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DEXMEDETOMIDINE TOXIC INFLUENCE ON ANMAL ORGANISMS BY PROLONGED APPLICATION ON THE RESEARCH EXAMPLE ON WHITE MICE

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Abstract

This study investigated the effects of dexmedetomidine on bodily functions in animals by prolonged use. The studies were carried out on laboratory mice, which were divided into 2 groups: the first (test) one was administered administered orally by the Dexmedetomidine drug at a 0.01 ml dose, the second (control) one did not introduce any drugs. During the experiment, control over both groups' mice's coordination of movements, metabolic parameters were carried out, and the bodyweight was measured. Vital signs monitoring was carried out in 3 stages: 1) before drug administration; 2) 15 minutes after administration; and 3) after awakening, respectively. Results revealed that in 2-3 days, the frequency of respiratory movements began to increase by 19,1%, the awakening began to increase, and the general condition (refusal to eat, inactivity) changed for the worse. There was a 11% decrease in the test group on the last day after the next body weight measurement, while in the control group, on the contrary, the weight increased by almost 5%, and also at autopsy, changes were found in the tissues of the lungs and liver. The research aimed to identify the toxic effects of drugs in the category of α2-adrenergic receptor agonists, and at the moment it is possible to talk about some toxic effects of this group, but research needs to continue.

Keywords: Dexmedetomidine, α2-adrenergic receptor agonists, veterinary medicine, anaesthesiology, laboratory mice

Introduction

In context of the experience accumulated over many years in theory and general anesthesia

practice of wild and domestic animals, the problem of 'perfection' of an anesthesiologist and patient health safety remains. Anaesthetic drugs used for inhalation and noninhalation anesthesia have side effects on various bodily functions. In such a situation, new combined anesthesia schemes continue to be developed and mastered in order to achieve an appropriate analgesic result when complex and long-term conduction surgical interventions. In general, wild animals, even minor surgical procedures, require general anesthesia in most cases. [1]

The main question a veterinarian thinks about is the choice of the type of anesthesia and premedication. To date, several animal anesthesia drugs have been proposed, for example, α2-adrenergic receptor agonists have been approved for veterinary use in Canada, the EU, and the USA for about 40 years, although the first founders of this category used in medicine as drugs for hypertension and pathologies central nervous system treatment. Clinical effects such as analgesia, anxiolysis, sedation, muscle relaxation were discovered to α2-adrenergic receptor agonists, which served as the basis for its continued widespread use in veterinary medicine to immobilize wild exotic animals and in domestic animal surgery. In addition to these clinical effects, the use of this group of drugs leads to a significant decrease in the dose of injection and inhalation anesthesia required for induction and maintenance of anesthesia. A2-adrenergic receptor agonists also weaken the stress response during trauma, reduce the level of catecholamines and cortisol in the blood after surgery. In the literature, the negative clinical effects of the agonists in different animal species are described in sufficient detail. Therefore, its use is limited in older animals with a history of cardiovascular problems [2]. A2-adrenergic receptor agonists, as in all drugs for anesthesia, due to some toxic effect on the body, in particular, changes in the cardiovascular system were found were found in human studies: arterial hypotension, bradycardia, arterial hypertension [3]. Therefore, the objective of the objective of the work was to identify the toxic effect of α2-adrenergic agonists on the bodies of animals of animals after prolonged introduction, using visual and instrumental control methods.

Research materials and methods:

The study was carried out according to the Regional State Laboratory of the Poltava region Derzhprodspozhyvsluzhba [State Food and Consumer Service] in the period from 05/17/2021 to 05/21/2021.

Two groups of 20-25 grams weight white mice (of one age group – 40-50 days, 5 heads in each) were formed for the experiment. On the fur, each mouse was marked with different coloured patches (blue, yellow, red, black, and green) in order to identify individual reactions and make the experiment clearer. Feeding was carried out with a full-fledged compound feed, water was not limited, and weighing was carried out before the experiment. The first group (control) contained animals that were not injected with any drugs.

The second group of mice (test) was injected with Dexmedetomidine („Orion Pharma", Finland) orally at a dose of 0.01 ml [4] by adding 2-3 ml of 0.9% sodium chloride saline solution to the drug solution once a day for 5 days.

During the experiment, the following indicators of vital activity were monitored:

1. coordination of movements;
2. changes in the respiratory rate (RR) system (the respiratory movements number in 1 minute, and the depth of respiratory movements);
3. changes in the metabolic functions of the body (loss of appetite, defecation, or urination problems);
4. The time it takes to wake up the animal. [5]

On the first and last days of the experiment, bodyweight measurements were also taken.

Vital signs monitoring was carried out in 3 stages:

1. before drug administration.
2. 15 minutes after drug administration (1 hour before awakening)
3. after awakening.

