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Interactions between Gabapentin and Cisatracurium in Experimental Animals and in Patients Undergoing Spinal Surgeries

(Pharmacological and Clinical Study)

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ABSTRACT

Background: gabapentin was originally discovered over 40 years ago by the Japanese, who initially were looking for an antispasmodic or muscle relaxant, but, later it was used as an antiepileptic and multimodal perioperative drug. **Objective** of this randomized study is to assess the some cardiovascular effects of gabapentin as well as its effect on the neuromuscular blockade induced by Cisatracurium. The interactions between both of them was also done in cats and rats & in patients undergoing elective spinal surgeries. **Materials & Methods:** The pharmacological study was carried out at the pharmacological lab of Al-Azhar University. The effect of different doses of cisatracurium (0.25 -4 µg/ml) and Gabapentin (6-96 µg/ml) & interactions between gabapentin (24µg/mL) and cisatracurium (0.25-4 µg/mL) were also done to test the effect on the amplitude of contraction of isolated Rat phrenic nerve -diaphragm preparation. Effect of intravenous (IV) injection of cisatracurium (1-16 mg/kg) and Gabapentin (15-240 mg/kg) and interactions between gabapentin (60mg/kg) and cisatracurium (1-16 mg/kg) on mean arterial blood pressure (MAP) and electrocardiogram (ECG) were also studied on anesthetized cats. Each experiment was done on six preparations. The *clinical Study* was carried out at Al-Zahraa University Hospital on 90 patients (ASA I or II) of both sexes undergoing spinal operations were randomized into three equal groups (30 patients) for each; one hour preoperatively they received oral capsules, group I; gabapentin (1200mg), group II gabapentin (800mg) and group III; placebo capsules. After induction of anesthesia with (IV) fentanyl, thiopental and cisatracurium & tracheal intubation, anesthesia was maintained by isoflurane (0.5-2%), Patients were assessed for heart rate (HR), MAP, neuromuscular blockade. Isoflurane concentration, fentanyl needed and cisatracurium consumption were recorded. **Results:** Experimentally: **In-vitro study:** Cisatracurium besylate (0.25-4µg/ml) produced dose-dependent significant reductions on the amplitude of muscle contractions. Gabapentin (6-96µg/ml) produced dose-dependent significant reductions on the amplitude of muscle contractions at 24-96 µg/mL while the first two doses 6-12 µg/mL have no effect. On interactions Gabapentin (24 µg/ml) produced synergistic effect on neuromuscular blocker effect of cisatracurium (0.25-4 µg/mL). ***In-vivo* study** cisatracurium, IV, (1-16 mg/kg) produced no effect on both mean arterial blood pressure (MAP) and heart rate (HR) of anesthetized cats. Gabapentin (15- 240 mg/kg) caused dose-dependent significant reductions on the MAP and the HR of the anesthetized cats except the first two doses (15-30 mg/kg). On interactions Gabapentin (60 mg/kg) potantiated the effect of cisatracurium (1-16mg/kg) and caused significant reduction on mean arterial blood pressure and heart rate. **Clinically:** Gabapentin 1200mg produced highly significant reduction in MAP&HR at pre-induction and immediately after intubation which extended for 120min. It also prolonged the duration of neuromuscular blockade of cisatracurium 0.15 mg/kg for 100min. While Gabapentin 800mg produced significant reduction in MAP &HR at pre-induction, immediately after intubation which extended for 45min. It also prolonged the duration of neuromuscular blockade of cisatracurium 0.15mg/kg up to for70min.

Conclusion: Gabapentin has a neuromuscular blocking effect on interactions Gabapentin produced synergeistic effect on the neuromuscular blocker effect of cisatracurium. It also has considerable hypotensive as well as negative chronotropic effect. On interactions, gabapentin potantiated the effect cisatracurium on MAP&HR and caused significant decrease in MAP & HR on experimental animals and on patients undergoing elective spinal surgeries.

Keywords: Cisatracurium, Gabapantin, Isolated rat phernic-nerve, Anaesthetized cats.

INTRODUCTION

Spinal fusion & lumber discectomy are the most common spinal surgical procedures performed for patients with back and leg symptoms associated with perioperative severe

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pain and intra-operative blood loss, so preemptive analgesia and controlled hypotension, (hemostasis) "to decrease blood loss" are major concerns of anesthetic management of such cases. It is also important to provide anxiolysis, prevent or decrease postoperative shivering, nausea, vomiting and lastly provide postoperative analgesia [1].

It is interesting that single drug may have all these effects. Gabapentin is that drug, it has multimodal perioperative effects. Subsequently, it was shown to be effective in treating seizures, variety of chronic pain conditions, all types of neuropathic pain and head-aches [2].

Studies on gabapentin use has been extended into the management of more acute conditions, particularly in the perioperative period as: Preoperative anxiolysis, attenuation of hemodynamic responses to direct laryngoscopy and intubation, postoperative analgesia, prevention of postoperative nausea and vomiting (PONV), postoperative delirium and prevention of chronic post-surgical pain have been published, so gabapentin has wide-ranging therapeutic actions [3].

Gabapentin; (1-aminomethyl cyclohexane acetic acid,) structurally related to gamma-amino butyric acid (GABA), but, does not modify GABAA or GABAB radioligand binding, not converted metabolically into GABA or a GABA agonist, and is not an inhibitor of GABA uptake or degradation. It has an alternative mechanism of action in CNS exerting GABA-menergic activity by binding receptors in the cortex and hippocampus, it acts by decreasing the synthesis of neurotransmitter glutamate and by binding to the alpha 2 delta subunits of voltage dependent calcium channels; acting as calcium channel blocker.

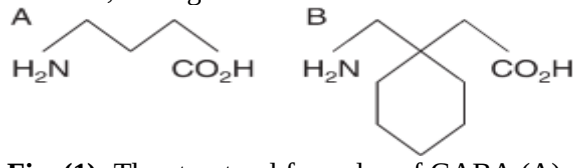


Fig. (1): The structural formulae of GABA (A) and gabapentin (B)[3] .

