effects therefore can antagonize nondepolarizing neuromuscular blockers through competitive antagonism in generally anesthetized patients. By the use of neuromuscular monitors, this effect could be evaluated and also to assess doses for reversal of residual drug-induced neuromuscular paralysis.

Aim of the Study: the aim of this study was to evaluate the effect of theophylline on facilitating the recovery from atracurium induced neuromuscular blockade. **Patients and Methods:** this study was performed on sixty (60) patients undergone elective surgeries had been expected to be about one-hour duration, with balanced general anesthesia after obtaining approval of the Ethical and Scientific Committee of Al Fayoum University, and written informed consents from patients. In this study, we used theophylline to antagonize atracurium induced muscle paralysis. **Results:** the results showed effective antagonism of atracurium paralyzing effect and rapid recovery from this paralysis. **Conclusion:** theophylline antagonizes atracurium induced neuromuscular blockade by several mechanisms either at the prejunctional or postjunctional level by AR antagonism or PDI or by RyR channel activation. **Recommendations**: we recommend further studies to be done on different categories of patients as diabetics, cardiac patients, elderly and etc. to assess its safety among those patients. We recommend further studies to be done on different categories of patients as diabetics, cardiac patients, elderly and etc. to assess its safety among those patients.

Keywords: Phosphodiesterase enzyme inhibition, theophylline, Neuromuscular blockade, atracurium, Neuromuscular monitoring, Train of four (TOF).

INTRODUCTION

Neuromuscular blockers are pharmacological adjuncts to general anesthesia used to facilitate endotracheal intubation and ease of instrumentation in certain types of surgeries. An undesirable sequale is residual neuromuscular blockade that is linked with aspiration, decreased response to hypoxia and obstruction of the upper airway soon after extubation [(1)]. Thus, many drugs are used to facilitate recovery from this blockade and prevent residual neuromuscular blockade as neostigmine, sugammadex, protease inhibitors, K-channel agonist nicorandil and phosphodiesterase inhibitors (PDI) [(2)].

In our study, we will test theophylline which is a non-selective PDI and non-selective Adenosine receptor (AR) blocker. It is commonly used in the treatment of upper airway obstruction disorders as Asthma and chronic obstructive pulmonary disease (COPD) [(3,4)]. Recently, it has been used to antagonize sedative and hypnotic effects – monitored by bispectral index (BIS) - of inhalational agents, barbiturates, benzodiazepines, opioids and propofol [(5,6)].

Also, theophylline has been reported to enhance resting calcium concentrations in skeletal muscles by antagonizing adenosine receptors and subsequently enhancing twitch tension upon electrical stimulation in animals [(7)]. Also, it had been reported to enhance diaphragmatic contractility and enhance neurotransmitter release at the motor nerve terminals in animals [(8,9)]. So, it has been used recently in anesthesia to antagonize the neuromuscular blocking effect of non-depolarizing neuromuscular blockers. It had been reported that theophylline antagonizes the effect of pancuronium [(10,11)]. Other studies have reported that milrinone and olprinone – a selective PDI III inhibitors commonly used in heart failure due to their inotropic and vasodilatory effect – facilitate the recovery from the neuromuscular blockade induced by vecuronium [(12,13).]

However, no published study has been made to assess the effect of theophylline on recovery from atracurium- which is an intermediate acting non-depolarizing neuromuscular blocker – in humans.

AIM OF THE STUDY

The aim of this study is to evaluate the effect of theophylline on facilitating the recovery from atracurium induced neuromuscular blockade.

PATIENT AND METHODS

This study was performed on sixty (60) patients undergone elective surgeries had been expected to

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be about one-hour duration, with balanced general anesthesia after obtaining approval of the Ethical and Scientific Committee of Al Fayoum University, and written informed consents from patients.

Inclusion criteria:

Patients aging 20-50 years old have undergone elective surgeries expected to be about one-hour duration, with American society of Anesthesiology (ASA) classification I and II physical status.

Exclusion criteria:

History of significant cardiovascular, respiratory, hepatic, renal, neurological, neuromuscular, psychiatric disease, cognitive dysfunction, pregnancy, recent infection or fever, alcoholism, drug dependence, previous adverse reactions to the study drugs, current treatment with xanthines, anticholinergic agents, tranquilizers, anticonvulsants or antidepressants and habitual coffee consumption exceeding 2 cups per day or any drug that may affect neuromuscular transmission.

