Cardiovascular Toxicology (2018) 18:400–406
https://doi.org/10.1007/s12012-018-9450-6

Evaluation of the Effectiveness of Sugammadex for Digoxin Intoxication: An Experimental Study

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Published online: 16 March 2018
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Abstract

Previous studies have shown that cyclodextrin group medicines bind to various drugs. The hypothesis of our study is to determine whether sugammadex could bind to digoxin and delay the cardiovascular toxicity of that drug. Twenty-eight sedated Wistar rats were infused with digoxin at 3 mg/h (0.25 mg/ml). Five minutes after the start of infusion, animals were treated with a bolus of either 16 mg/kg (Sgdx16), 100 mg/kg (Sgdx100), or 1000 mg/kg (Sgdx1000) sugammadex. The control group infusion did not contain sugammadex. Heart rate, electrocardiography, and respiratory rate were monitored. The primary endpoint was time to asystole. Digoxin infusion continued until the animals arrested. The time to asystole for the Sgdx1000 group was significantly longer compared to that for the control group ($p < 0.05$). The mean lethal dose of digoxin was 5.35 ± 2.06 mg/kg in the saline-treated rats. On the other hand, the mean lethal dose of digoxin was 8.54 ± 1.51 mg/kg in the sugammadex 1000 group ($p < 0.05$). The mean lethal dose of digoxin was significantly higher than control group ($p < 0.05$). We found that the 1000 mg/kg dose of sugammadex delayed digoxin cardiotoxicity in a rat model of digoxin toxicity. We conclude that further research must be conducted on the interaction between digoxin and sugammadex.

Keywords Cyclodextrin · Digoxin · Toxicity · Sugammadex

Introduction

Cardiovascular drugs are the second most common cause of mortality in intoxications, after overdoses by sedative hypnotic/antipsychotic drugs. According to the 2012 Annual Report of the American Association of Poison Control Centres, these drugs were responsible for 10.77% of fatalities, either directly or as a potential contributor to death [1].

Digoxin is a cardiac glycoside commonly used in heart failure and atrial fibrillation rate control [2, 3]. Despite the new agents and a large number of sophisticated treatments used in the management of heart failure, digoxin has been one of the most commonly prescribed medicines for many years [4, 5]. Although there is a current trend of decreased digoxin use in the management of heart failure, digitalis toxicity is still a prevalent. The main disadvantage of digoxin is that its therapeutic index is very narrow [6].

Digital glycoside intoxication is an important clinical problem, and the number of patients who receive digital therapy and are at risk of toxicity is high [7, 8]. Mortality rate of digoxin intoxication in the literature is varied, but it is generally reported between 20 and 30% [9]. In the study of the Digitalis Investigation Group (DIG), hospitalization rates for digoxin intoxication were reported as 2% [10]. Digoxin intoxication is more common, especially in the elderly patient population due to decreased renal function, comorbid diseases and increased amount of drugs used for the treatment of their diseases [11]. In another study conducted in elderly patients based on this view, the mortality rate was determined to be 7% [12].

Digoxin is like a double-edged sword since it can cause a variety of life-threatening arrhythmias [13]. AV block, atrial fibrillation with slow ventricular response,

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rapid atrial, ventricular or junctional rhythms due to the increased automaticity are among the arrhythmias likely to occur [14]. In patients developing a life-threatening AV block, a temporary pacemaker can be inserted, or digoxin-specific antibodies can be used in the presence of digoxin toxicity which causes serious arrhythmias [12]. These specific antibodies are effectively used in the treatment of severe intoxications. However, they are expensive and difficult to obtain in areas with limited facilities [15–18]. Based on this property of digoxin antibodies, several studies have been conducted to evaluate the effects of different drugs on digoxin-intoxicated animal models [19, 20]. The effects of glucose–insulin infusions on survival and the effects of magnesium therapies on tachyarrhythmia have been evaluated [16].