Gabapentin absorption occurs through active transport by a low-capacity nutrient transporter expressed in a narrow region of the upper small intestine. As a result, gabapentin bioavailability decreases with increasing dose [4]. It is easily absorbed, reaching peak plasma concentrations in 2 to 3 hours, it is not protein bound, does not undergo metabolism, and is excreted unchanged in the urine. It is well tolerated in dosages upto3600mg/day. The side effects of peri-operative gabapentin are rare; include dizziness, somnolence, confusion, ataxia, nausea, vomiting and headache [5].

MATERIALS & METHODS

Pharmacological study:

The doses used in this study, corresponding to the therapeutic doses in human, were calculated according to the method reported by ***Paget and Barnes*** [6]. Statistical analysis was performed using the student "t" test for significance.

1-

amplitude of contraction of the isolated muscle in response to indirect electrical stimulation was studied. Also drug interactions between gabapentin (24µg/ml) and different doses of cisatracurium (0.25-4 µg/ml) was studied.

2-

ECG records were studied. MAP was recorded according to the staff of department of pharmacology University of Edinburg[8]. ECG was recorded by an electrocardiograph (Cardiohpen 531) Philips, using lead II on anesthetized cats.

Clinical Study:

After obtaining the approval of the Ethical Committee of Al Zahraa University Hospital and obtaining the informed written consent, 90 patients ASA physical status I or II, of both sex, 27 to 64 years, undergoing elective lumbar discectomy or spinal fusion surgeries were included in this study. All patients were subjected to physical, radiological examination and routine laboratory investigations.

Exclusion criteria: Patients with history of known allergy to any of the study drugs, uncontrolled hypertension, ischemic heart disease, uncontrolled Diabetes mellitus, cerebrovascular disease, renal or hepatic disease, bronchial asthma, drug or alcohol abuse and pregnancy.

The patients were randomly divided into three equal groups of 30 patients for each 2h. before surgery they received oral capsules as follow: Group I: Gabapentin 1200 mg. Group II: gabapentin 800 mg. Group III: placebo capsules.

The Study Drugs: Gabapentin (capsule 400 mg; Pfizer, Goedecke GmbH, Germany). Cisatracurium Besylate ampoules 10ml (1mg/ml).

Preoperatively, the patients were assessed for MAP, HR, sedation and any side effect. In OR

standard monitoring; [(MAP), HR, end-tidal CO2 (capnography) and peripheral oxygen saturation ($spao_2$) were monitored by (Drager model Infinity Vista XL made in USA, Inc.3135Quarry Road Telford, PA18969-1042). Anesthesia was induced intravenously with 1µg/kg fentanyl, sleeping dose of thiopental, 0.15 mg/kg cisatracurium and tracheal intubation, and then maintained by isoflurane (0.5-2%) with (%50 air in oxygen) by Dragger Fabius plus, GmbH 23542 Lumbeck, made in Germany).the degree of neuromuscular blockade was assessed by the peripheral nerve stimulator INNERV-TOR model:NS272A by Fisher & Paykel electronics Ltd Aukland. Newzealand.

Isoflurane concentration & fentanyl infusion (0.2-1µg / kg/h) were titrated according to each patient's need; to maintain MAP; 55-70 mmHg and HR; 60-85beat/min. Cisatracurium poster doses were given on need guided by Train of four and capnography, the time to first poster dose of cisatracurium was recorded. At the end of surgery, isoflurane and fentanyl were turned off, the neuromuscular blockade was reversed with (0.05 mg/kg neostigmine plus 1.0 mg atropine), the trachea was extubated and the patients were transferred to the PACU.

The total intra-operative, cisatracurium, fentanyl consumption, total IV fluids, and blood transfusion for each patient were recorded. The patients were questioned during the first hour in the PACU and were later evaluated in the ward fore, HR, MAP, occurrence of any adverse effects, such as nausea and vomiting, fatigue, malaise, respiratory depression, dizziness, somnolence, diarrhea, headache, and pruritis.

Statistical analysis: We calculated the sample size of 30 patients in each group using the programme of Biostatics version 3.01 based on the data with the α-error level was fixed at 0.05 and the power was set at 90%. Data values are presented as means (SD), median (range) or number (percentage). Parametric data were analyzed by using one way ANOVA and Student's paired *t*-test where appropriate. Nonparametric data were analyzed by using the Kruskal–Wallis test [4]. A value of $P < 0.05$ was considered significant. All statistical analysis was performed using Microsoft Excel.

RESULTS

Experimentally:

1- ***In-vitro study*** on rat phrenic nerve - diaphragm preparation.

Cisatracurium (0.25- 4 µg /ml) produced dose dependent reductions on the amplitude of muscle contractions fig (2). The mean percentage reductions were ranged from 5.8±1.8 to 35± 2.8 and were found to be statistically significant at all doses (Table 1). Gabapentin (6-96µg/ml) produced dose dependent reductions on the amplitude of muscle contractions at all doses except the first two doses (6-12 µg/mL) fig. (3). The mean percentage reductions were ranged from 5.22±0.81 to 20±1.9 and was found to be statistically significant (Table 2). On interactions gabapentin (24µg/ml) produced synergistic effect on neuromuscular blocker effect of cisatracurium (0.25-4µg/mL). The mean percentage reductions were ranged from, 12.5± 1.7 to 53.3±3.1 and were found to be statistically significant at all doses (Fig. 4) and (Table 3).

