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The pharmacodynamics of dexmedetomidine in elderly cardiac patients undergoing analgosedation in the ICU

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ABSTRACT

Aim. This study aimed to evaluate the pharmacodynamics of dexmedetomidine in elderly cardiac patients.
Material and Methods. Twelve patients of 60 years or older and need for analgesia after surgery or as a result of critical health conditions were included into our study. Dexmedetomidine was administered intravenously as a continuous infusion without the initial dose. At the beginning the infusion was started at the rate of 0.7 μg/kg/h and then it was continued in the range of 0.17–1.39 μg/kg/h according to desired level of sedation. Information about heart rate, systolic, diastolic and mean arterial blood pressure, bispectral index and cardiac index were collected a few minutes before, during and in 12 hours after infusion of dexmedetomidine.
Results. The hemodynamic data as well as BIS level were collected from 12 patients. The duration of dexmedetomidine infusion was less than 9 hours. For each patient the reduction in blood pressure and heart rate compared to the value before dexmedetomidine infusion was observed. We did not observe bradycardia in any patient. Appropriate sedation level was achieved using only dexmedetomidine and ranged from 60 to 80. In only 2 cases it was necessary to give a single dose of another sedative.
Conclusions. To conclude, in the patients' population involved in the study, which included older cardiac patients dexmedetomidne has been shown as a sedative agent which enabled to achieve desire level of sedation in the recommended ranges without episodes of bradycardia, however hypotension events were noted.

Keywords: dexmedetomidine, pharmacodynamics, bradycardia, hypotension, sedation.

Introduction

Dexmedetomidine (dex) is a newly discovered drug that has gained great popularity in neuroanesthesia, intensive care unit (ICU) and cardiac anesthesia in recent years. It was approved in 1999 by the FDA as a short-acting sedative. In Europe, it was introduced to health care in 2011 [1, 2]. Dexmedetomidine is a highly selective α2-adrenergic receptors agonist with high affinity for the α2-receptor (α2/α1 1600:1) compared with clonidine (α2/α1 200:1), which makes it a complete α2 agonist [3, 4]. Dexmedetomidine by α2-adrenergic receptor activation causes sedation similar to natural sleep, which helps in the early postoperative period [5, 6]. It also exhibits analgesic, anxiolytic and sedative effects without causing severe respiratory depression. Sedative action is responsible for the stimulation of receptors located at the sinus of the upper part of the brain stem [7]. Analgesic activity consists of a central component – stimulation of receptors in the brain stem and hind corners of the spinal cord, and peripheral – stimulation of the receptors in the nerve roots of the posterior nerve roots [8].

Dexmedetomidine is a highly lipophilic drug. After *i.v.* administration it shows rapid distribution with biological half-life ($t_{0,5}$) in the distribution phase being of 6 min. The drug is 94% bound to plasma proteins. Metabolism occurs as a result of direct conjugation to glucuronic acid and cytochrome P-450 isozymes. $T_{0,5}$ in the elimination phase equals 2 h. The drug is in 95% excreted in the urine, 4% in the feces in the form of metabolites [3, 9, 10].

Unique action allows for sedation without causing excessive sedation (cooperative sedation), difficult to achieve by other drugs. Drug administration is particularly useful in situations where there is a need for awareness during sedation [11]. The sedation combined with the analgesic effect without respiratory depression is used at the time of weaning from ventilation therapy, after long-term use of other sedative medicinal products, and in the elderly or other severe illness. Sedation and diminution in muscle tone is well tolerated in patients with withdrawal syndrome and delusional syndromes after major and long-term surgical procedures such as extracorporeal cardiac surgery [9]. This action reduces psychomotor excitability and has cardioprotective activity. Reduction of muscle tremor is used to control chills while cooling the body as well as for hypothermia. Because of its different mechanism of action, it can also be given in terminal illness as a supplement to other painkillers and sedatives. Dexmedetomidine has also promising results in patients with pulmonary hypertension undergoing mitral valve replacement [11].