Randomization:

Randomization was performed using computer generated random numbers in opaque sealed envelope and has been done by an independent statistician and concealed from patients and investigators until completion of statistical analysis.

Patients were randomly divided into 2 groups;

Theophylline group or group I (n=3o) received theophylline 5 mg/kg over 10 minutes with induction of anesthesia, and if TOFR has not returned to a value of >90% at the end of the operation, intravenous atropine 0.02 mg/kg and Neostigmine 0.035 mg/kg were given.

Control group or group II (n=30) received Neostigmine 0.035 mg/kg and Atropine 0.02 mg/kg at the end of operation.

Anesthetic technique:

Premedication consisting of 0.01 mg/kg atropine and 0.05 mg/kg midazolam was administered intravenously (i.v) one hour before the induction of anesthesia.

Routine monitoring by Nihon Kohden monitor with Electrocardiogram ECG, automated non-invasive blood pressure, peripheral oxygen saturation (SpO_2) and end tidal CO_2 ($ETCO_2$) were attached to the patients and results were recorded. Anesthesia was induced with Propofol 2 mg/kg and Fentanyl 2µ /kg and after loss of verbal response was confirmed, atracurium 0.5 mg/kg was given i.v. to facilitate endotracheal intubation. Theophylline 5 mg/kg was given to group I over 10 minutes with induction of anesthesia and group II received saline at a rate of 0.1 mL/kg/h as a placebo.

Neuromuscular monitoring was done using nerve stimulator (Neuro Technology Microstim PLUS). Two surface stimulating electrodes were placed over the ulnar nerve at the wrist, and two surface recording electrodes were placed over the adductor pollicis muscle. One grounding electrode was attached between the stimulating and recording electrodes.

TOF stimuli, each stimulus consisting of a 0.2-msduration square-wave pulse given at a frequency of 2Hz, were delivered every 20s at a supramaximal current, and the evoked electromyographic responses of the adductor pollicis muscle were recorded. TOF stimuli were applied every 20s for approximately5 min. until the electromyographic responses stabilized. The electromyographic amplitude in response to first twitch of the TOF (T1) was taken to be the control reading, the disappearance of the response to T1 (1st response in TOF) was regarded as the onset of neuromuscular blockade. The times from the injection of atracurium to the return of T1, T2, T3 and T4 (the 1st, 2nd, 3rd and 4th response in TOF) were also compared between the groups. TOFR was recorded every 10 minutes and was compared between the two groups.

Anesthesia was maintained by O_2 100 %, Isoflurane at minimum alveolar concentration (MAC) of 1.15, boluses of Fentanyl of 1-2 µ/kg was given when needed and it was recorded. Lung ventilation was adjusted to maintain normocapnia.

At the end of operation, if TOFR had not returned to a value of >90%, intravenous atropine 0.02 mg/kg and Neostigmine 0.035 mg/kg was given.

Statistical analysis

Sample size estimated to be at least 26 patients in each group assuming α error=0.05, power = 80%, and effect size d = 0.7. Enrollment of 30 patients per group was done to adjust for possible dropouts. Sample size calculated using G*Power 1.3.7. Software [(14)].

Parametric continuous variables were presented as Mean ±SD and comparison between groups was done by using unpaired student t-test, intergroup variability for paired data was tested using ANOVA test with Bonferroni's adjustment. Categorical variables were expressed as numbers (%) and intergroup variability was assessed by Chi-Square test or Fisher exact test (when appropriate). P-values < 0.05 was considered to be statistically significant.

The demographic data: age, weight, sex and ASA classification showed no difference between the two groups as shown in tables 1,2 and3.

Table (1): Demographic data (sex, age and weight)

		Theophylline group		Control group		P value
		Count	%	Count	%	
Sex	Male	4	13.3%	6	20.0%	0.488
	Female	26	86.7%	24	80.0%	
		Theophylline group		Control group		P value
		Mean		Mean		
Age in years		33.00		33.67		0.765
Weight in KG		80.47		81.90		0.655

Table (3): Demographic data (ASA classification)

		Count	%
ASA	I	42	70%
	II	18	30%

Hemodynamic data: Heart rate, blood pressure (systolic and diastolic), peripheral oxygen saturation (SpO2) and end tidal CO2 (ETCO2) was measured every 15 minutes including the baseline reading at induction showed no significant difference between the two groups as shown in the following tables.