2- ***In-vivo study*** on mean arterial blood pressure and heart rate of anesthetized cats:

Cisatracurium, IV, (1-16 mg/kg) produced no effect on mean arterial blood pressure of anesthetized cats (fig 5). Gabapentin (15- 240 mg/kg) caused dose dependent reductions in the MAP; fig. (6). The mean percentage reductions were ranged from 6.17±1.4 to 14.73±1.08, and were found to be statistically significant at all doses except the first two doses (15-30mg/kg) have no effect; (Table 4). On interactions gabapentin (60 mg/kg) potantiated the effect of cisactracurium (1-16mg/kg) on mean arterial blood pressure and caused significant reduction on MAR. The mean percentage reductions were ranged from, 13.09±1.78 to 42.3±3.10 and were found to be statistically significant at all doses (Fig. 7 and table 5). ECG records of intact anesthetized cat showed that no changes in HR with all doses of cisatracurium (1-16mg/kg) as shown in fig. (8). Gabapentin (15- 240 mg/kg) caused dose-dependent reductions in the HR as in fig. (9). The mean percentage reductions were ranged from, 10± 1.15 to 30± 1.51 and were found to be statistically significant at all doses except the first two doses (15-30mg/kg) have no effect (table 6). Gabapentin (60 mg/kg) potantiated the effect of cisatricurium (1-16mg/kg) on heart rate and caused significant reduction as in Fig (10). The mean percentage reductions were ranged from, 19.69 ± 2.60 to 58.01±1.90 and

were found to be statistically significant at all doses as in (table 7).

DISCUSSION

The primary objective of the research was to assess the cardiovascular effects of gabapentin 1200mg, but we found many cases of delayed recovery due to prolonged neuromuscular blockade, we tried to reduce the doses of cisatracurium up to reduction of the intubating dose to 0.1mg /kg which was effective for more than 120 min. We repeated the clinical study with two doses of gabapentin (800, 1200 mg) and their effects on the MAP, HR and neuromuscular blockade, in addition to starting the pharmacological study on the interactions between gabapentin & cisatracurium.

As regard the mechanisms of actions of gabapentin; as a calcium channel blocker. ***Stefani et al.*** recorded that gabapentin inhibits calcium currents in isolated rat brain neurons [9]. ***Fink et al.*** reported that gabapentin inhibits neuronal Ca (2+) influx and subsequent reduced the neurotransmitter release from rat neocortical slices [10]. ***Dooley et al.*** reported that gabapentin inhibits the K (+)-evoked glutamate release from rat neocortical and hippocampal slices [11]. Also, ***Sarantopoulos et al.*** found that gabapentin decreases membrane calcium currents in injured as well as in control mammalian primary afferent neurons [12]. ***Thorpe and Offord*** reported that gabapentin acts on the alpha2-delta protein: an auxiliary subunit of voltage-dependent calcium channels which was recognized as a drug target [13].

Cisatracurium is a stereoisomer of atracurium but is four times more potent. its benzylisoquinoline structure is responsible for its unique method of degradation, Cisatracurium produces good intubating conditions following a dose of 0.1–0.15 mg/kg within 2 min and results in muscle blockade of intermediate duration. As regard the side effects; Unlike atracurium, cisatracurium does not produce a consistent, dose-dependent increase in plasma histamine levels following administration. Cisatracurium does not alter heart rate or blood pressure and it doesn't produce autonomic effects, even at doses as high as eight times ED 95 [14].

As regard neuromuscular blocking effect: Gabapentin produced dose dependent reduction on the amplitude of muscle contractions and increased the effect of cisatracurium experimentally. The same results were confirmed clinically when gabapentin 1200mg prolonged the duration of the intubating dose of cisatracurium to about 100min while gabapentin 800mg prolonged the duration to about 70min. The time of 1st poster dose of cisatracurium was 96.6±13.3min. in the 1st group and was 72.4±14.5min. In the second group compared to 42.3±11.2min. in the control group. Also, the total consumption of cisatracurium was 12.5± 2.1mg in the 1st group and 16.2 ± 4.36 mg. in the second group compared to, 20.6± 3.7mg in the control group.

Some reports by ***Boneva et al.*** have included the observation of seropositive myasthenia gravis occurring after three months of gabapentin therapy for painful neuropathy. Following withdrawal of the drug, the patient became asymptomatic, concluding that gabapentin should be used with some caution in myasthenia gravis who have muscle cramps, because such patients had been a common practice to prescribe gabapentin for control of muscle cramps [15].

Pascuzzi reported that from the agents that impair neuromuscular transmission; the calcium channel blockers, and antiepileptic drugs, which adversely affect neuromuscular transmission, by presynaptic reduction in ACh release and also postsynaptic curare-like effects, have been observed in experimental settings. Also, the same author suggested that calcium channel blockers can potentiate the effect of neuromuscular blocking drugs. In vitro studies of nerve-muscle preparations have shown that phenytoin reduces the quantal release of acetylcholine from the motor nerve terminals; one explanation for this effect is the reduction in the size of the nerve action potential at the motor nerve terminals [16].

Other studies by ***Dunevsky & Perel and Priebe et al.*** have been reported that gabapentin is effective in treating spasticity [17,18]. Also ***Kita and Goodkin*** used gabapentin to treat spasticity [19]. ***Casale et al.*** reported that gabapentin has been used for treatment of amylotrophic sclerosis, possibly through inhibition of glutamatergic transmission in the central nervous system [20].

As regard hemodynamic effects, gabapentin, our study showed reductions in MAP & HR and caused significant decrease of them with cisatracurium experimentally which was confirmed clinically, before and after induction, (intubation), were highly significant

in group I (1200 mg) P value <0.002, while significant in group II (800 m g) P value <0.05, both compared to the placebo control group III. These results can be explained by the action of gabapentin on the membrane VGCCs by inhibition, thus acting like a calcium channel blocker as mentioned before.