Side effects of dexmedetomidine are mainly limited to hemodynamic changes. These include hypertension, bradycardia and hypotension due to pre-and post-synaptic activation of the α2 receptor, which causes vasospasm. Furthermore, it has been shown that dexmedetomidine alleviates stress responses, thus creating a more stable hemodynamic profile during surgery or induction of anesthesia. In case of overdosage atrioventricular block I degree, bradycardia and hypotension had been seen. Co-administration of dexmedetomidine with anesthetics, sedatives, hypnotics and opioids may increase observed effects [9, 11].

Aim

The aim of the study was to evaluate the pharmacodynamics of dexmedetomidine in elderly cardiac patients. Cardiac patients require comprehensive interdisciplinary teamwork to ensure the best possible outcome. Perioperative care is to carefully select sedatives to provide comfort to the patient, while avoiding physiological stress and heart instability [1].

Material and Methods

The study was conducted among intensive care patients in clinical hospital after approval of protocol by institutional Bioethics Committee. The approval number was 213/13 and 572/16. The inclusion criteria were: age – 60 years or older and need for analgosedation after surgery or as a result of critical health conditions. We excluded patients that were younger than 60 years and/or have hemodynamic instability. Dexmedetomidine (Dexdor, Orion Pharma Poland Sp. z.o.o.) was administered in continuous infusion without a loading dose. The infusion was started at the rate of 0.7 μg/kg/h and was continued in the range 0.17–1.39 μg/kg/h according to desired level of sedation. Information was recorded about heart rate (HR), systolic, diastolic and mean arterial blood pressure (SBP, DBP and MAP), bispectral index (BIS), cardiac index (CI) a few minutes before, during and in 12 hours after infusion of dexmedetomidine. BIS was monitored by Philips Medical Systems B.V (Netherlands) and CI by FloTrac System (Edwards Lifescences, USA). All the parameters were recorded every hour during the infusion as well as in any case when other drug which might have influenced collected parameters was administrated, e.g. noradrenalin, midazolam, ephedrine, propofol.

Bradycardia and hypotension were monitored among the patients as the pharmacodynamics of dex and potential side effects of the drug.

Heart rate was measured in bites per minutes (bpm) and blood pressure in millimetres of mercury (mmHg). Bradycardia was defined for the heart rate less than 40 bites per minutes. Hypotension was defined for systolic blood pressure less than 80 mmHg and diastolic blood pressure less than 50 mmHg. Bradycardia and/or hypotension was defined also when the fall by at least 30% compared to baseline value was noticed (heart rate and/or blood pressure, respectively) [12].

Bispectral index was used to assess the level of consciousness. It is a parameter to measure brain activity and is based on electroencephalogram. BIS is used to estimate the level of sedation and anaesthesia. BIS values ranged between 0 (no cortical activity) and 100 (completely awake). The values between 40 and 60 signified general anaesthesia, whereas for adequate sedation in ICU BIS should remain in the range 60–80 [13, 14].

Cardiac index is a cardiac output (CO) indexed to body surface area (BSA). Cardiac output is the sum of the systemic flow per minute and calculated by the product of heart rate and stroke volume. The cardiac index reference range for elderly patients is 2.2–3.8 L/min/m^2 [15]. According to study performed by Cattermole at al [16], reference range of CI is 1.88–4.71 L/min/m^2. They offered this range for healthy patients over 60. In our study we used the norm given by Cattermole et al.

Results

12 patients were enrolled to the study, 10 of which were postsurgical patients. **Table 1** lists patients' demographics and characteristics of dexmedetomidine infusion. The monitored hemodynamic parameters e.g. DBP, SBP, MAP, HR, CI as well as BIS were also presented (**Table 2**). The duration of dexmedetomidine infusion was less than 9 hours. In each patient a decrease in heart rate and blood pressure was calculated by comparing the values of these parameters before and during the infusion (**Table 2**). During the study period any episodes of bradycardia were not observed among the patients. However, in 8 patients incidents of hypotension were observed. In one case the administration of noradrenalin was needed whereas in the other dosage changes ensured the adequate hemodynamic stability.

