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Farklı Sugammadeks Dozlarının Plazma Serbest Hormon Düzeylerine Etkisi

Effect of Different Sugammadex Doses on Plasma Free Hormone Levels

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ÖZ

Giriş: Sugammadeks steroidal yapıdaki nöromüsküler blokerlere yüksek afinitesi olan yeni nesil bir siklodekstin halkasıdır. Plazma steroid hormon seviyelerine etkisi bazı çalışmaların konusu olmuştur. Bu çalışmada ise yüksek doz sugammadeks uygulamasının hem steroid hormonlar hemde büyüme hormonu üzerine etkileri araştırılmıştır.

Yöntem: Deneysel hayvan çalışmamız için anestezi altında 0mg/kg, 4mg/kg ve 16mg/kg sugammadeks uygulanan winstar albino cinsi ratlar 3 gruba ayrılmıştır. Ratlardan sugammadeks uygulaması sonrası 15. dakikada plazma östrojen, progesteron, total ve serbest testesteron, kortizol ve büyüme hormonu seviyeleri bakılmış ve gruplar arasında karşılaştırılmıştır.

Bulgular: Yüksek doz sugammadeks uygulanan grupta plazma progesteron ($p<0.05$) ve kortizol seviyesi daha az ($p<0.05$), büyüme hormonu ($p<0.05$) ve serbest testesteron seviyesi daha fazla($p<0.05$), östrojen ($p>0.05$) ve total testesteron seviyesi ($p>0.05$) ise diğer gruplar ile istatistiksel olarak benzer bulunmuştur

Sonuç: Literatürde sugammadeksin steroid hormon seviyelerine etkileri ile ilgili farklı bulgular mevcuttur. Bulgularımız yüksek dozda uygulanan sugammadeksin ratlarda hormon seviyelerinde daha etkin bir değişim sağladığını düşündürmektedir. Ayrıca büyüme hormonu seviyelerindeki değişimin sugammadeksin plazma proteinler ile etkileşimi de olabileceği fikrini ortaya çıkarmıştır. Yüksek doz sugammadeks ile kortizol seviyelerindeki azalma ise cerrahiye stres yanıt açısından dikkate değerdir. Yüksek dozlarda uygulanan sugammadeks ratlarda hem steroid hemde non steroidal hormon seviyelerini etkilemiştir. Yüksek doz sugammadeks ratlarda plazma serbest büyüme hormonunda artış sağlamıştır. Bulgularımız sugammadeksin hormon bağlayıcı proteinleri de etkilediğini düşündürmektedir. Sugammadeksin bulguların klinik önemi daha fazla çalışma ile desteklenmelidir.

Anahtar Kelimeler: sugammadeks, steroid hormon, hayvan modeli, anesteziyoloji

ABSTRACT

Objective: Sugammadex is a new generation cyclodextine ring with high affinity for steroidal normuscular blockers. Its effect on plasma steroid hormone levels has been the subject of some studies. In this study, the effects of high-dose sugammadex administration on both steroid hormones and growth hormone were investigated.

Method: For our experimental animal study, winstar albino rats administered 0mg/kg, 4mg/kg and 16mg/kg sugammadex under anesthesia were divided into 3 groups. Plasma estrogen, progesterone, total and free testosterone, cortisol and growth hormone levels were measured at the 15th minute after sugammadex administration in rats and compared between groups.

Results: In the high-dose sugammadex group, plasma progesterone ($p<0.05$) and cortisol levels ($p<0.05$), were lower, growth hormone ($p<0.05$) and free testosterone levels ($p<0.05$ were higher, and estrogen ($p>0.05$) and total testosterone levels ($p>0.05$) were statistically similar to the other groups.

Conclusion: There are different findings in the literature regarding the effects of sugammadex on steroid hormone levels. Sugammadex administered at high doses provides a more effective change in hormone levels. It also revealed the idea that the change in growth hormone levels may have an effect on the plasma proteins of sugammadex. Our finding regarding the decrease in cortisol levels with high-dose sugammadex is remarkable in terms of stress response to surgery. Sugammadex administered at high doses affected both steroid and non-steroidal hormone levels in rats. High-dose sugammadex increased plasma free growth hormone in rats. Our findings suggest that sugammadex also affects hormone-binding proteins. The clinical significance of the findings should be supported by further studies

Keywords: sugammadex, steroid hormone, animal model, anesthesiology

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INTRODUCTION

Sugammadex is a modified gamma-cyclodextrin molecule. It encapsulates and antagonizes rocuronium and vecuronium molecules, which are amino steroid muscle relaxant agents. While it is used in low doses for post-surgical extubation in elective cases, high doses may be required to reverse the newly formed block in patients who cannot be intubated or ventilated (1, 2). In such emergency situations, the possible endocrine side effects of the drug may be overlooked. Data on the potential interactions of sugammadex with other drugs and endogenous steroid molecules are limited (3).