Our results are partially agree with ***Ali et al.*** who compared the effect of same doses of gabapentin (1200 mg and 800 mg) on the stress response to laryngoscopy and intubation. They reported that Gabapentin 1200 mg prevented the increase in HR, and MAP secondary to laryngoscopy and intubation, and kept them below the baseline till 10 minutes after intubation with *P*< 0.001, while with gabapentin 800 mg, the increase in HR, MAP was non-significant (*P*> 0.05) and returned to levels below the baseline at 5 and 10 min. after intubation and they Concluded that Preoperative gabapentin 1200 mg effectively prevented the stress response to laryngoscopy and intubation; while, gabapentin 800 mg only prevented significant stress response [21].

Mahmoud et al. used gabapentin 1200 mg as oral premedication which successfully provided an intra-operative hypotension during functional endoscopic sinus surgery [22], ***Ayatollahi et al***. studied the effect of 800 mg oral gabapentin given 90 min before microlaryngoscopy surgery attenuating the rise of diastolic blood pressure and mean arterial blood pressure in the first 15 min after surgery, but has no effect on systolic blood pressure [23].

Geeta and Shahi studied the effects of gabapentin 900 mg on arterial pressure and heart rate, at induction of anesthesia and at tracheal intubation they recorded that the DBP was significantly less than the placebo group ($p<0.05$) and there was a significant decrease in heart rate in Group G as compared to Group P ($p<0.05$) [24].

Usha & colleagues used gabapentin 1000 mg given 1 h before operation and found that it significantly attenuated the haemodynamic response to laryngoscopy and intubation (Significant decrease in MAP & HR) compared to 600 mg gabapentin and placebo groups [25].

Marashi et al. compared the effect of oral premedication with 900 mg gabapentin, and 0.2 mg clonidine, 120 minutes before operation in modifying the hyperdynamic response following laryngoscopy and tracheal intubation, and they found that the lowest heart rate, systolic, diastolic and mean arterial blood pressure were in the gabapentin group [26].

A study by ***Kaya et al.*** showed that oral gabapentin (800 mg) 2 h before surgery, effectively reduced the intraocular pressure, MAP and HR and attenuated their increases secondary to tracheal intubation [27].

Memiş et al. compared the effects of gabapentin (400 mg or 800 mg) on arterial pressure and heart rate at induction of anesthesia and tracheal intubation and they found that gabapentin 400 mg has no effect on arterial pressure and heart rate, while there was significant decrease in heart rate and arterial pressure in the dose (800mg) [28].

Misra et al. demonstrated that 900 mg of gabapentin administered orally 2 hours before induction of anesthesia, abolished the hemodynamic response after skull pin insertion [29].

REFERENCES:

1- Weinstein JN, Tosteson TD, Lurie JD, Tosteson ANA, Hanscom B, Skinner JS, Abdu WA, Hilibrand AS, Boden SD and Deyo RA (2006): Surgical vs Nonoperative Treatment for Lumbar Disk Herniation The Spine Patient Outcomes Research Trial (SPORT): A Randomized Trial FREE. JAMA., 296(20): 2441-2450.

2- Parke-Davis A (2008): Gabapentin (Neurontin) History of Gabapentin - eMedExpert.com. Division of Pfizer Inc 6 Oct 2008, NY, NY 10017 http://www.emedexpert.com/facts/gabapentin-facts.shtml.

3- Kong VKF and Irwin MG (2007): Gabapentin: a multimodal perioperative drug? Br J Anaesth., 99: 775–86.

4- Lee DO, Ziman RB, Thomas Perkins A, Steven Poceta J, Walters AS and Barrett RW (2011): A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Gabapentin Enacarbil in Subjects with Restless Legs Syndrome. J Clinical Sleep Med.,7(3): 282–292.

5- Cundy KC, Sastry S, Luo W, Zou J, Moors TL and Canafax DM (2008): Clinical pharmacokinetics of XP13512, a novel transported prodrug of gabapentin. J Clin Pharmacol., 48(12):1378-1388.

6- Paget GE and BARNES JM (1964): Toxicity tests In : Evaluation of drug activities. Pharmacometrics, edited by Laurence DR and Bacharach AL; vol. 1, chap. 6,135

7- The staff of the department of pharmacology, university of Edenburgh (1970): Pharmacological experiments on isolated preparations pp: 18-21 & S Livingstone, Edinburgh London.

8- The staff of the department of pharmacology, university of Edenburgh (1970): Pharmacological experiments on intact preparations pp: 18-21 & S Livingstone, Edinburgh London.

9- Stefani A, Spadoni F and Bernardi G (1998): Gabapentin inhibits calcium currents in isolated rat brain neurons. Neuropharmacology, 37:83-91.

10- Fink K, Meder W, Dooley DJ and Gothert M (2000): Inhibition of neuronal Ca(2+) influx by gabapentin and subsequent reduction of neurotransmitter release from rat neocortical slices. Br J Pharmacol.,130:900-06.

11- Dooley DJ, Mieske CA and Borosky SA (2000): Inhibition of K (+)-evoked glutamate release from rat neocortical and hippocampal slices by gabapentin. Neurosci Lett., 280:107-10.

12- Sarantopoulos C, McCallum B, Kwok WM and Hogan Q (2002): Gabapentin decreases membrane calcium currents in injured as well as in control mammalian primary afferent neurons. Reg Anesth Pain Med.,27:47-57.

13- Thorpe AJ and Offord J (2010): The alpha2-delta protein: an auxiliary subunit of voltage-dependent calcium channels as a recognized drug target. Curr Opin Investig Drugs,11(7):761-70.

14- Naguib M and Lien CA (2010): Pharmacology of muscle relaxants and their antagonists. In: Miller's Anesthesia, 7th ed. Miller RD, Eriksson LI, Wiener-Kronish JP, Young WL (editors). Churchill Livingstone.

15- Boneva N, Brenner T and Argov Z (2000): Gabapentin may be hazardous in myosthenia gravis. Muscle Nerve, 23(8):1204-1208.