The infusion of dex started after the surgery, it was 39 (± 20) minutes after stop of sevoflurane administration and 226,5 (± 51,8) minutes after premedication with propofol. In one patient values were above 60, in 3 patients they were less than 60. In two cases 5 mg midazolam was given less than one hour (45 and 55 minutes) before beginning of dexmedetomidine administration and as the result the baseline values of BIS were affected. Adequate sedation dex infusion was started 15 minutes after end of sevoflurane administration so that the baseline BIS could have been affected by the anesthesia period. At the start of infusion BIS level was maintained by using only dexmedetomidine in the range between 60 and 80. In only 2 cases it was necessary to give a single dose of another sedative (midazolam or propofol). However, it caused decreasing BIS values below 60. Bispectrac index values during dex infusion were presented on **Figure 1**.

Cardiac index was registered in 11 patients. In general, there was a reduction in cardiac index following commencement of dex infusion when compared to the baseline. In two patients there were also such episodes during continued administration of dex, necessitating adjustment of the rate of infusion (**Table 2**, **Figure 2**). In two patients before start of dex infusion CI was above references values (7, 6 and 5.6) and during infusion CI was reduced to normal range (average values: 2.7, 3.8 and 3.7, respectively).

Table 1. Demographic characterization of patients. Results are expressed as number or median with range

Parameter [Unit]	Number or Median [Range]
Male/Female	11/1
Age [years]	64.5 [61–79]
Weight [kg]	74.5 [55–85]
Height [cm]	169 [160–177]
Infusion time [minutes]	287.5 [220–505]
Total dose of dexmedetomidine [μg]	276.35 [142.40–602.40]
Mean ratio of infusion [μg/kg/h]	0.83 [0.46–1.15]
Use of inotropes during infusion [yes/no]	1/11

Table 2. Hemodynamic and pharmacodynamic (BIS) parameters of dexmedetomidine infusion (mean values with standard variation for all subjects)

Parameter [unit]	Baseline[1]	During infusion	After infusion	% changes[2]
Bispectral index	68,0 ± 11,0	67,7 ± 10,2	82,8 ± 6,9	1,0
Systolic blood plessure [mmHg]	146,0 ± 36,0	117,3 ± 23,9	115,2 ± 10,9	19,7
Diastolic blood plessure [mmHg]	72,0 ± 17,0	59,1 ± 10,6	58,0 ± 8,8	17,9
Heart rate [bpm]	90,0 ± 18,0	71,3 ± 9,6	74,0 ± 11,6	20,8
Cardiac index [L/min/m^2]	3,9 ± 1,7	2,9 ± 0,7	2,9 ± 0,8	25,6

[1] just before the start of the infusion
[2] percentage change of the mean value of the infusion period compared to the baseline

