

Effect of Dexmedetomidine on Neuromuscular Blockade in Patients Undergoing Complex Major Abdominal or Pelvic Surgery

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ABSTRACT

Background and objectives: Dexmedetomidine is a highly selective α_2 agonist with anesthetic, analgesic and sympatholytic properties. Its neuromuscular effects in humans are unknown. This study evaluates the effect of dexmedetomidine on neuromuscular block and hemodynamics during thiopental/isoflurane anesthesia for patients with complex abdominal or pelvic surgery.

Patients and methods: During thiopental/isoflurane anesthesia, the rocuronium infusion rate was adjusted in 20 complex surgery patients to maintain a stable first response (T1) in the train of four sequence of $50\% \pm 3$ of the pre-rocuronium value. Dexmedetomidine was then administered by infusion pump, targeting a plasma dexmedetomidine concentration of 0.6 ng/dL for 45 min. The evoked mechanical responses of the adductor pollicis responses (T1 response and T4/T1 ratio), systolic blood pressure, diastolic blood pressure and heart rate (HR) were measured during the dexmedetomidine infusion using repeated measures analysis of variance. Plasma levels ranged from 0.73 to 1.38 ng/mL.

Results: T1 values decreased during the infusion from 55 ± 2 to 38 ± 9 ($p < 0.05$). T4/T1 values did not change during the infusion. Dexmedetomidine increased SBP ($p < 0.001$) and decreased HR ($p < 0.05$) (10 min median values) during the infusion compared with values before the infusion. This study demonstrated that dexmedetomidine decreased T1, increased SBP and decreased HR during thiopental/isoflurane anesthesia.

Conclusion: We conclude that dexmedetomidine induced direct vasoconstriction may alter pharmacokinetics of rocuronium, therefore increasing plasma rocuronium concentration. Although these effects were statistically significant, further studies should be held for understanding and characterizing the peripheral vasoconstrictive effects of α_2 agonists that allow better management and determination of drug dosing regimens.

Key Words: Dexmedetomidine - Neuromuscular blockade - Hemodynamics - Thiopental/isoflurane anesthesia.

INTRODUCTION

Dexmedetomidine is a novel, highly selective α_2 adrenoreceptor agonist that reduces the requirements of anesthetic, analgesic and sedative and hypnotic drugs.

Dexmedetomidine has a relatively high ratio of α_2/α_1 activity (1620:1) as compared with 220:1 for clonidine [1] and therefore is considered a full agonist of the receptors. This may result in more potent effects of sedation without unwanted cardiovascular effects from α_1 receptor activation. The 2h half life of dexmedetomidine is nearly 4 folds shorter than clonidine [2], which increases the likelihood, that a continuous infusion of dexmedetomidine might be useful for sedation.

Dexmedetomidine also has a minimum alveolar anesthetic concentration (MAC) sparing properties, but its use as an anesthetic adjuvant has been complicated by persistent hypotension that has mandated IV fluid administration and vasopressor administration [4,5]. Its use in large doses is complicated by hypertension from receptor mediated vascular constriction [6].

Dexmedetomidine (DMED), an imidazole derivative, is a selective and full α_2 adrenoreceptor agonist possessing sedative properties [7,8,9] that may have different clinical properties than clonidine for the following reasons:

- 1- DMED is seven times more selective than clonidine for the alpha adrenergic receptor [10,11].
- 2- DMED is a full agonist at the α_2 adrenergic receptor, whereas clonidine is only a partial agonist [12] and

- 3- The maximum reduction in inhalational anesthetic requirement to maintain 1 MAC provided by clonidine is 50% [7], whereas DMED has been shown to result in approximately a 90% reduction [8,9].

These differences in DMED's pharmacologic characteristics may lead to therapeutically beneficial properties. The known cardiovascular properties of these compounds include a biphasic response (pressor followed by depressor when these compounds are administered IV) [13].

PATIENTS AND METHODS

The local research ethics committee of the National Cancer Institute approved the study and written consent was obtained from all patients. The study was carried out in NCI. We studied 20 adult patients undergoing complex major abdominal or pelvic surgery with the different demographic characteristics (Table 1).

Table (1): Patients and operative characteristics.