16- Pascuzzi RM (2007): Medications and Myasthenia Gravis, Indianapolis, IN 46202 USA, Prepared by the Professional and Public Information Committee Myasthenia Gravis Foundation of America, October, 2000 Most recent revision January 2007 Department of Neurology Indiana University School of Medicine Telephone: 317/274-4455 E-mail: rpascuzz@iupui.edu Emerson Hall 125 545 Barnhill Drive

17- Dunevsky A and Perel A (1998): Gabapentin for relief of spasticity associated with multiple sclerosis. Am J Phys Med Rehabil, 77: 451-46.

18- Priebe MM, Sherwood AM, Graves DE *et al.* (1997): Effectiveness of gabapentin in controlling spasticity: a quantitative study. Spi-nal Cord; 35: 171-5.

19- Kita M and Goodkin DE (2000): Drugs Used to Treat Spasticity Department of Neurology, University of California at San Francisco, School of Medicine UCSF/Mt Zion Multiple Sclerosis Center, San Francisco, California, USA DISEASE MANAGEMENT Drugs, 59 (3): 487-495.

20- Casale R, Glynn GJ, Buon Core M *et al.* (2012): Reduction of Spastic hypertonia in patients with spinal cord injury. Arch Phys Med Rehabil., 60: 76.

21- Ali AA, Elnakera MA and Samir A (2013): Effect of Two Different Doses of Gabapentin on the Intraocular Pressure and Hemodynamic Stress Responses to Laryngoscopy and Tracheal Intubation. Hindawi Publishing Corporation ISRN Anesthesiology Volume 2013, Article ID 698205, 5 pages http://dx.doi.org/10.1155/2013/698205.

22- Mohammed MH, Fahmy AD and Hakim KY (2012): Preoperative gabapentin augments intraoperative hypotension and reduces postoperative opioid requirements with functional endoscopic sinus surgery, Egyptian Journal of Anaesthesia Received 15 December 2011; revised 19 February 2012; accepted 21 February 2012Available online, 28 -189--192

23- Ayatollahi V, Mirshamsi P, Behdad S, Amirdosara M and Vaziribozorg S (2014): Effect of oral gabapentin on haemodynamic variables during microlaryngoscopic surgery. Anaesthesiol Intensive Ther., 46(1):17-22.

24- Bhandari G and Shahi KS (2012): Effect of Gabapentin on Pressor Response to Laryngoscopy and TrachealIntubation: A Double Blind Randomized Placebo Controlled Study. Department of Anaesthesiology, *Surgery Medical College, Haldwani - 263139 (Uttarakhand). Journal of Neurosurgical Anaesthesiology ,23(2):110-117.

25- Bafna U, Goyal VK and Garg A (2011): A comparison of different doses of gabapentin to attenuate the haemodynamic response to laryngoscopy and tracheal intubation in normotensive patients. Journal of Anaesthesiology Clinical Pharmacology, 27(1): 43.

26- Marashi SM, Ghafari MH and Saliminia A (2009): Attenuation of hemodynamic responses following laryngoscopy and tracheal intubation -- comparative assessment of clonidine and gabapentin premedication. Middle East J Anaesthesiol .,20(2):233-7.

27- Kaya FN, Yavascaoglu B, Baykara M, Altun GT, Gülhan N and Ata F (2008): Effect of oral gabapentin on the intraocular pressure and haemodynamic responses induced by tracheal intubation. Acta Anaesthesiol Scand .,52(8):1076-80.

28- Memiş D, Turan A, Karamanlioğlu B, Seker S and Türe M (2006): Gabapentin reduces cardiovascular responses to laryngoscopy and tracheal intubation. Eur J Anaesthesiol., 23(8):686-90.

29- Misra S, Koshy T, Unnikrishnan KP, Suneel PR and Chatterjee N (2011): Gabapentin Premedication Decreases the Hemodynamic Responses to Skull Pin Insertion in Patients Undergoing Craniotomy. Journal of Neurosurgical Anaesthesiology ,23(2):110-117.

Table (1): Mean percentage reductions caused by Cisatracurium (0.25- 4 µg /ml) on Rat phrenic -nerve diaphragm preparation (cm). (Mean % ± SEM)

Cisatracurium (µg /ml)					
	0.25 µg /ml	0.5 µg /ml	1 µg /ml	2 µg /ml	4 µg /ml
Mean%	5.8	10	17.8	25	35
±SEM	1.8	2.1	1.6	1.9	2.8
P	<0. 05	< 0.01	< 0.001	< 0.001	< 0.001

P<0.05 is sign, P<0.001 is highly sign.

Table (2): Mean percentage reductions of Gabapentin (6-96µg/ml) on Rat phrenic- nerve diaphragm preparation (cm). (Mean % ± SEM)

Gabapentin (6-96µg/ml)					
	6	12	24	48	96
Mean%	0.0	0.0	5.22	11.67	20
±SEM	0.0	0.0	0.81	1.70	1.90
P	---	---	<0.05	<0.001	<0.001

P<0.05 is sign. P<0.001 is highly sign.

Table (3): Mean Percentage reductions caused by Gabapentin (24 µg/ml) and cisatracurium (0.25-4µg/ml) on Rat phrenic- nerve diaphragm preparation (cm).(Mean % ± SEM)

Gabapentin (24 µg/ml) plus Cisatracurium (0.25-4µg/ml)					
	0.25	0.5	1	2	4
Mean%	12.5	25	37	44	53.3
±ESM	1.7	1.8	2.1	2.3	3.1
P	<0.01	<0.01	<0.01	<0.01	<0.01

P<0.05 is sign. P<0.001 is highly sign.

Table (4): The mean percentage reductions caused by gabapentin (15-240 mg/kg) on the mean arterial blood pressure (mmHg) of anesthetized Cats. (Mean % ± SEM)

	15	**30**	**60**	**120**	**240**
Mean%	0.00	0.00	6.17	9.73	14.73
±SEM	0.00	0.00	1.40	0.93	1.08
P	----	------	< 0.05	<0.001	<0.001

P<0.05 is **sign**. P<0.001 is highly sign.