The data obtained were recorded in the experiment registration form. Subsequently, the animals were sacrificed, followed by a post-mortem examination of the organ systems. The studies were carried out in accordance with the „European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes". [6]

The formula of calculation of mass coefficients [7]:

MC =

Results and Discussion

Before the experiment, all animals were examined for diseases (mucous membranes, body temperature, respiratory rate, appetite) that could threaten the objectivity of the data obtained. On the first day, the mice were placed in two groups, 5 research mice each. Before the drug administration in the test group, the general condition of the animals was satisfactory on the first day of the experiment: no feeding refusal was observed, the defecation and urination acts were without any pathological changes. For a minute, the average respiratory rate was 152 (Table 1). 15 minutes after the administration of the research drug, a significant decrease in mobility (anaesthesia state) was observed in all mice, and the mean RR was 135.2. After awakening in 14.8 minutes (Table 2), there was a movement discoordination, but over some time they became more accurate and returned to normal. Metabolic functions did not change.

Table 1. Vital activity indices in the control group before Dexmedetomidine administration

Animal patch colour	Day 1	Day 2	Day 3	Days 4 and 4	Days 5
Blue	150 breaths per minute. Coordination is not impaired. No metabolic changes are detected.	160 bpm. Coordination is not impaired. Appetite decreased.	157 bpm. Partly decreasing mobility. Appetite and bowel movements worsening.	180 bpm. Mobility decreases. Appetite decreasing, delayed bowel movements.	196 bpm. Mobility decreases. No appetite.

Yellow	145 bpm. Coordination is not impaired. No metabolic changes are detected.	140 bpm. Coordination is not impaired. No metabolic changes are detected.	178 bpm. Partly decreasing mobility. Appetite and bowel movements worsening.	189 bpm. Mobility decreases. Appetite decreasing, delayed bowel movements.	200 bpm. Mobility decreases. No appetite.
Red	160 bpm. Coordination is not impaired. No metabolic changes are detected.	156 Coordination is not impaired. Metabolic disorders are not detected.	170 Coordination is not impaired. Metabolic disorders are not detected.	150 Coordination is not impaired. Metabolic disorders are not detected.	154 Coordination is not impaired. Metabolic disorders are not detected.
Black	165 bpm. Coordination is not impaired. No metabolic changes are detected.	154 bpm. Coordination is not impaired. Appetite impaired.	179 bpm. Partly decreasing mobility. Worse appetite.	195 bpm. Mobility decreases. Appetite decreasing, delayed bowel movements.	190 bpm. Mobility decreases. No appetite.
Green	140 bpm. Coordination is not impaired. No metabolic changes are detected.	167 bpm. Coordination is not impaired. Worse appetite.	178 bpm. Partly decreasing mobility. Appetite and bowel movements worsening.	200 bpm. Mobility decreases. Appetite decreasing, delayed bowel movements.	200 bpm. Decreased mobility, worsening appetite.
Mean	152±5,1	155,4±4,9	172,4±4,6*	182,8±9,9*	188±9,7*

*$p<0.05$ * – relative to the healthy mice group, bpm – breaths per minute*

Before the drug administration, general condition changes on the *second* day of the experiment: three out of five mice (blue, black, green) were revealed an appetite decrease,

but after a while, it returned to normal. The respiratory rate was averaged at 155.4 per minute (Table 1). After drug administration, motor activity decreased. The respiratory rate was 137, an awakening occurred on average after 13,7 minutes, which was 7,4% less than on the first day (14,8 minutes) (Table 2). After awakening, movement discoordination was also observed, which passed rather quickly and did not affect the general condition of the mice.

Before drug administration on the *third* day, 4 out of 5 mice showed a decrease in decrease in mobility and a greater decrease in appetite compared to day 2. The worsening of the body movements was also revealed, and the respiratory rate increased to 172,4 per 1 minute, which was 9,8% more than at the day 2 (155,4) (Table 1). After drug administration, the respiratory rate decreased to 135,8 bpm, an awakening occurred after 15 minutes, which was 8,6% more than on day 2 (13,7 minutes) (Table 2). After awakening, appetite did not improve and metabolic processes were also impaired (the bowel movements and number of urination acts decreased).

On the fourth day before drug administration, all mice, except for the red one, began to refuse food and had quite pronounced apathy. The frequency of respiratory movements averaged 182,8 per 1 minute, which was 5.6% more than on day 3 (172.4) (Table 1). The black and green mice showed signs of breath shortness signs (the chest deeper breathing movements). There was no physical activity after oral administration, the respiratory rate is 133,6. The awakening time was 17,1 minutes, which was 12,2% more than on day 3 (15 minutes) (Table 2). Apathy persisted after awakening.