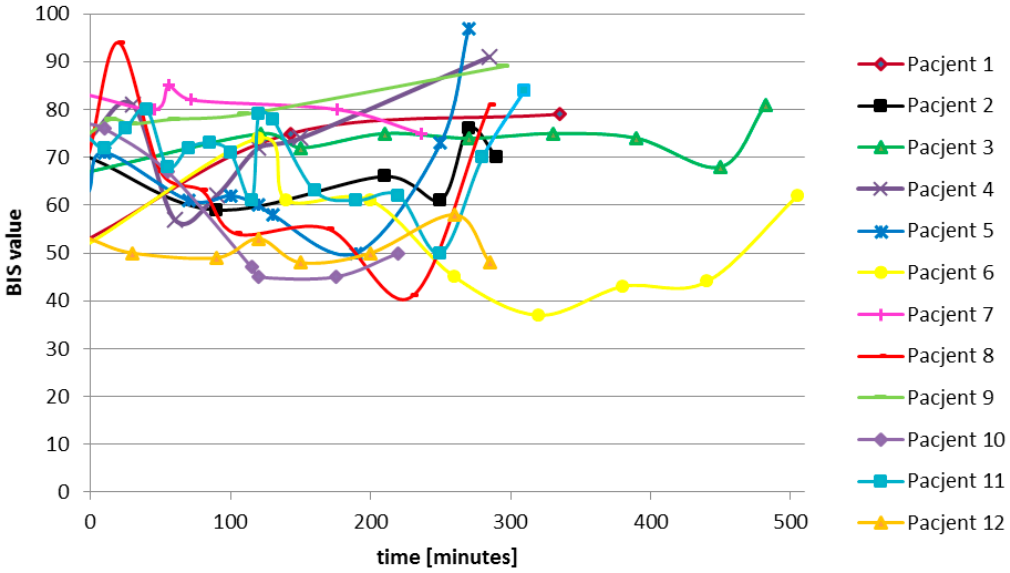

Figure 1. Bispectral index values for each patient before and during dex infusion