Table (5): The mean percentage reductions caused by gabapentin (60 mg/kg) and cisatracurium (1-16mg/kg) on mean arterial blood pressure (mmHg) of anesthetized cats. (Mean % ± SEM)

Mg/kg	**60 gabap. + 1cisatr**	**60 gabap. + 2 cisatr**	**60 gabap. + 4 cisatr**	**60 gabap. + 8 cisatr**	**60 gabap. + 16 cisat**
Mean%	13.09	19.69	24.04	30.5	42.3
±SEM	1.78	2.60	2.34	2.20	3.10
P	< 0.001	< 0.001	< 0.001	0.001	0.001

P<0.05 is sign. P<0.001 is highly sign.

Table (6): The mean percentage reductions caused by Gabapentin (15-240 mg/kg) on HR of the anesthetized cats. (Mean % ± SEM)

	Gaba. 15mg/kg	**Gaba 30mg/kg**	**Gaba 60mg/kg**	**Gaba 120mg/kg**	**Gaba 240mg/kg**
Mean%	0.0	0.0	10	18	30
±SEM	0.0	0.0	1.15	1.32	1.51
P	0.0	0.0	<0.05	<0.01	<0.001

Gaba = gabapentin P<0.05 is sign. P<0.001 is highly sign.

Table (7): The mean percentage reductions caused by gabapentin (60 mg/kg) and cisatracurium (1-16mg/kg) on the HR of the anesthetized cats. (Mean % ± SEM)

Mg/kg	**60 gabap. + 1cisatr**	**60 gabap. + 2 cisatr**	**60 gabap. + 4 cisatr**	**60 gabap. + 8 cisatr**	**60 gabap. + 16 cisat**
Mean%	19.69	28.1	44.04	50.04	58.01
±SEM	2.66	2.22	2.34	2.10	1.90
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

P<0.05 is sign. P<0.001is highly sign.

Clinical results

Table (8): Demographic Data

Groups / Criteria	Group: I gaba (1200mg)	Group: II gaba. (800mg)	Group: III (Control)	Test	P-value
Age	50.045 ±17	52.6 ± 12	51 ± 16	0.182*	0.834
Sex: Male/ Female	14 (56%)/ 11(44%)	12 (48%)/13(52%)	15 (60%)/10(40%)	0.753**	0.686
Body weight	78.30 ± 14. 64	84.5 ± 11	82.5 ± 9.8	1.741*	0.183
Height (meter)	1.64 ± 0.067	1.70 ± 0.03	1.69 ± 0. 08	1.650.*	0.650
ASA I/ II	15 /10	14 /11	13 /12	1.833**	0.766
Fatigue	2 (8%)	1 (4%)	0 (0%)	2.083**	0.352
Malaise	2 (8%)	1 (4%)	0 (0%)	2.083**	0.352

* One way ANOVA ** Chi square test P > 0.05: NS P < 0.05: S P < 0.01: HS

Table (9): Intraoperative Details.

Groups / Patient Criteria	**Group: I gaba.(1200mg)**	**Group: II gaba.(800mg)**	**Group: III (Control)**	**Test**	**P-value**
Duration of surgery (min)	132 ± 27	137 ± 23	142 ±22	1.076*	0.346
Total IV fluids (ml): Crystalloids Total IV fluids (ml): colloids	1250±300	1300 ± 400 250 ±70	1500±400 380±60	3.201* 6.332	0.047 0.001
Blood transfusion (ml)	-------	250 ±40	350 ± 70	6.202**	0.001
Time of 1st poster dose of cistr. Total Cisatracurium (mg)	96.6±8.3min. 12.5± 2.1	72.4±6.5min. 16.2 ± 4.36	42.3±7.2min. 20.6± 3.7	40.8 15.619*	0.001 0.001
Isoflurane concentration (%)	0.7± 0.4	1.1 ± 0.30	1.7 ± 0.44	0.803*	0.452
Total Intraoperative Fentanyl Total Intraoperative morphine	100 ± 30 µg.	140± 20 µg 5±2 mg	180± 30 µg 8±2 mg	66.667* 2.774**	0.001 0.007

* One way ANOVA ** Independent t-test

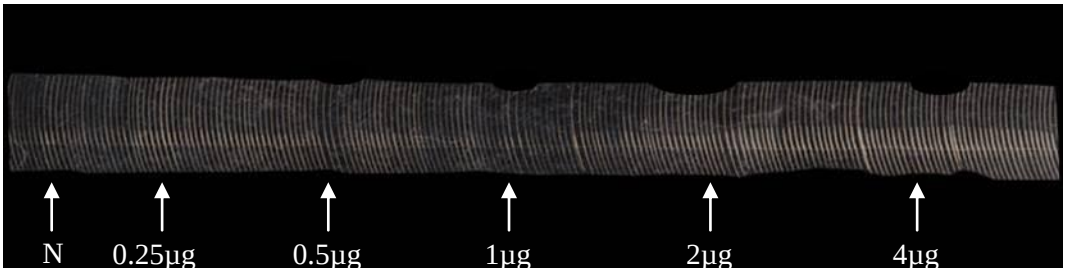
Table (10): Perioperative Changes in MAP of patients.