	Sex	Age	Operation	Operation time
1	Female	40	Radical hysterectomy	3h
2	Female	45	Radical cystectomy	4h
3	Male	44	Hypernephroma resection	3h
4	Male	46	Subtotal gastrectomy	4h
5	Male	36	Lt heminephrectomy	5h
6	Male	41	Excision of abdominal sarcoma	4h
7	Male	45	Radical cystectomy	3h
8	Male	46	Abdominoperineal resection of rectum	
9	Female	40	Ovariectomy	3h
10	Female	46	Whipple procedure	6h
11	Male	44	Colectomy/partial pancreatectomy (leiomyosarcoma)	5h
12	Male	40	Total gastrectomy	4h
13	Male	35	Oesophagogastrectomy	6h
14	Female	45	Salpingo-oophorectomy, removal of ovarian tumors and loop ileostomy	6h
15	Female	46	Radical hepatectomy	3h
16	Male	41	Hemihepatectomy	7h
17	Male	43	Extended whipple procedure	7.5h
18	Female	31	Removal of ovarian tumor	3.5h
19	Female	30	Excision of abdominal leiomyosarcoma	5h
20	Female	41	Rt lobe hepatectomy	4.5h

Patients who had a history of cardiac, pulmonary, hepatic, renal, vascular or neuromuscular disorders were excluded. Those with a history of small joint arthritis, chronic smokers, taking prescription medication, drug abuse, > 46 years of age, or with a body weight < 130% of normal, allergy to any trial drugs, pregnancy, were also excluded. Patients fasted for 8 hours before arriving at the operating room and rested supine on the morning of the operation. A catheter was inserted into a hand vein for study during drug administration and blood samples were collected. All patients were premedicated with oral diazepam (10-15 mg) given approximately 90 minutes before surgery. In the operating room, lactated Ringer's solution with 5% dextrose was administered at a rate of 4-6 ml/kg/h via peripheral arm vein. The ECG was monitored continuously. Patients breathed 100% oxygen while anesthesia was induced with midazolam 2-3 mg, fentanyl 2 µg/kg and thiopentone 5-7 mg/kg.

After tracheal intubation, anesthesia was maintained with 70% nitrous oxide in oxygen. This was followed by the addition of isoflurane 0.5-1% end tidal concentration to the anesthetic mixture.

A radial artery cannula was placed to permit measurement of arterial blood pressure. Ventilation was adjusted to maintain end tidal CO₂ between 35 and 40 mm Hg. Nasopharyngeal temperature was monitored and maintained at a level of 36-37, C by warm blankets and heated IV fluids. Skin temperature over the thenar eminence and the forehead was also monitored and maintained at a level of 32-33, C.

Concentrations of isoflurane, N₂O, CO₂ and O₂ saturation were determined by a multiple gas analyzer (Capnomac Ultima-SVI, Datex Corporation, Helsinki, Finland).

Supra maximal stimuli (duration 0.2 ms) in a train-of-four (TOF) sequence were applied every 12 s via surface electrodes (Digistim II, neurotechnology Inc, Houston, TX) to the ulnar nerve at the right wrist. The resulting evoked mechanical responses of the adductor pollicis were carried out using a TOF guard neuromuscular monitor (Biometer International Odense, Denmark). All graphical and numerical data were recorded on a memory card and subsequently a computer print out was obtained using

TOF Guard Reader Software (Biometer International, Odense, Denmark). (T1 response and T4/T1 ratio) were digitalized, displayed and recorded on a Macintosh Computer.

Approximately 20 min after the induction of anesthesia, once the blood pressure and HR varied < 5% over a 5-min period, the twitch tension was measured and the value of the T1 response was taken as 100%. Rocuronium was then administered as a bolus (200 µg/kg), followed by an infusion (200 µg/kg/hr). The rocuronium administered was adjusted to target a stable T1 response within the range of 50% ± 5% of the pre-rocuronium value by administering additional rocuronium bolus doses and by changing the infusion rate. When the T1 response was stable (< 2% variation) and within the range of 47%-53% and the rocuronium infusion rate had been constant for at least 10 min, the dexmedetomidine infusion was begun.