Table (4): Hemodynamic data (Heart rate)

	Theophylline group	Control group	P value
	Mean	Mean	
Heart rate at induction	77.47	68.87	0.076
Heart rate after 15 min	78.83	73.00	0.053
Heart rate after 30 min	79.30	74.70	0.056
Heart rate after 45 min	80.53	79.33	0.491
Heart rate after 60 min	79.80	78.57	0.426

Table (5): Hemodynamic data (systolic blood pressure)

	Theophylline group	Control group	P value
	Mean	Mean	
SBP at induction	111.77	118.33	0.060
SBP at 15 min	116.17	119.87	0.069
SBP at 30 min	117.70	119.60	0.337
SBP at 45 min	122.10	118.80	0.081
SBP at 60 min	125.33	118.90	0.102

Table (6): Hemodynamic data (Diastolic blood pressure)

	Theophylline group	Control group	P value
	Mean	Mean	
DBP at induction	70.57	76.10	0.211
DBP at 15 min	71.20	75.07	0.052
DBP at 30 min	71.67	75.30	0.068
DBP at 45 min	74.43	74.23	0.908
DBP at 60 min	78.03	74.57	0.051

Peripheral oxygen saturation (SpO2) showed no significant difference between the two groups as shown in table 7.

Table (7): SpO2

	Theophylline group	Control group	P value
	Mean	Mean	
SpO2 at induction	98.97	99.13	0.483
SpO2 at 15 min	98.90	98.80	0.683
SpO2 at 30 min	98.53	98.73	0.447
SpO2 at 45 min	98.63	98.83	0.430
SpO2 at 60 min	98.73	99.03	0.201

End tidal CO2 (ETCO2) showed also no significant difference between the two groups as shown in table 8.

Table (8): ETCO2

	Theophylline group	Control group	P value
	Mean	Mean	
ETCO2 at induction	39.37	39.50	0.810
ETCO2 at 15 min	39.37	39.90	0.415
ETCO2 at 30 min	39.70	40.03	0.551
ETCO2 at 45 min	39.90	40.27	0.584
ETCO2 at 60 min	39.67	40.63	0.192

The return of neuromuscular function and muscle contraction was monitored by the TOF standards. The two groups showed significant difference (P-value <0.001) according to the variables measured which are: The time to return of the four twitches T1, T2, T3 and T4 of the TOF as shown in table (9) and also the return of the TOFR to 25%, 50% and 75% of its value as shown in table (10).
The return of the four TOF twitches is a good indicator of drug action at the postjunctional level of the MEP.

Table (9): Time to return of the four twitches of TOF

	Theophylline group	Control group	P value
	Mean	Mean	
Time to return of T1 in min	23.47	32.95	< 0.001
Time to return of T2 in min	31.97	41.36	< 0.001
Time to return of T3 in min	35.77	45.75	< 0.001
Time to return of T4 in min	40.47	47.95	< 0.001

The TOFR is a good indicator to muscle activity at the prejunctional level of the MEP and equals the amplitude of the fourth twitch divided by the amplitude of the first twitch.

Table (10): Time to the return of TOFR to 25%, 50% and 75% of its value

	Theophylline group	Control group	P value
	Mean	Mean	
Time to return of TOFR to 25% in min	51.67	66.71	< 0.001
Time to return of TOFR to 50% in min	69.17	86.25	< 0.001
Time to return of TOFR to 75% in min	91.97	112.75	< 0.001

DISCUSSION

Neuromuscular blockers are pharmacological adjuncts to general anesthesia used to facilitate endotracheal intubation and ease of instrumentation in certain types of surgeries. An undesirable sequale is residual neuromuscular blockade that is linked with aspiration, decreased response to hypoxia and obstruction of the upper airway soon after extubation [(1)].

In order to optimize patient safety, tracheal extubation in the operating room should not occur until complete recovery of muscle strength is present and the residual effects of neuromuscular blockers have been fully reversed (or spontaneously recovered). Therefore, clinicians have methods to detect and treat residual muscle weakness. Three methods are commonly used in the operating room to determine the presence or absence of residual neuromuscular blockade: clinical evaluations for signs of muscle weakness, qualitative neuromuscular monitors, and quantitative neuromuscular monitors. In both types of monitoring a peripheral nerve stimulation (PNS) is used; in qualitative monitoring muscle contraction and movement is assessed subjectively by visual or tactile means, while in quantitative monitoring muscle acceleration is sensed by a piezoelectric monitor attached to muscle and this acceleration is proportional to muscle contraction strength. Many PNS patterns is used to assess neuromuscular activity as TOF, tetanic stimulation and DBS [(15)].