Data / Time	Mean Arterial Blood Pressure (± SD)			One Way ANOVA	
	Group I	**Group II**	**Group III**	**F**	**P-value**
Basal	85 ± 11mmHg	84 ± 8 mmHg	83 ± 10mmHg	0.316	0.730
Pre-induction	73 ± 11 mmHg	80 ± 9 mmHg	92 ± 9 mmHg	29.364	<0.001
1min. after int.	75± 12 mmHg	90 ± 7 mmHg	106 ± 11 mmHg	68.885	<0.001
Post.ind. 5min	69 ± 13 mmHg	68± 10 mmHg	99 ± 12 mmHg	67.627	<0.001
10 min.	63± 8.5 mmHg	72 ± 10 mmHg	82 ± 10 mmHg	29.862	<0.001
15 min.	56 ± 9.5 mmHg	76 ± 7.6 mmHg	71 ± 7.6 mmHg	47.383	<0.001

int.: intubation ind.: induction

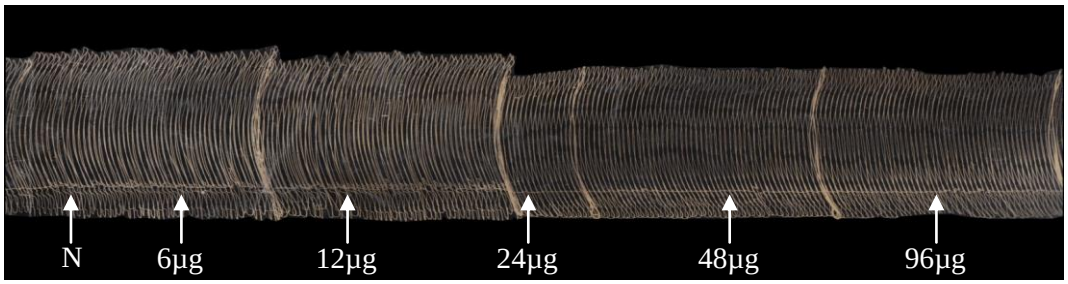
Table (11): Perioperative changes in Heart Rate in patients.

Data / Time	Heart Rate beat/min mean ± SD			One Way ANOVA	
	Group I	**Group II**	**Group III**	**F**	**P-value**
Basal	85 ± 9	86 ± 10	84 ± 9	0.344	0.714
Pre-induction	71 ± 8	77 ± 9	88 ± 9	29.602	<0.001
1min. after int.	76 ± 12	95± 6	116± 15	88.963	<0.001
Post.ind. 5min	72 ± 9	82 ± 5	107 ±12	117.000	<0.001
10 min.	67± 11	77± 8	97± 10	73.684	<0.001
15 min.	62 ± 5	70 ± 7	78 ± 9	37.161	<0.001



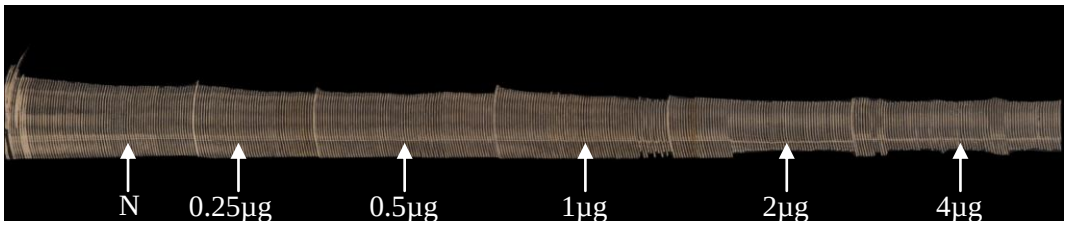
Cisatracurium (µg /ml)

Fig. (2): Effect of Cisatracurium (0.25- 4 µg /ml) on rat phrenic nerve diaphragm preparation.



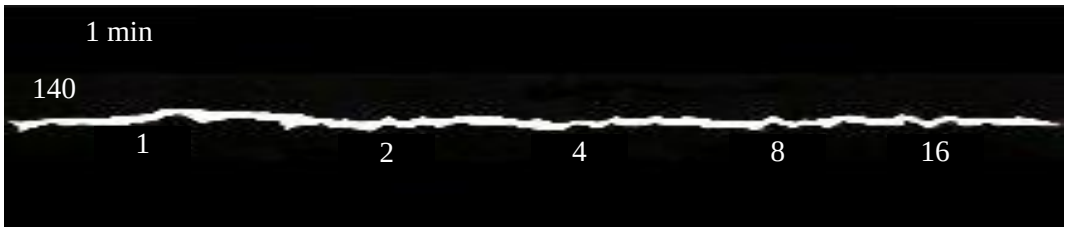
Gabapentin (µg/ml)

Fig. (3): Effect of Gabapentin (6-96µg/ml) on Rat phrenic nerve -diaphragm preparation.



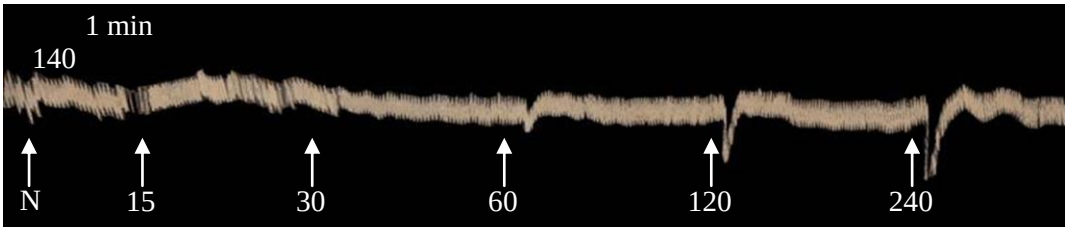
Cisatracurium (0.25-4 µg/ml) plus Gabapentin (24µg/ml)

Fig. (4): Effect of Gabapentin (24µg/ml) plus Cisatracurium (0.25-4µg/ml) on Rat phrenic nerve - diaphragm preparation.