Patients received an I.V. infusion of dexmedetomidine starting 55±10 min after the beginning of the rocuronium administration and continuing for 45 min. Targeting plasma dexmedetomidine concentrations of 0.6 ng/ml, dexmedetomidine (4 µg/ml) was administered using infusion pump (MORING) arterial blood pressure (systolic, diastolic and mean) and HR were measured non invasively from 5 min before induction of anesthesia until the introduction of arterial cannula. Thereafter, arterial blood pressure was measured continuously via the radial artery cannula, which was connected to a Transpac III transducer (Abbott Laboratories, North Chicago, IL). Hemoglobin oxygen saturation SPO₂ was measured non invasively using a pulse oximeter (prop 106; protocol systems, Beaverto, OR) with the probe placed on a distal phalanx.

The hemodynamic and SPO₂ data were recorded at 10 s intervals using an automated data acquisition system.

Arterial blood samples for determination of plasma dexmedetomidine and plasma rocuronium concentrations were collected just before the start of the rocuronium and dexmedetomidine infusions and 15, 30 and 45 mins after the start of the dexmedetomidine infusion. The plasma clearance (CL) of rocuronium at the beginning and end of the dexmedetomidine

infusion was calculated by dividing the plasma concentration.

Dexmedetomidine concentrations were assayed by using gas chromatography and mass spectrometry. All drugs and fluids administered were recorded.

The effect of dexmedetomidine on blood pressure, HR, T1, T4/T1, blood volume was determined by using repeated measures, analysis of variance followed by Turkey's Multiple Comparison test. Data are reported as the means ± SD. $p \leq 0.05$ identified statistical significance.

RESULTS

The average dose of dexmedetomidine administered was 0.98±0.01 µg/kg (range 0.95-0.99 µg/kg). Plasma dexmedetomidine concentrations exceeded the target concentration of 0.6 ng/ml in all patients at all measured time points (Table 2). The T1 and T4/T1 values during Dexmedetomidine infusion are illustrated in Fig. (1). Inspection of the results showed that T1 values decreased over time ($p < 0.05$), becoming significantly lower than pre-Dexmedetomidine values.

30 min after the beginning of infusion T4/T1 values did not change during the Dexmedetomidine infusion.

There was a mean decrease in twitch tension after 45 min of the dexmedetomidine infusion. Dexmedetomidine increased SBP ($p < 0.001$) (Fig. 3) and decreased HR ($p < 0.05$) at all time points during the infusion (Fig. 4). Relative values for T1 (top panel) and T4/T1 (bottom panel) are shown during dexmedetomidine infusion while subjects were receiving a steady state of rocuronium infusion.

To control values before the infusion (Table 2). SBP increased from baseline to a maximum of 125±8.5 mmHg 5 min after the beginning of the dexmedetomidine infusion. HR decreased from 70±11 bpm to a minimum of 60±5 bpm after the beginning of the dexmedetomidine infusion.

Percent change from the baseline for systolic blood pressure (top panel) and heart rate (lower panel) 5 min before and 10 min after the beginning of the dexmedetomidine infusion, for all two variables were significantly different $p < 0.05$ from the pre dexmedetomidine values.

Table (2): Hemodynamic plasma dexmedetomidine data.

	Time from beginning of dexmedetomidine infusion (min)										
	A Awake	B Baseline	C 5	D 10	E 15	F 20	G 25	H 30	I 35	J 40	K 45
SBP	(110-150) 130±9	(96-120) 98±9	(113-150) 125±8	(105-135) 122±5	(102-134) 119±6	(102-137) 117±7	(102-138) 117±7	(102-139) 118±8	(101-140) 119±8	(100-139) 119±9	(100-139) 119±9
HR	(50-90) 75±13	(45-80) 70±11	(36-70) 60±10	(38-75) 59±8	(39-76) 57±8	(40-78) 58±8	(40-80) 59±9	(40-78) 60±9	(41-78) 60±8	(41-78) 60±7	(43-80) 60±7
DBP	(60-90) 70±10	(48-70) 52±7	(62-86) 66±8	(58-87) 64±9	(57-87) 64±10	(57-86) 64±9	(57-86) 64±9	(57-86) 64±9	(57-87) 64±9	(57-87) 64±9	(57-87) 64±9
Dex (ng/ml)					(0.9-1.38) 1.05±0.15			(0.81-1.36) 0.99±0.15			(0.73-1.22) 0.96±0.14

SBP: Systolic blood pressure.
 DBP: Diastolic blood pressure.
 HR : Heart rate.
 Values are mean ± SD (range).