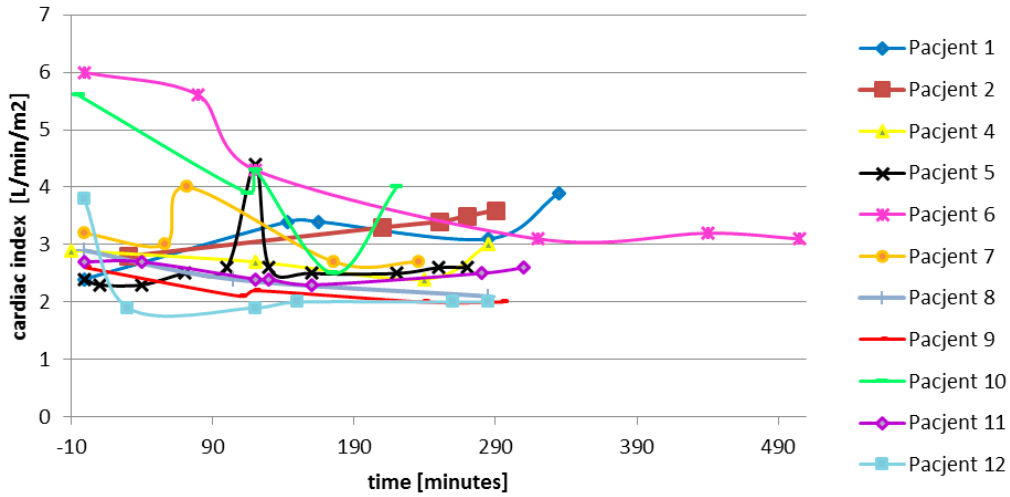

Figure 2. Cardiac index values for each patient before and during dex infusion

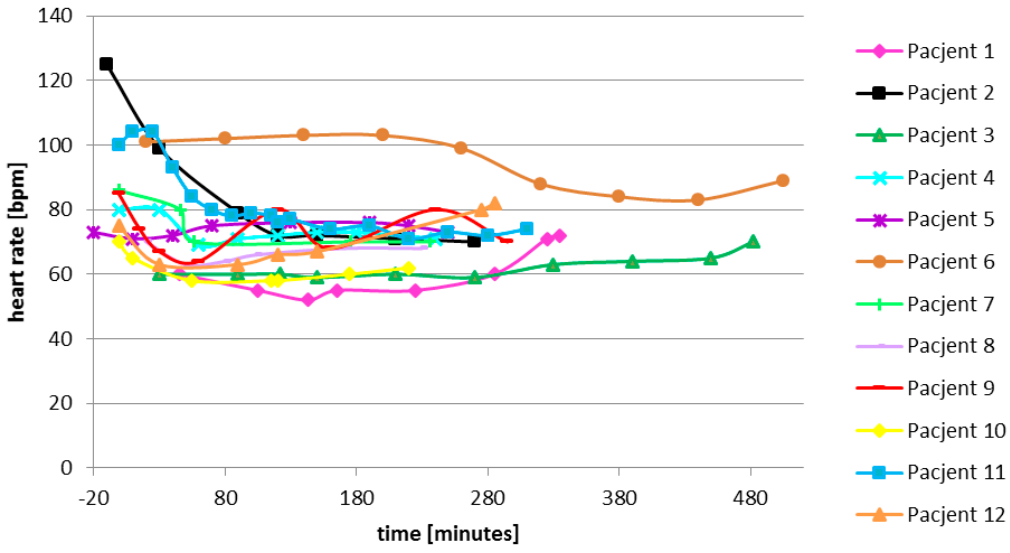

Figure 3. Heart rate values for each patient before and during dex infusion

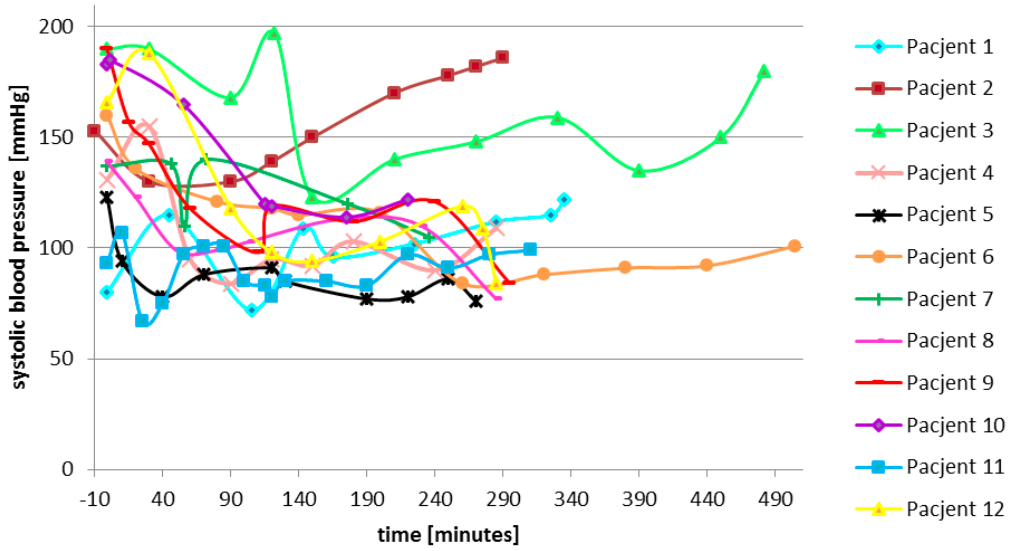

Figure 4. Systolic blood pressure values for each patient before and during dex infusion