Before the drug administration on the fifth day, the motor activity of the mice, except for the red one, is rather weak: they hardly moved, had no appetite, and breathing was deep and frequent. The respiratory rate was 188 (Table 1). At stage 2, there were no changes in motor activity, the RR was 127,4, the awakening time was 17,8 minutes (Table 2). The general state did not change after awakening. If we pay attention to the difference between the first and last days in the study group, then the difference between the RR in period I was already 19,1%, in period II 5,7%, upon awakening it increased by 16,8%, while the general condition of the animals of the animals worsened every day.

Table 2. Vital activity indices in the test group 15 minutes after Dexmedetomidine administration.

Animal patch colour	Day 1	Day 2	Day 3	Days 4 and 4	Days 5
Blue	RR – 130 bpm. No movement, palpebral fissure dilation observed, awakening time – 15 min	RR – 136 bpm. No movement, palpebral fissure dilation, awakening time – 14,4 min.	RR – 150 bpm. No motor activity, palpebral fissure dilation, awakening time – 16.2 min	RR – 130 bpm. No motor activity, palpebral fissure dilation, awakening time – 18.2 min	RR -123 bpm. No motor activity, palpebral fissure dilation, awakening time – 19.0 min
Yellow	RR – 134 bpm. Significant decrease in mobility, palpebral fissure dilation, awakening time – 16,3 min.	RR – 143 bpm. Motor activity decrease, palpebral fissure dilation, awakening time 15 min	RR – 129 bpm. No motor activity, palpebral fissure dilation, awakening time 15 min	RR – 132 bpm. No motor activity, dilated palpebral fissure, awakening time – 17.3 min	RR – 120 bpm. No motor activity, dilated palpebral fissure, awakening time – 20.3 min

Red	RR – 145 bpm., Significant decrease in mobility, palpebral fissure dilation, awakening time – 13,2 min.	RR – 146 bpm. Significant decrease in mobility, palpebral fissure dilation, awakening time – 14,1 min	RR – 135 bpm. No motor activity, dilated palpebral fissure, awakening time – 15.2 min	RR – 138 bpm. Motor activity decreased, the the palpebral fissure was was dilated, awakening time 15.4 min	RR – 140 bpm. Motor activity decreased, the palpebral fissure dilated, awakening time – 14.1 min
Black	RR – 130 bpm. No movement, palpebral fissure dilation observed, awakening time – 15,1 min	RR – 130 bpm. Significant decrease in mobility, palpebral fissure dilation, awakening time – 11,3 min	RR – 127 bpm. No motor activity, dilated palpebral fissure, awakening time – 14.3 min	RR – 138 bpm. No motor activity, palpebral fissure dilated, awakening time – 16.5 min	RR – 129 bpm. No motor activity, palpebral fissure dilated, awakening time – 17.1 min
Green	RR – 137 bpm. Significant decrease in mobility, palpebral fissure dilation, awakening time 14,5 min.	RR – 130 bpm. Significant decrease in mobility, palpebral fissure dilation, awakening time – 14,0 min	RR – 138 bpm. Significant decrease in mobility, palpebral fissure dilation, awakening time – 14,3 min	RR – 130 bpm. No motor activity, palpebral fissure dilated, awakening time – 18 min	RR – 125 bpm. No motor activity, dilated palpebral fissure, awakening time – 18,4 min
Average RR	135,2±3.1*	137±3.6*	135,8±4.5*	133,6±2.0*	127,4±3.8*
Awakening time, min	14,8	13,7	15	17,1	17,8

p <0,05 — relative to stage I of the test group, bpm – breaths per minute*

On the first day, the control group mice felt satisfied – the respiratory rate averaged 154, coordination without pathologies, and metabolic disorders were not detected. On the second day, the respiratory rate was 155,6. There were no metabolic dysfunctions. The coordination of the movements also did not change. On the third day, the respiratory rate averaged 151,4. The general condition was satisfactory. On the fourth day, the respiratory rate averaged 150,8. The appetite was persisted, the bowel movements and urination were without pathologies. On the last day, the respiratory rate was 152. The general condition of the animals was satisfactory. The difference between all days' indices in the control group was insignificant (less than 3%).

Table 3. The mice control group, without drug administration

Animal patch colour	Day 1	Day 2	Day 3	Days 4 and 4	Days 5
Blue	BPM – 149, coordination is not impaired, no metabolic changes are detected.	BPM – 158, coordination is not impaired, no metabolic changes are detected.	BPM – 150, coordination is not impaired, no metabolic changes are detected.	BPM – 160, coordination is not impaired, no metabolic changes are detected.	BPM – 146, no motor activity, palpebral fissure dilated, awakening 16 min