Table (3): Neuromuscular data range (mean ± SD).

	Time from beginning of dexmedetomidine infusion (min)									
	B (Baseline)	5	10	15	20	25	30	35	40	45
T1 (%)	(46-58) 55±2	(41-57) 45±4	(43-59) 45±5	(41-59) 42±5	(41-59) 42±6	(40-59) 42±6	(38-59) 41±7	(36-58) 40±7	(34-57) 39±8	(33-56) 38±9
T4/T1 ratio	(15±8) (13-18)	18±8 (16-26)	20±11 (12-30)	18±5 (12-26)	18±9 (11-23)	15±5 (10-20)	14±12 (8-24)	18±9 (11-22)	15±6 (9-21)	18±9 (11-25)

T1 = First response in the train of four sequence.
 T4 = Fourth response in the train of four sequence.

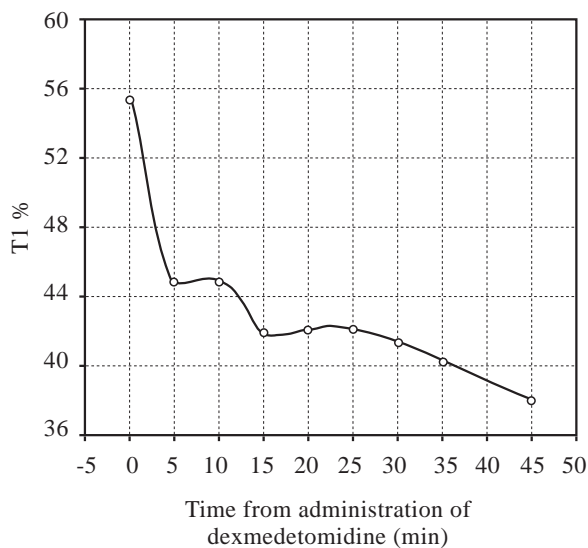


Fig. (1): (Top panel). Values for T1 are shown during dexmedetomidine infusion while patients were receiving a steady rate rocuronium infusion. Data are mean $p < 0.05$ versus pre dexmedetomidine values.

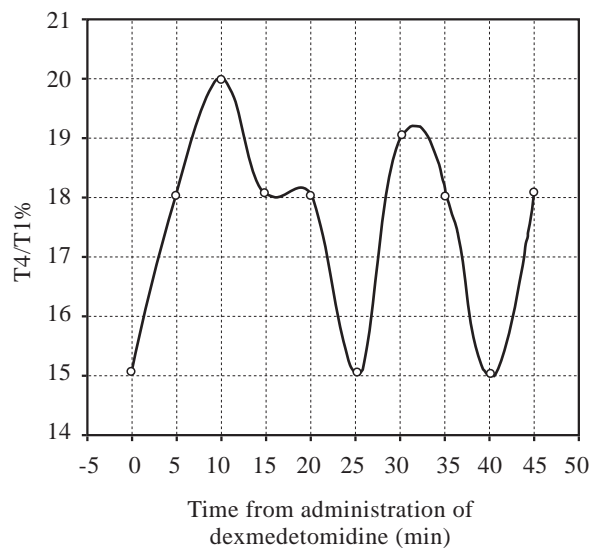


Fig. (2): (Bottom panel). Values for (T4/T1%) are shown during dexmedetomidine infusion while patients were receiving a steady state rocuronium infusion. Data are mean $p > 0.05$ versus predexmedetomidine values.