Sugammadex is a modified gamma cyclodextrin molecule and has been recently introduced into a commercial use. Sugammadex removes rocuronium, a neuromuscular blocker, from the neuromuscular junction by encapsulating it. Therefore, it is used for the selective and rapid reversal of neuromuscular blockade [21]. Sugammadex can also interact with drugs other than rocuronium. In previous studies, it has been demonstrated that sugammadex interacts with protamine, amiodarone and dobutamine, and causes precipitation [22]. In addition, sugammadex can interact with more than 40 lipophilic steroidal and nonsteroidal drugs. These drugs are propofol, thiopental, fentanyl, remifentanil, vancomycin, gentamicin, salbutamol, aminophylline, atropine, ephedrine, phentolamine, verapamil, cortisone and hydrocortisone [19]. Interaction between sugammadex and steroidal hormones has also been reported [19]. It is reported that sugammadex can bind to verapamil, a cardiovascular agent, with 120–700 times lower affinity than rocuronium [23]. However, in our review of the literature, we could not find a clinical study investigating the interaction either between digoxin and beta cyclodextrins or between digoxin and sugammadex. Although beta cyclodextrins' interaction with verapamil in animal experiments has been reported, there is only one antidote study conducted with sugammadex, which is clinically used [24]. In the literature, there are no experimental or clinical studies investigating the interaction between sugammadex and digoxin.

The hypothesis of the study is that sugammadex will have a delaying effect in a cardiotoxicity model induced by digoxin. In order to test this hypothesis, we aimed to evaluate the effects of 16, 100 and 1000 mg/kg doses of sugammadex on digoxin cardiotoxicity in rats administered digoxin infusion.

Materials and Methods

After obtaining the approval of the Local Ethical Board of the Animal Experiments of Dokuz Eylul University Faculty of Medicine (DEUFM) (decision no 02/2013, dated March 05, 2013, Yilmaz O), we conducted the study in the Experimental Animals Laboratory of DEUFM.

Twenty-eight Wistar albino rats ranging in weight from 250 to 350 g were included in the study. The rats were kept in temperature-controlled (22–24 °C) and illuminated (12 h light/12 h dark) rooms before the study. All the rats were fed with standard rat pellets. During the course of the application, the experiments were conducted in compliance with The International Animal Research Regulations regarding the care and use of laboratory animals.

Data on the weights and ages of all the rats were recorded. Rats were divided into four groups, each consisting of seven rats: Group C, Group Sgdx16, Group Sgdx100 and Group Sgdx1000.

The rats were anesthetized with ketamine administered intraperitoneally. All the rats were monitored with electrocardiogram (ECG), and their heart rates were observed throughout the experiments. Then, in order to administer liquid and drugs, a 24 G cannula (Vasofix Safety FEP, Braun, Germany) was inserted into the lateral tail veins of all the rats using sterile techniques. After the stabilization period, arterial blood gas analysis was performed in order to determine whether the rats were hypoxic. In order to compensate for the blood loss which occurred during the blood gas analysis and cannulation procedure, normal saline was infused into the rats. After the saline infusion, control heart rates were recorded. Via a nasal cannula, oxygen was administered at the rate of 1 l/min.

Digoxin infusion was performed by means of an infusion pump via the lateral tail vein at the rate of 12 ml/h (0.25 mg/ml), and the time was assumed as 0 (T0). Digoxin infusion rate was determined based on the doses determined to have cardiotoxic effects on rats in previous experimental studies [19, 25]. Heart rates were recorded every minute until the death of the animals. At the 5th minute (T5) of the onset of the digoxin infusion, administration of saline infusion to the rats in the control group (Group Control) was initiated. Saline infusion was administered at the rate of 12.4 ml/kg/h for 5 min via the lateral tail vein. During saline infusion, digoxin infusion was continued. In the experimental groups, at the 5th minute (T5) of the onset of the digoxin infusion, doses of 16, 100 and 1000 mg/kg sugammadex added to 12 ml/kg of normal saline were infused to the Sgdx16, Sgdx100 and Sgdx1000 groups, respectively, for 5 min. During sugammadex infusion, digoxin infusion was continued. These sugammadex doses used in the rats were based on the doses used in previous experimental studies [20, 24].