In our study, we used qualitative monitoring using peripheral nerve stimulator (Neuro Technology Microstim PLUS), and we used TOF pattern to stimulate ulnar nerve and assess adductor pollicis muscle movement in response to stimulation. The variables measured are the times to the return of the four TOF twitches T1, T2, T3 and T4 and also the time taken for TOFR to return to 25%, 50% and 75% of its value. These variables were taken for the two groups in the study: The theophylline group and the control group with 30 patients each.

The return of four twitches of the TOF is an indicator of postjunctional AChRs action while the return of TOFR to normal values is an indicator of activity at the prejunctional side of the motor endplate (MEP) [(16)].

Many drugs are used to facilitate recovery from neuromuscular blockers and prevent residual neuromuscular blockade as neostigmine, sugammadex, protease inhibitors, K-channel agonist nicorandil and phosphodiesterase inhibitors (PDIs) [(2)].

In our study, we used theophylline a non-selective PDI to evaluate its effect on neuromuscular blockade achieved by atracurium. In theophylline group, 5 mg/kg of theophylline was given over 10 minutes with induction of anesthesia, while saline was given to the control group as a placebo.

Theophylline is commonly used as a treatment to chronic upper airway disorders and also as a CNS stimulant and could be used to counteract many drugs that suppress the CNS [(3)].

As regard to theophylline effect on skeletal muscles, many studies have been done on animals that prove that it enhances contractility of skeletal muscles and resist diaphragmatic fatigue [(7,9)]. Other PDIs as milrinone and olprinone which are specific PDI III has been shown to do the same as theophylline as regarding skeletal muscles contractility [(17,18)].

In human, reports have been made about cases showing antagonism of pancuronium neuromuscular blocking effect by theophylline [(10,11)].

In our study, theophylline hastened the recovery from atracurium neuromuscular blockade. It showed antagonism of atracurium at the prejunctional and postjunctional AChRs.

The time to return of the four twitches was significantly shorter in the theophylline group than in the control group. The time to return of T1 was (23.47±0.92) min. in theophylline group and (32.95±1) min. in the control group. That of T2 was (31.97±0.92) min. in theophylline group and (41.36±1) min. in the control group. That of T3 was (35.77±0.92) min. in the theophylline group and (45.75±1) min. in the control group. That of T4 was (40.47±0.92) min. in the theophylline group and (47.95±1) min. in the control group. All these four twitches showed a significant difference (p value < 0.001) between the two groups and that theophylline antagonizes atracurium at the postjunctional side of the MEP.

Mechanisms of this postjunctional action of theophylline include activation of ryanodine receptor (RyR) channels in the skeletal muscles sarcoplasmic reticulum and endoplasmic reticulum resulting in calcium release a process involved in excitation contraction coupling [(19,20)].

Nakajima *et al.* [(12)] recorded also a significant difference between the times to return of the four TOF twitches of the two groups: T1 in (18.5±6.5) min. in milrinone group and (23.9±7.3) min. in the control group, T2 in (25.9±7.3) min. in the milrinone group and (32.1±8.2) min. in the control group, T3 in (30.4±8.2) min. in the milrinone group and (37.3±9.4) min. in the control group and finally T4 in (32.4±8.5) min. in the milrinone group and (39.7±9.8) min. in the control group (p value <0.05) however the difference was larger in our study (p value<0.001). These results denote that

theophylline actions on the postjunctional side of MEP may be greater than milrinone as both atracurium and vecuronium are intermediate acting neuromuscular blockers with atracurium is slightly longer acting than vecuronium [15].

On the other hand, **Katayama *et al*.** [13] recorded no significant difference between the two groups when using olprinone with vecuronium regarding the time to return of the four TOF twitches: T1 in (22.8±7.2) min. in the olprinone group and (26.3±7.7) min. in the control group, T2 in (31.1±8.8) min. in the olprinone group and (35.4±9.4) min. in the control group, T3 in (35.1±9.6) min. in the olprinone group and (40.6±10.9) min. in the control group and finally T4 in (36.5±10.3) min. in the olprinone group and (43.7±11.6) min. in the control group, suggesting that it has minimal effect on the postjunctional side of the MEP (P value > 0.08).