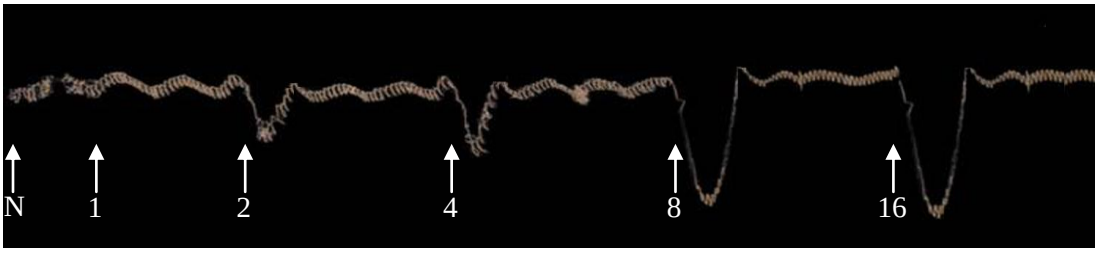
Cisatracurium (1-16 mg/kg)

Fig. (5): Effect of IV Cisatracurium, (1-16 mg/kg) on mean arterial blood pressure (mmHg) of anesthetized cats



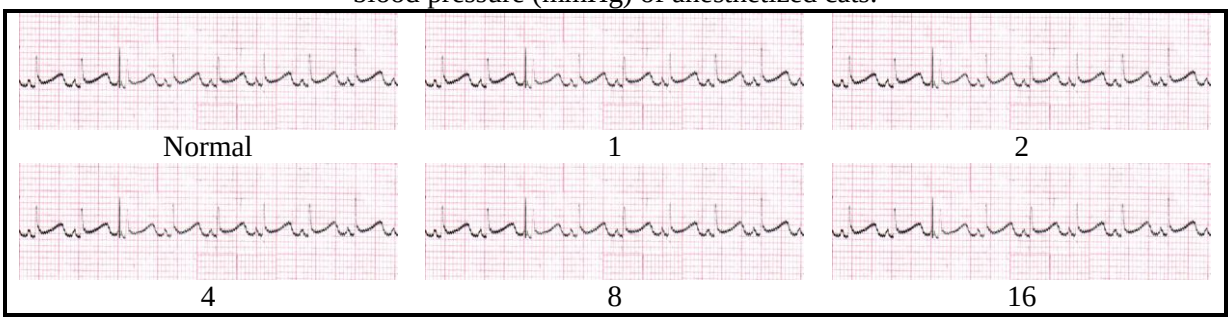
Gabapentin (15- 240 mg/kg)

Fig. (6): Effect of Gabapentin (15- 240 mg/kg) on the mean arterial blood pressure (mmHg) of anesthetized cats.



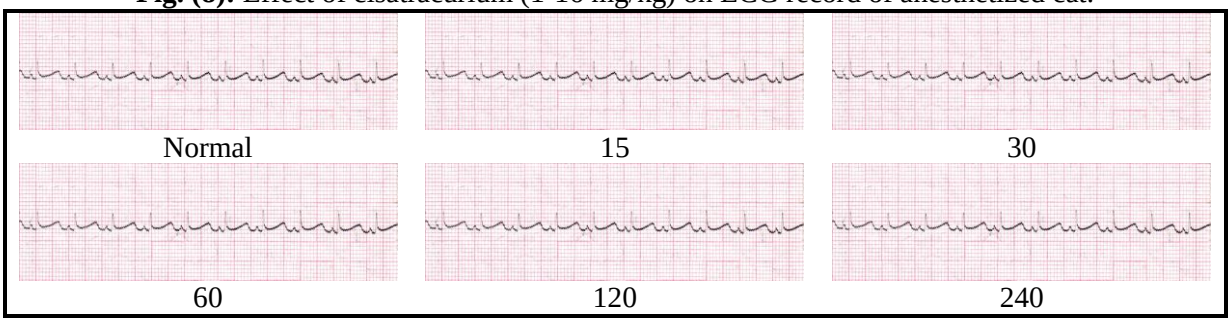
Cisatracurium (1-16mg/kg) plus gabapentin (60 mg/kg)

Fig. (7): Effect of gabapentin (60 mg/kg) and cisatracurium (1-16mg/kg) on the mean arterial blood pressure (mmHg) of anesthetized cats.



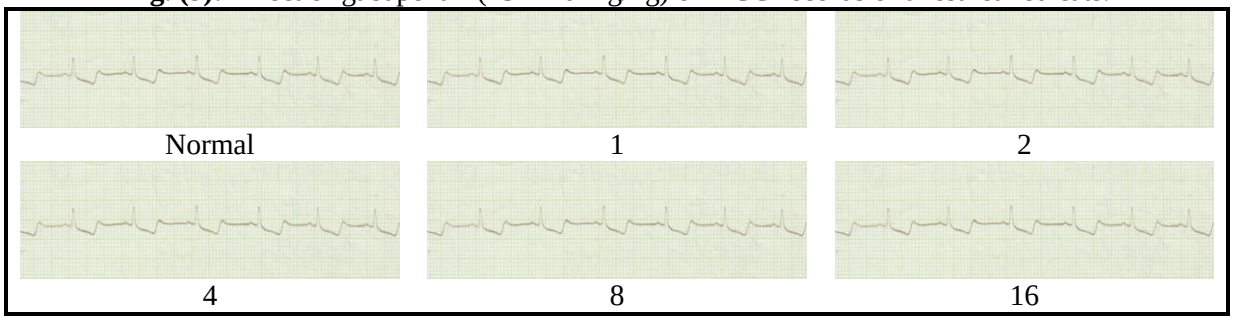
Cisatracurium (mg/kg)

Fig. (8): Effect of cisatracurium (1-16 mg/kg) on ECG record of anesthetized cat.



Gabapentin (mg/kg)

Fig. (9): Effect of gabapentin (15- 240 mg/kg) on ECG records of anesthetized cats.



Gabapentin (60 mg/kg) plus Cisatracurium (1-16 mg/kg)

Fig. (10): Effect of gabapentin (60 mg/kg) plus cisatracurium (1-16mg/kg) on HR of the