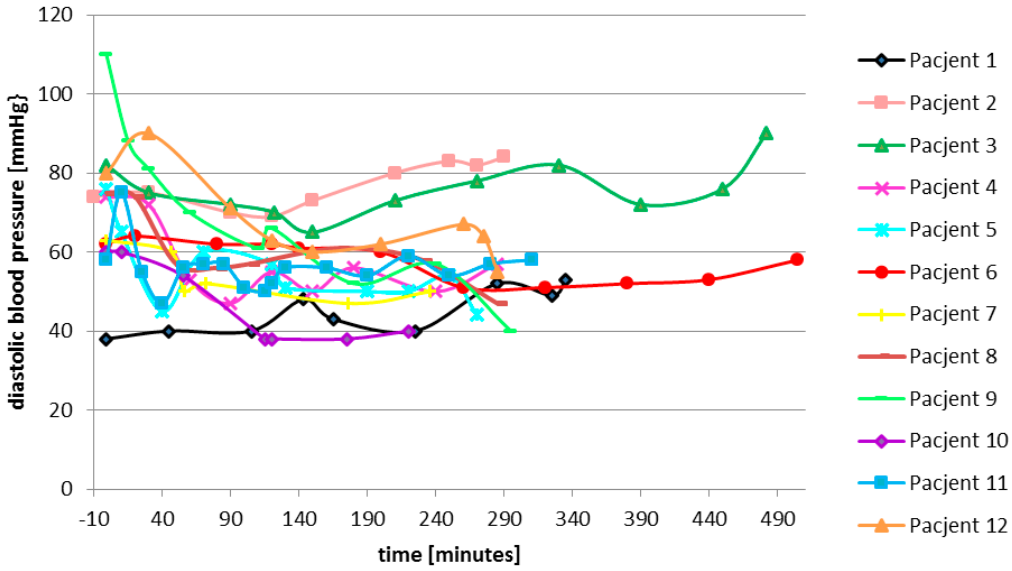

Figure 5. Diastolic blood pressure values for each patient before and during dex infusion

Discussion

Our results showed that dexmedetomidine may have stabilizing effect on blood pressure and heart rate in postoperative period in ICU. Dexmedetomidine has a binary effect: on one side it decreases blood pressure response to surgical stress and on the other hand minimizes surge in blood pressure and heart rate during operation and postoperative ICU. The use of α2-agonists aims at blunting the hemodynamic stress response. Dexmedetomidine is a good sedative agent in cardiac patients as it is a sympatholytic and reduces heart rate [17].

In the study group, the recommended dosage of dexmedetomidine was sufficient to maintain postoperative sedation. During the entire period of dexmedetomidine infusion, deep sedation was maintained. Difference between the baseline value of BIS and the average value of dex infusion was small – 1%. It was due to short time from end of sevoflurane administration and beginning of infusion. Baseline value for each patients was in the range 52–83 denoting deep sedation. Dex administration caused maintaining the appropriate level of sedation for ICU. It is very important that it is possible to keep deep sedation (BIS in the range

60–80) using only dexmedetomidine. In the present study in three cases baseline BIS value was below 60. Two of them received additionally 5 mg midazolam 45 and 55 minutes before beginning of dexmedetomidine infusion and one patient had started infusion only 15 minutes after end of sevoflurane administration.

Dexmedetomidine has been shown to affect the patients' hemodynamic parameters. On the Figures 3–5 a decrease is visible of blood pressure and heart rate values after start of infusion. However, we have not reported any bradycardia episodes in patients. Hui et al [18] reported clinically significant bradycardia during simultaneous administration of dexmedetomidine and fentanyl. We didn't find this relationship using dex in combination with oxycodone or morphine, heart rate did not differ between patients who were administered opioids and patients that were administered another analgesics. Nevertheless, we reported in 8 patients episodes of hypotension and in 2 cases the hypotension was followed by too deep sedation (BIS below 60). In all these three cases dex infusion was stopped and patients were recovered from sedation. No other sedative agent was given instead because there weren't any further indications to continue sedation in these patients.

In all patients the infusions were during the day, and the parameters after the infusion were measured in the afternoon, in the evening and at night. In these periods the pressure is normally more than 10 mmHg at night lower than in the day [19]. In our opinion, this might had an effect on the median of blood pressure and heart rate after stopping the infusion however to make a conclusion on this field circadian rhythmicity of the physiological parameters should be included in the protocol of further studies.

During the infusion, a significant decrease in CI (25,6%) was observed when compared the baseline value to the average value of the infusion period. In two patients, CI values were above the reference range before the infusion of dexmedetomidine, and then during the infusion period they fell to the references values whereas at the end of the infusion increased again to the above the references values. Further studies are needed to assess the relation between dexmedetomidine and cardiac output in which the influence of this hemodynamic parameter on the drug elimination clearance should be also taken into account. Lower cardiac output may potentially decrease the elimination rate of the drug and as a result increase its pharmacological effect [20].

In conclusion, in our patients' population including elderly cardiac patients, dexmedetomidine has been shown as a drug which given as the only sedative agent enabled to achieve desire level of sedation in the recommended ranges (60–80 of BIS) without any episodes of bradycardia. However hemodynamic parameters should be closely monitored during the infusion, because hypotension events were reported.

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Conflict of interest statement
The authors declare no conflict of interest.

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