Table 1 Baseline characteristics of groups (mean ± SD)

Group	Control ($n=7$)	Sgdx16 ($n=7$)	Sgdx100 ($n=7$)	Sgdx1000 ($n=7$)	p
Age (days)	187 ± 34	173 ± 32	168 ± 27	172 ± 30	0.615
Weight (g)	310.71 ± 26.44	301.57 ± 26.88	300.28 ± 18.40	304.71 ± 18.58	0.619
Heart rate (beats/min)	399.28 ± 24.62	401.85 ± 22.87	402.57 ± 21.81	402.28 ± 23.95	0.952
Respiratory rate (breaths/min)	87.28 ± 13.49	83.71 ± 13.98	85.71 ± 14.64	87.00 ± 14.39	0.910

Table 2 Toxicological characteristics of groups (mean ± SD)

Group	Control ($n=7$)	Sgdx16 ($n=7$)	Sgdx100 ($n=7$)	Sgdx1000 ($n=7$)
Time to asystole (min)	33.14 ± 12.91	47.42 ± 17.03	42.00 ± 10.06	52.28 ± 11.49*
Lethal dose of digoxin (mg/kg)	5.35 ± 2.06	7.84 ± 2.70	7.01 ± 1.70	8.54 ± 1.51*
Blood digoxin level (ng/ml)	407.14 ± 1.39	409.34 ± 1.75	408.60 ± 0.83	408.35 ± 2.11

*$p < 0.05$ compared with group control, Mann–Whitney U-test

The digoxin infusion was continued at the same rate until death occurred. Asystole observed longer than 1 min in the ECG or absence of respiratory effort was considered as the indicator of deaths in the rats.

In all the rats, the time that elapsed between the initiation of digoxin and the development of asystole was recorded in minutes. The total amount of digoxin infused into the rats and the lethal dose of digoxin for each rat were separately recorded as mg/kg. Data such as the age, weight, heart rate, respiratory rate, time of death, the lethal dose of digoxin for each group were determined. The levels of digoxin in the blood samples taken intracardially immediately after the asystole were measured. Blood sample digoxin levels have been measured with Beckman AU5800 auto-analyzer via EMIT (enzyme multiplied immunoassay technique) method.

Statistical Analysis

For statistical analysis, Statistical Package of Social Sciences 15 (SPSS 15.0, Chicago, IL, USA) was used. Data distribution was analyzed with the Kolmogorov–Smirnov test. Data were expressed as mean ± standard deviation. The Kruskal–Wallis test, Mann–Whitney U-test and the Chi-square test were used for the analysis of the significance of the data between the groups. The p value of < 0.05 was considered statistically significant.

Results

The mean age and weight of the rats in all the groups included in the study and their mean heart and respiratory rates prior to drug infusion were similar (Table 1).

The T5 heart rates of the control, Sgdx16, Sgdx100 and Sgdx1000 groups prior to sugammadex infusion were determined as 383.14 ± 25.48, 386.00 ± 22:33, 23:52 ± 381.85 and 380.57 ± 35.29 min, respectively. The mean heart rates of the groups measured at T5 prior to the sugammadex infusion were similar ($p < 0.05$).

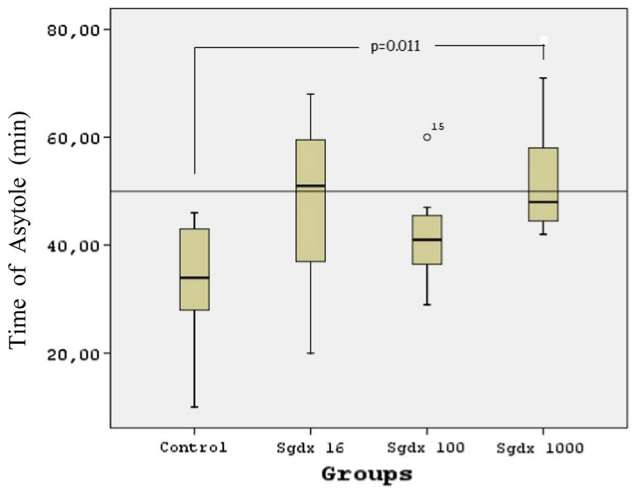


Fig. 1 Box-and-whisker plot of asystole duration by sugammadex (Sgdx16, Sgdx100, Sgdx1000) and control group status. Median is indicated by black line and upper and lower quartiles indicated by box edges