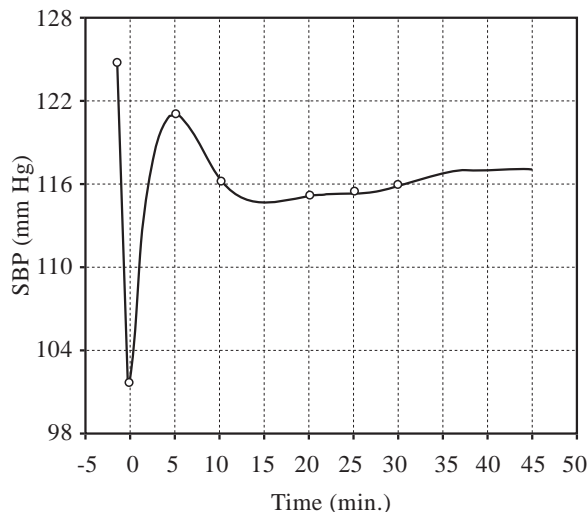


Fig. (3): (Top panel). Systolic blood pressure 5 min before and 45 min after the beginning of the dexmedetomidine infusion. All data points after the beginning of the dexmedetomidine infusion were significantly different ($p < 0.001$) from the pre-dexmedetomidine values.

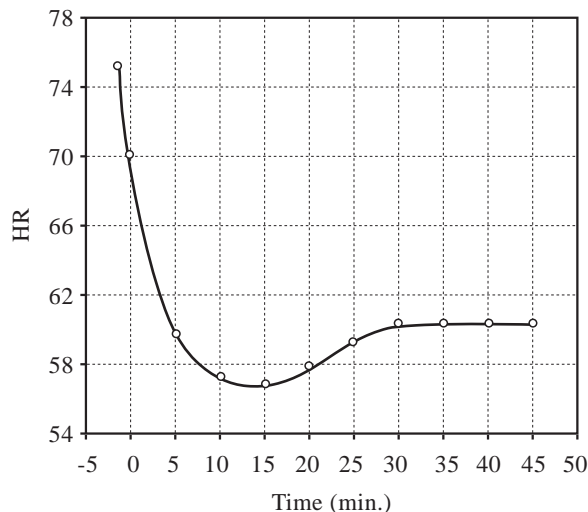


Fig. (4): (Bottom panel). Heart rate 5 min before and 45 min after the beginning of dexmedetomidine infusion were significantly different ($p < 0.005$) from the pre-dexmedetomidine values.

DISCUSSION

α_2 agonists decrease blood pressure by centrally mediated sympathetic effects and by decreasing norepinephrine release via peripheral pre-synaptic α_2 agonist stimulation [14]. In addition, α_2 agonists induce peripheral vasoconstriction by directly activating vascular smooth muscle α_2 receptors [15,16]. The hemodynamic effects of α agonists are therefore thought to be a combination of their central sympatholytic and peripheral vasoconstrictive effects.

The present study report that dexmedetomidine (at the same dose found to increase blood pressure and HR) has a sustained peripheral vasoconstrictive effect in patients anesthetized with thiopental and fentanyl. Previous clinical studies have shown that α_2 agonists decrease blood pressure and HR in healthy volunteers and patients during inhaled anesthesia [5,17]. An increase in blood pressure with a concomitant decrease in HR and cardiac output has been reported when a large IV dexmedetomidine dose is administered rapidly, resulting in high plasma dexmedetomidine concentrations [6]. This increase in blood pressure starts immediately after dexmedetomidine administration but lasts only a few minutes.

Our study demonstrates that dexmedetomi-

dine has a persisting vasoconstrictive effect in clinically feasible doses. In the present study, increase in systemic blood pressure started within 30-90 s of the administration of dexmedetomidine. This suggest a direct effect (vasoconstriction) of dexmedetomidine on vascular smooth muscle α_2 receptors. That the increase in blood pressure was sustained throughout the dexmedetomidine infusion, whereas plasma dexmedetomidine concentrations remained stable, implies that vasoconstriction was not due to a transient increase in dexmedetomidine plasma levels, but to a sustained direct effect on the vascular smooth muscle cells. This hypothesis is further supported in another study, which consisted of a computer controlled infusion pump driven by the latest dexmedetomidine pharmacokinetic data, theoretically providing stable dexmedetomidine plasma concentrations [18].

The time course of the rapid decrease (3-4 min) in HR we observed during the dexmedetomidine infusion is consistent with reflex bradycardia in response to increase in blood pressure in HR typically observed over 30-45 min secondary to the central sympathetic effect with similar dexmedetomidine dosing [19].

This study is limited by the use of a single dexmedetomidine dose. Therefore, we cannot comment on the potential neuromuscular and

vasoconstrictive effects of dexmedetomidine at smaller doses. We studied the effect of dexmedetomidine on rocuronium induced neuromuscular relaxation.