In the study of Zwiers et al (4); 300 drugs were studied for potential interaction and substitution with sugammadex, including commonly used cardiovascular drugs in the perioperative period, commonly prescribed antidepressants, drugs acting on receptors (both steroidal and non-steroidal) such as corticosteroids, and the selective estrogen receptor modulator toremifene. According to the results, many drugs can interact with sugammadex at different rates. Only three of these drugs (flucloxacillin, fusidic acid and toremifene) showed a potential for displacement with high association values (> 104).

According to the report of the European Medicines Agency, it has been reported that intraoperative administration of 4mg/kg sugammadex may interact with vitamin K antagonists, unfractionated heparin, rivaroxaban or some other drugs. It has also been shown to reduce progesterone levels (34% of AUC) and, to a lesser extent, estrogen levels in women using hormonal contraceptives during the fertile period. This situation has a similar effect to taking the oral contraceptive dose 12 hours late, potentially increasing the risk of unwilling gravidity (5,6). In a study examining this interaction, it was reported that administration of a high-dose sugammadex rocuronium combination in pregnant rats did not cause an increase in the rate of stillbirth in the first trimester, although it decreased endogenous progesterone levels (7). However, in 2019 the Society for Obstetric Anesthesia and Perinatology published a recommendation to avoid or use caution with sugammadex in early pregnancy (8). These confusions indicate that the hormonal effects of sugammadex are not conclusive (9). Although the effect of sugammadex on progesterone is the subject of some studies, there are not enough studies in the literature about its interaction with other steroids or non-steroidal hormones such as growth hormone (7,10,11).

High-dose sugammadex (>16 mg/kg) administration is not frequently performed in humans (12,13). For these reasons, which preclude a controlled clinical trial, the animal model was used. This study, it was aimed to investigate the effects of different doses of sugammadex administration on growth hormone, testosterone, progesterone, estrogen and cortisol levels in rats.

MATERIALS AND METHODS

This study was carried out in the Erciyes University Experimental and Clinical Research Center with approval 20/073 from the Erciyes University Medical Faculty Animal Studies Ethics Committee and was supported by the Yozgat Bozok University Scientific Research Projects Unit (6602a-TF/20- 429).

Thirty rats of the Winstar Albino breed (>8 weeks) weighing between 250-350 g were included in the study. The rats were kept in the same environment in standard plastic cages and fed with standard rat food. Tap water was used as drinking water. The room temperature was maintained at 22 ◦C, with 12 h of darkness and 12 h of illumination each day. Experimental animals were randomly divided into 3 groups, with 10 rats in each group. Administration of all injections and collection of samples was performed under anesthesia. For anesthesia, intraperitoneal administration of 50 mg/kg ketamine (Ketalar, Parke Davis Eczacıbaşı, İstanbul, Turkey) and 10 mg/kg xylazine (Rompun, Bayer, Toronto, Canada) was applied.

After anesthesia; Group 1 (control group; n=10); intraperinetoeal 1 ml 0.9% NaCl, Group 2 (n=10); intraperinetoeal 4 mg/kg, sugammadex (Bridion, Merck Sharp & Dohme, Istanbul, Turkey) at a volume of 1 mL, Group 3 (n=10); intraperitoneally 16mg/kg sugammadex at a volume 1 ml was applied.

Intracardiac blood samples were taken from the rats 15 minutes after the injections. No neuromuscular blocker was administered in any of the groups. After the procedure, the rats were sacrificed by cervical dislocation under anesthesia.

All samples were centrifuged at 3000 rpm for 10 minutes. The obtained serum samples were stored at -80 OC until the time of analysis. From the samples obtained; estrogen, progesterone, total and free testosterone, cortisol and growth hormone levels were studied using the ELISA method. Progesterone levels were measured in the serum samples using Unicel DXI 800 Access Immunoassay System after 1/10 dilution with Beckman Coulter solution.

Statistical analysis: The number of subjects was determined according to the power analysis and it was found sufficient to have at least 8 rats for each group (7). Statistical analysis of the data was performed using the SPSS 23 (IBM Corp., Armonk, NY, USA) program. The Shapiro-Wilk normality test was used to assess whether the data was normally distributed. For the variables showing normal distribution, one-way analysis of variance (ANOVA) was used to test for differences between groups. Tukey tests were used for multiple comparisons in the groups where there was a difference. For the evaluation of non-normally distributed data, the Kruskal-Wallis test, a non-parametric test, was used. $p < 0.05$ was considered statistically significant.

RESULTS

No mortality was observed during the procedure. Growth hormone, estrogen, progesterone, total testosterone, free testosterone and cortisol levels of the rats were evaluated and mean hormone levels were presented (Table 1).