In our study, the time taken for the TOFR to return to 25%, 50% and 75% of its values were also significant between theophylline and control group. The times to return of the TOFR to 25% were (51.67±0.92) min. in the theophylline group and (66.71±0.93) min. in the control group, to 50% were (69.17±0.92) min. in the theophylline group and (86.25±1) min. in the control, to 75% were (91.97±0.92) min. in the theophylline group and (112.75±1) min. in the control group. These results confirm the significant action of theophylline (p value < 0.001) in the motor nerve ending in antagonizing atracurium effects as returning of TOFR to normal values is an indicator of prejunctional effects [16].

Mechanisms which demonstrate theophylline action include: antagonism of adenosine A1 receptors at the presynaptic membrane [21], PDE inhibition leading to increase intracellular cAMP [22] and finally RyR channel activation in the motor nerve ending [23]. All these mechanisms lead to increase acetylcholine release that competes with atracurium for the postsynaptic AChRs thus improving muscle contraction.

Nakajima *et al.* [12], showed that return of TOFR to 25% in (45.5±11) min. in the milrinone group and (57±12.3) min. in the control group, to 50% in (62.3±16) min. in the milrinone group and (77.4±20.5) min. in the control group and to 75% in (83.5±25.7) min. in the milrinone group and (101.1±25.4) min. in the control group. This result is also significant at 25% and 50% of TOFR (p value <0.05) but not at 75% of TOFR value (p value >0.05). Also, **Katayama *et al.*** [13] showed that olprinone antagonizes vecuronium at the prejunctional level but the same as milrinone significant at 25% and 50% of TOFR but not significant at 75% of its value. They explained that milrinone and olprinone do better at deeply paralyzed or fatigued muscles and they supported this hypothesis as **Fujii *et al.*** [24] showed that milrinone enhances contractility of fatigued dog diaphragm but not the non-fatigued muscle. In our study, theophylline effect was significant at all TOFR values, even the 30 patients of theophylline group didn't require neostigmine 0.035mg/kg plus atropine 0.02mg/kg as TOFR has returned to >90% before the end of operation as this is considered the standard criterion of extubation [25] and all patients were extubated with no residual blockade. On the other hand, **Nakajima *et al.*** [12] and **Katayama *et al.*** [13] gave neostigmine and atropine to some patients at the end of operations to reverse residual blockade as TOFR was not yet 0.9.

In our study, theophylline was given only at induction and over 10 minutes only with no continuous infusion. On the other hand, milrinone and olprinone was started 30 minutes before induction at a dose of 5mg/kg over 10 to 15 minutes and then a continuous infusion till end of operation. This also may confirm superiority of theophylline and it may resist non-depolarizing agents with continuous infusions or higher doses as reported by **Doll and Rosenberg** [10].

Doll and Rosenberg [10] reported a case of 21 years old woman 45kg who suffered bronchospasm and therefore aminophylline infusion was started at 1.55mg/kg/hr. for 48 hours and then because of its respiratory status mechanical ventilation was considered and muscular paralysis with pancuronium was planned. After 5 minutes of 6mg intravenous pancuronium administration no paralysis occurred and was confirmed by sustained tetanus and sustained twitch height in the four TOF twitches in response to PNS. Then additional 16mg pancuronium was given over the next 20 minutes but still no response happened until succinylcholine 100mg was administered. After almost 10 minutes, spontaneous respiration had returned despite all these doses of pancuronium. Later, aminophylline infusion was then reduced and 8mg of pancuronium was enough to obtain paralysis for mechanical ventilation. They concluded that cyclic nucleotides as cAMP and cGMP play a role in neurotransmitter release and theophylline inhibits phosphodiesterase the enzyme responsible for their degradation thus increasing their intracellular level. And this is a point of interest that needs more research to be done to estimate doses needed for optimum reverse of nondepolarizing agents but also without complete resistance to them.

Our study suffers from a limitation that the effect of sex couldn't be excluded as it has been done on male and female patients and this was done unintentionally.

CONCLUSION

Theophylline antagonizes atracurium induced neuromuscular blockade by several mechanisms either at the prejunctional or postjunctional level by AR antagonism or PDI or by RyR channel activation.

Recommendations:

We recommend further studies to be done on different categories of patients as diabetics, cardiac patients, elderly and etc. to assess its safety among those patients.

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