The technique of measuring finger blood volume and changes in blood volume is subject to its limitations. Any changing pressure at the sensor site by touching or resting the finger tip on a surface changes the blood volume and transmitted light path. There are two new findings in our study of the neuromuscular effects of dexmedetomidine.

First, after the administration of dexmedetomidine in a clinically relevant dose, T1 decreased.

Second, during the dexmedetomidine infusion, there was a sustained increase in systemic blood pressure, which suggests a persistent dexmedetomidine induced peripheral vasoconstriction. This finding is supported by the sustained decrease in finger blood volume during dexmedetomidine infusion. We administered dexmedetomidine for 45 min to a target plasma concentration of 0.6 ng/ml this concentration is effective in decreasing post operative hypotension and tachycardia and is the highest dexmedetomidine concentration presently used in perioperative clinical trails. We considered the 45 min infusion long enough to observe potential centrally mediated effects because these effects are maximal 30-45 min from the time of administration [8]. The direct peripherally mediated vascular effect (vasoconstriction) occurs immediately after administration [6].

In a study of perioperative clonidine [11], the oral administration of 5 ug/kg clonidine had no effect on the onset or duration of vecuronium-induced neuromuscular relaxation. The authors concluded that clonidine did not interact with neuromuscular relaxation. In contrast, we found that T1 decreased during a dexmedetomidine infusion. The decrease in twitch tension during the dexmedetomidine infusion was probably due to increased plasma concentration of rocuronium. We believe that the change in twitch tension was the result of the increased rocuronium concentration [18]. The reason for the increase in plasma rocuronium concentration in the presence of dexmedetomidine is not clear. Dexmedetomidine may have altered the biodisposition of rocuronium. The clearance of rocu-

ronium decreased by 6% over the course of dexmedetomidine infusion, which suggest that dexmedetomidine influences the pharmacokinetics of rocuronium [18].

Dexmedetomidine decreases both renal and hepatic blood flow [20] and decreases thiopental distribution volume and distribution CLs [21]. Thus, pharmacokinetic mechanisms may, in part explain the increase in plasma rocuronium concentration. Neuromuscular block was maintained at 50% before the administration of dexmedetomidine because this level of block is on the steepest part of the concentration-activity curve. Thus, changes in the concentration of rocuronium or sensitivity of the neuromuscular junction have most effect on twitch tension.

We used rocuronium for two reasons. First, its principal metabolite does not reach a pharmacologically active concentration, which may have caused difficulty in obtaining a stable level of block [22]. Second, it is eliminated by both renal and hepatic mechanisms which suggest that CL may be affected by dexmedetomidine-related changes in perfusion of these organs [23]. Although statistically significant, the decrease in T1 during dexmedetomidine infusion is not clinically significant. A rocuronium concentration change of a similar magnitude at 90% neuromuscular block would increase the block by < 3% [24]. At doses that induce peripheral vasoconstriction, dexmedetomidine may influence its own pharmacokinetics and that of other drugs. Whether this has implications for dosing of medications and is dependant on individual patient differences, baseline sympathetic tone and responsiveness of peripheral α_2 receptors will be studied in the future. Understanding and characterizing the peripheral vasoconstrictive effects of α_2 agonists will allow better management and determination of drug dosing regimens to avoid harmful hypertensive episodes.

REFERENCES

- 1- Viurtanen R., Savola J.M., Sauno V. and Nyman L.: Characterization of selectivity, specificity and potency of dexmedetomidine as α_2 adrenoreceptor agonist. *Eur. J. Pharmacol.*, 1988, 159: 9-14.
- 2- Davis D.S., Wing L.M.H. and Reid J.L.: Pharmacokinetics and concentration effect relationship of intravenous and oral clonidine. *Clin. Pharmacol. Ther.*, 1977, 12: 593-601.