Table 1. Mean Hormone Levels Measured in Experimental Animals				
	N	Mean±SD	Minimum	Maximum
Growth hormone (ng/dl)	30	134.08±11.91	119.19	156.83
Progesterone (ng/dl)	30	2.81±0.67	1.89	3.89
Cortisol (ng/dl)	30	52.59±9.16	35.91	66.24
Total Testosterone (ng/dl)	30	5.59±1.16	3.58	7.57
Free Testosterone (ng/dl)	30	88.08±9.32	73.03	105.33
Estrogen (ng/dl)	30	49.09±6.32	40.43	60.36

Group 3 GH levels were statistically significantly higher than Group1 and Group 2 (p=0.002; p=0.014). Progesterone levels were found to be significantly lower in Group 3 compared to Group 1 and Group 2 (p=0.019; 0.021). Cortisol levels were significantly lower in both Group 2 and Group 3 compared to Group 1 (p<0.001). Group 3 cortisol level was also found to be significantly lower than Group 2 (p=0.015). There was no statistically significant difference between the groups in estrogen and total testosterone levels (p=0.112; 0.135). Free testosterone level was statistically significantly higher in Group 3 compared to Group 1 (p=0.014). The comparison of the hormone levels of the groups is shown in Table 2.

Table 2. Comparison of Hormone Levels Between Groups				
	Group 1 (n=10)	Group 2 (n=10)	Group 3 (n=10)	p
Growth hormone (ng/dl)	123.7± 3.39	129.3 ±2.24	149.2 ±6.4[a]	0.03*
Progesterone (ng/dl)	3.24 ±0.68	2.97 ±0.37	2.21 ±0.46[b]	0.009
Cortisol (ng/dl)	63.7 ±1.32	51.0 ±1.39[b]	42.9 ±4.7[b,c]	<0.001*
Total Testosterone (ng/dl)	5.59 ±0.67	4.47 ±0.51	6.70 ±0.94	0.135
Free Testosterone (ng/dl)	80.0 ±3.8	88.2 ±9.74	96.0 ±5.2[a]	0.014
Estrogen (ng/dl)	42.9 ±1.29	48.7 ±3.32	55.5 ±5.37	0.112

The values are given as mean ± standard deviation (X ± SD); p < 0.05 significant
*; Kruskall-wallis test
a; Significantly higher than Group 1
b; Significantly lower than Group 1
c; Significantly lower than Group 2

DISCUSSION

In this experimental study, high-dose sugammadex administration affected serum levels of steroid and non-steroidal hormones.

Sugammadex is a cyclodextrin ring designed to antagonize steroid neuromuscular blocks such as rocuronium and vecuronium (12). It encapsulates muscle relaxants, making the lipophilic structure more hydrophilic. The carboxyl group is negatively charged and electrostatically binds the positively charged nitrogen molecules of rocuronium (13,14).

The selectivity of sugammadex to steroidal muscle relaxants, its potential to bind positively charged molecules, and its possible effect on other steroidal substances or drugs in plasma have been the subject of some research (9, 15). The inconsistent findings in studies examining the interaction between endogenous steroids and sugammadex suggest that there is not enough evidence yet and more studies are needed in this area. In the study conducted by Et et al (7) in pregnant rats, it was observed that the administration of 30 mg/kg sugammadex did not cause a significant change in progesterone levels, nor did it cause an increase in spontaneous abortion rates. Singh et al. (16) examined the fetal and maternal outcomes of sugammadex on 25 pregnant women who underwent surgery during the antenatal period and concluded that it is safe in pregnant women. As it stated in the prospectus approved by the American Food and Drug Administration (FDA), sugammadex may interact with oral contraceptives, and that the drug dose should be considered to be skipped for contraception in sugammadex-administered patients (17,18). In the review of Mirakhur RK et al. (19), it was reported that sugammadex would cause a 34% decrease in plasma free progesterone levels with simulation methods. Studies with all these different results make the effects of sugammadex on the progesterone level controversial. Since progesterone levels affect embryo attachment during early pregnancy, changes in plasma progesterone levels will increase the potential for spontaneous abortion. (2, 17, 18). For this reason, the detection of a decrease in plasma progesterone levels after high-dose sugammadex in the rats in our study is an important finding. However, its single-shot usage effect on pregnancy and fetal development seems to originate from a theoretical aspect and needed larger studies its effect on pregnancy.