Yellow	BPM – 154, movement coordination is not impaired, good appetite, bowel movements, and urination without pathologies.	BPM – 147, coordination is not impaired, no metabolic changes are detected.	BPM – 160, movements coordination is not impaired, good appetite, bowel movements, and urination without pathologies.	BPM – 148, movement coordination is not impaired, good appetite, bowel movements, and urination without pathologies.	BPM – 159, movement coordination is not impaired, good appetite, bowel movements,, and urination without pathologies.
Red	BPM – 153, movement coordination is not impaired, good appetite, bowel movements, and urination without pathologies.	BPM – 147, coordination is not impaired, no metabolic changes are detected.	BPM – 145, coordination is not impaired, no metabolic changes are detected.	BPM – 160, coordination is not impaired, no metabolic changes are detected.	BPM – 156, coordination is not impaired, no metabolic changes are detected.
Black	BPM – 161, movement coordination is not impaired, good appetite, bowel movements,, and urination without pathologies.	BPM – 176, coordination is not impaired, no metabolic changes are detected.	BPM – 141, movement coordination is not impaired, good appetite, bowel movements, and urination without pathologies.	BPM – 146, movements coordination is not impaired, good appetite, bowel movements, and urination without pathologies.	BPM – 145, movements coordination is not impaired, good appetite, bowel movements, and urination without pathologies.

Green	BPM – 153, coordination is not impaired, no metabolic changes are detected.	BPM – 150, coordination is not impaired, no metabolic changes are detected.	BPM – 161, movement coordination is not impaired, good appetite, bowel movements, and urination without pathologies.	BPM – 140, movements coordination is not impaired, good appetite, bowel movements, and urination without pathologies.	BPM – 154, movement coordination is not impaired, good appetite, bowel movements, and urination without pathologies.
Average respiratory rate	154±2,1	155,6±6,1	151,4±4,4	150,8±4,4	152±3,1

bpm – breaths per minute

After 5 days of the experiment, all animals were weighed and sacrificed. Subsequently, a pathoanatomical examination of the organ systems was carried out. Compared to the first day in the study group, the mice' body weight decreased by 11%, but in the control group it increased by 4,7%. The difference between the control and the test group was 16,4% in the decrease direction in the test one. When researching the organ mass coefficient by body weight on the last day, a decrease in the control group mice's organs was found (liver by 20%, heart by 23,4%, left kidney by 18,7%, right kidney by 23,5%).

After autopsy, the experimental group was detected with venous hyperaemia, pulmonary tissue oedema in the chest cavity and liver venous hyperaemia in the abdominal cavity. The kidneys, small and large parts of the bladder of the bladder of the bladder of the intestine did not show visible pathological changes. The control group did not have visible pathological changes.

Table 4. Influence of drugs on the body weight of the body weight of the body weight of the body weight of the body weight of test animals.

Mice groups	Day 1 of the experiment, grams (n=5)	Day 5 of the experiment, grams (n=5)
Test	21,7±0.8	19,3±0.6*
Control	22±0.7	23,1±0.7

*p<0.05 * – relative to the mice control group*

Table 5. Organs of Laboratory Animals Mass Coefficients

	Internal organ mass coefficient (%)				
Organs Groups	Liver	Lungs	Heart	Kidneys	
Left	Right				
Test	25,4±0,4*	33,6±0.3*	9,8±0,3*	16±0,1*	11,9±0,1*
Control	20,3±0,2	24,2±0,1	7,5±0,1	13±0,1	9,1±0,1

*p<0,05 * – relative to the mice control group*

According to literary sources, there is no unequivocal opinion about the α2 agonist group 2 – toxicity of adrenergic receptor drugs. [5,3] During the investigation, it was found that in the experimental group, the frequency of respiratory movements on average increased by 19,1% (Dexmedetomidine introducing in stage I). In stage II, changes in the frequency of respiratory movements did not change as much as expected, 5,7% compared to the first day. This indicator increased by 16.8% (compared to the first day) when awakening after analgesia. In the control group, the state of the animals of the animals was without pathological changes. The frequency of respiratory movements was averaged 152,7. Therefore, we can say that with the prolonged use of drugs of this group, toxic damage occurs to the respiratory system and the liver.

Conclusions

1) When dexmedetomidine was used, RR increased by an average of 5% with each subsequent day. The difference demonstrates the cumulative effect of the drug: Between day 1 and day 5, the respiratory rate increased by 19.1% in the first period of study, by 5.7% in the second period.

2) The time to wake up mice increased by 16.8% comparing the first to the last test day, which indicates possible liver and kidney damage, a decrease in their „detoxification" function.

3) Compared to healthy mice individuals on the first and last day of last day of the experiment, the total weight decrease of the mice test group was found to be 11%, indicating muscle tissue loss, the organ mass coefficient increased at the same time, which may mean acute inflammatory processes detected in the animals' body.

4) Also, changes in organ morphology during dissection serve as an argument that toxic effects are present, causing acute processes in liver and lung tissues, but still require detailed study.

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