- 3- Segal I.S., Viekey R.G. and Walton J.K.: Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic α_2 adrenergic receptor. *Anesthesiology*, 1988, 69: 816-23.
- 4- Jalonen J., Hynynen M. and Kuitunen A.: Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting. *Anesthesiology*, 1977, 86: 331-45.
- 5- Talke P., Jain U. and Leung J.: Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. *Anesthesiology*, 1995, 82: 620-33.
- 6- Bloor B.C., Ward D.S., Belleville J.P. and Maze M.: Effects of intravenous dexmedetomidine in humans. II: Hemodynamic changes. *Anesthesiology*, 1992, 77: 1134-42.
- 7- Savola J.M. and Virtanen R.: Central α_2 adrenoreceptors are highly stereoselective for dexmedetomidine, the dextro enantiomer of medetomidine. *Eur. J. Pharmacol.*, 1991, 195: 193-9.
- 8- Kallio A., Scheinin M. and Koulu M.: Effects of dexmedetomidine, a selective α_2 adrenoreceptor agonist, on hemodynamic control mechanisms. *Clin. Pharmacol. Ther.*, 1989, 46: 33-42.
- 9- Annta R., Kanto J., Scheinin H. and Kallio A.: Dexmedetomidine premedication for minor gynaecologic surgery. *Anesth. Analg.*, 1990, 70: 407-13.
- 10- Engelman E., Lipszyc M. and Gilbert E.: Effects of clonidine on anesthetic drug requirements and hemodynamic response during aortic surgery. *Anesthesiology*, 1989, 71: 178-87.
- 11- Ghignone M., Noe C., Cavillo O. and Quintin L.: Anesthesia for ophthalmic surgery in the elderly: the effects of clonidine on intraocular pressure, perioperative hemodynamics and anesthesia requirements. *Anesthesiology*, 1988, 68: 707-16.
- 12- Quintin L., Roudot F. and Roux C.: Effect of clonidine on the circulation and vasoactive hormones after aortic surgery. *Br. J. Anesth.*, 1991, 66: 108-15.
- 13- Auntau R.: Assessment of the selective effects of dexmedetomidine, an α_2 adrenergic receptor agonist, with analysis of saccadic eye movements. *Pharmacol. Toxicol.*, 1991, 68: 394-8.
- 14- Flacke J.W.: α_2 adrenergic agonists in cardiovascular anesthesia. *J. Cardiothorac. Vasc. Anesth.*, 1992, 6: 344-59.
- 15- Saeed M., Holtz J., Elsner D. and Bassenge E.: Sympathetic control of myocardial oxygen balance in dogs mediated by activation of coronary vascular α_2 adrenergic receptors. *J. Cardiovasc. Pharmacol.*, 1985, 7: 167-73.
- 16- Chen D.G., Dai X.Z., Zimmerman B.G. and Bache R.J.: Post synaptic α_1 and α_2 adrenergic mechanisms in coronary vasoconstriction. *J. Cardiovasc. Pharmacol.*, 1988, 11: 61-7.
- 17- Dyck J.B., Maze M. and Haack C.: The pharmacokinetics and hemodynamic effects of IV and IM dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology*, 1993, 78: 813-20.
- 18- Pekka O., Talke M.D. and James E.: The effect of dexmedetomidine on neuromuscular blockade in human volunteers. *Anesth. Analg.*, 1999, 88: 633-9.
- 19- Talke P., Richardson C., Scheinin M. and Fisher D.: Postoperative pharmacokinetics and sympathetic effects of dexmedetomidine. *Anesth. Analg.*, 1997, 85: 1136, 42.
- 20- Lawrence C.J., Prinzen F.W. and De Lange S.: The effect of dexmedetomidine on nutrient organ blood flow. *Anesth. Analg.*, 1996, 83: 1160-5.
- 21- Buhner M., Mappes A. and Lauber R.: Dexmedetomidine decreases thiopental dose requirements and alters distribution pharmacokinetics. *Anesthesiology*, 1994, 80: 1216-27.
- 22- Van Miert M.M., Eastwood N.B. and Boyd A.H.: The pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic cirrhosis. *Br. J. Clin. Pharmacol.*, 1997, 44: 139-44.
- 23- Bevan D.R.: Rocuronium bromide and organ function. *Eur. J. Anesthesiol. Suppl.*, 1994, 9: 87-91.
- 24- Holford N.H. and Sheiner L.B.: Understanding the dose-effect relationship: Clinical application of pharmacokinetic-pharmacodynamic models. *Clin. Pharmacokinetic*, 1981, 6: 429-53.