Rezonja et al. (20) showed that the efficacy of sugammadex was decreased in in vitro muscle cells treated with high-dose steroids. On the contrary, the same researchers reported that the effectiveness of sugammadex did not decrease in patients who were administered dexamethasone in their clinical study. Buonanno et al. (21) also reported that the use of dexamethasone did not change the duration of antagonizing the rocuronium block with sugammadex. In these studies, the effects of steroids on sugammadex were examined. In our study, contrary to these studies, the effect of sugammadex use on plasma cortisol levels was investigated and it was shown that it decreased significantly in high-dose sugammadex use. Gul et al. (11) examined the effects of sugammadex and neostigmine use on plasma cortisol levels, and lower cortisol levels were reported in the sugammadex group at the end of the operation. Modulating the endocrine response to surgical stress is an important issue for anesthetists in terms of patient recovery and clinical outcomes. The reduction of plasma cortisol by sugammadex is a valuable result that should be supported by clinical studies and may change our view of sugammadex in a more positive way.

Lyu et al. (22) published a study in which they examined GH receptors in GH-treated cell culture groups. And it has been reported that sugammadex given alone without GH does not affect the receptors, but when GH and sugammadex are administered together, they observed a down-regulation of GH receptors. In our study, it was observed that the plasma GH level increased with the administration of high-dose

sugammadex. These findings may be due to an affinity change or a cleavage in the GH-GH receptor complex due to sugammadex. In addition, GH is transported in plasma by GH-binding protein (23). This protein may have interacted with sugammadex. These possible scenarios may also explain the down-regulation of the sugammadex GH receptor demonstrated by Lyu et al. The elimination half-life of sugammadex is approximately 100 minutes (24). Therefore, the clinical effect of sugammadex-induced changes in plasma steroidal and non-steroidal hormone levels is unknown. However, the potential to change the levels of GH receptors made us think that the interaction with hormones should be investigated in different dimensions.

In the study of Gül et al. (11) the administration of sugammadex at a dose of 4 mg/kg caused a significant but borderline increase in plasma free testosterone and aldosterone levels. Accordingly, the authors advocated the idea of testing high-dose sugammadex in new studies. In our study, a significant increase was found in plasma free testosterone levels in the sugammadex group administered at a dose of 16 mg/kg. However, the clinical significance of this condition is unknown.

The solubility of steroid structures can be changed chemically with cyclodextrins. In the study by Schwartz et al. (25) in 2017, the solubilization of testosterone, estradiol, progesterone, hydrocortisone, prednisone, dexamethasone and finasteride using various β-cyclodextrin derivatives was investigated. Some thioether derivatives have been reported to outperform methylated and hydroxypropylated ones. The highest solubility increase was obtained with heptakis-6-sulfoethylsulfanyl-6-deoxy-β-cyclodextrin for progesterone (19.000-fold). As Fenyesi et al. (26) stated in a review, it is very difficult to establish a general rule for the effects of cyclodextrins on molecular complexes, since different cyclodextrin derivatives are used in different study groups. It is also seen that a cyclodextrin subgroup may not be effective in all steroidal structures in the same direction due to different affinity coefficients. The effect of sugammadex, which is a gamma-cyclodextrin structure, on testosterone and estradiol may be different from progesterone and its mechanism is worth investigating. The findings of our study are in this direction. In addition, the increase in free testosterone without changing total testosterone and estrogen levels suggested that there may be an interaction between sugammadex and sex hormone binding globulin. In our findings, it was noted that there was an increase in the free parts of hormones that bind heavily to proteins, such as testosterone, but that this effect was absent in hormones that bind less (about 50%) such as estrogen.

Limitations: The most important limitation of our study is that it is not a clinical but an experimental study. Although the results obtained in experimental models have similar effects in humans, clinical studies are still necessary for definitive results. In addition, intravenous sugammadex was administered intraperitoneally in our experimental model, similar to the literature. We do not know whether this application may affect the pharmacodynamic and pharmacokinetic properties of the drug in the clinic.

Strengths of our work; the relationship between steroid hormones and sugammadex, which contains inconsistent results in the literature and which is generally examined individually, was examined in a single study. Another force is that; sheds light on the interaction of sugammadex with non-steroidal hormones such as GH that has not been considered before. We think that our findings will form the basis of clinical studies to be conducted on this subject.

Our study findings showed that sugammadex may cause a decrease in plasma progesterone levels, similar to the literature. In addition, a decrease in plasma cortisol levels and an increase in free growth hormone levels were observed. Our findings suggest that sugammadex may affect not only steroid but also non-steroidal hormone levels, and perhaps also interact with hormone carrier proteins. Clinical studies are needed to evaluate the impact of these new findings on perioperative outcomes in patients.

Ethics Committee Approval: For this study, approval was obtained from the animal studies ethics committee of Erciyes University (Date: 04.03.2020 Number: 20/073) and the study was carried out within the framework of ethical guidelines.

Author contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by (AY), (CY) and (GT). Formal analysis and laboratory studies by (AYG). Review and Editing by (GT). The first draft of the manuscript was written by (AY) and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

Conflict of Interest: The authors declare no competing interests

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Availability of data and materials: The data used and analyzed during the current study are available from the corresponding author upon reasonable request.

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