The time to asystole duration of the control, Sgdx16, Sgdx100 and Sgdx1000 groups were determined as 33.14 ± 12.91, 47.42 ± 17.03, 42.00 ± 10.06 and 52.28 ± 11.49 min, respectively. The comparison of the time to asystole duration in the groups revealed that it was shorter in the control group than in Sgdx16, Sgdx100 and Sgdx1000 groups; however, the only significant difference was between the control group and Sgdx1000 group ($p < 0.05$) (Table 2; Figs. 1 and 2).

While 5 rats in the Sgdx1000 group survived until the 45th minute, only one rat survived longer than 45 min in the control group (Figs. 1, 2 and 3).

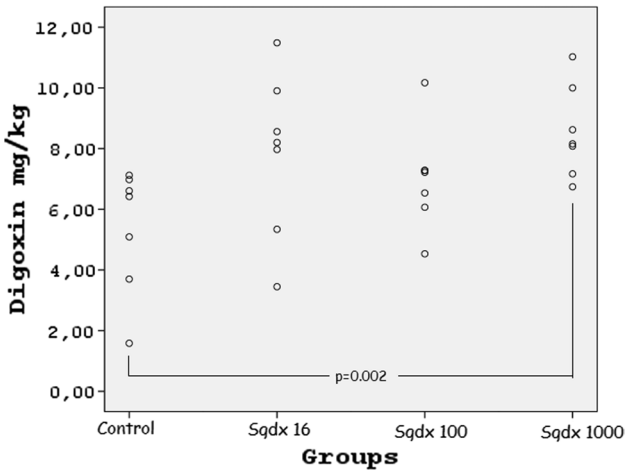


Fig. 2 Dot plot of lethal dose of digoxin in sugammadex (16, 100, 1000 mg/kg) and control groups status

The mean lethal doses of digoxin in the control, Sgdx16, Sgdx100 and Sgdx1000 groups were 5.35 ± 2.06, 7.84 ± 2.70, and 7.01 ± 1.70, and 8.54 ± 1.51 mg/kg, respectively. The mean lethal dose was significantly higher in the Sgdx1000 than in the control group ($p < 0.05$).

Heart rate decreased with time during digoxin infusion; however, the rate of decrease was significantly faster in the control group compared to the Sgdx 16 and Sgdx 1000 groups (Fig. 4).

ECG analysis showed the dominant rhythm to be sinus bradycardia, with some rats developing junctional or idioventricular rhythms, ventricular extrasystole, or varying degrees of heart block.

In control arterial blood gases analyses, none of the rats exhibited respiratory acidosis, hypoxia or hypercarbia. In all animals, the terminal event was respiratory arrest, most often preceded by primary apnea and then gasping respirations.

There were no between-group differences between the digoxin levels in the intracardiac blood samples taken immediately after death occurred in the rats ($p = 0.157$).

Discussion

The results of this study, in which the efficacy of sugammadex administered at different doses in the digoxin-induced cardiotoxicity model was evaluated, indicated that the 1000 mg/kg dose of Sugammadex delayed digoxin-induced cardiotoxicity.

Digoxin is a substrate of P-glycoprotein multidrug transporter, which is a member of the adenosine triphosphate (ATP) family and is located in the endothelial cells forming the blood–brain and blood–testis barrier, renal proximal tubules, bile canalicular membrane of the liver and the luminal surface of the epithelial cells of the small intestine. Most of the body load of digoxin is excreted unchanged by the kidneys through tubular secretion and glomerular filtration [26]. Digoxin causes an increase in intracellular calcium and sodium ions and thus increases contraction by blocking the sodium–potassium ATPase pump. Digoxin leads to atrioventricular (AV) node block and reduces the speed of his-Purkinje conduction. Digoxin can relieve the symptoms of congestive heart failure, control heart rate in atrial fibrillation and improve ventricular function [2, 27].

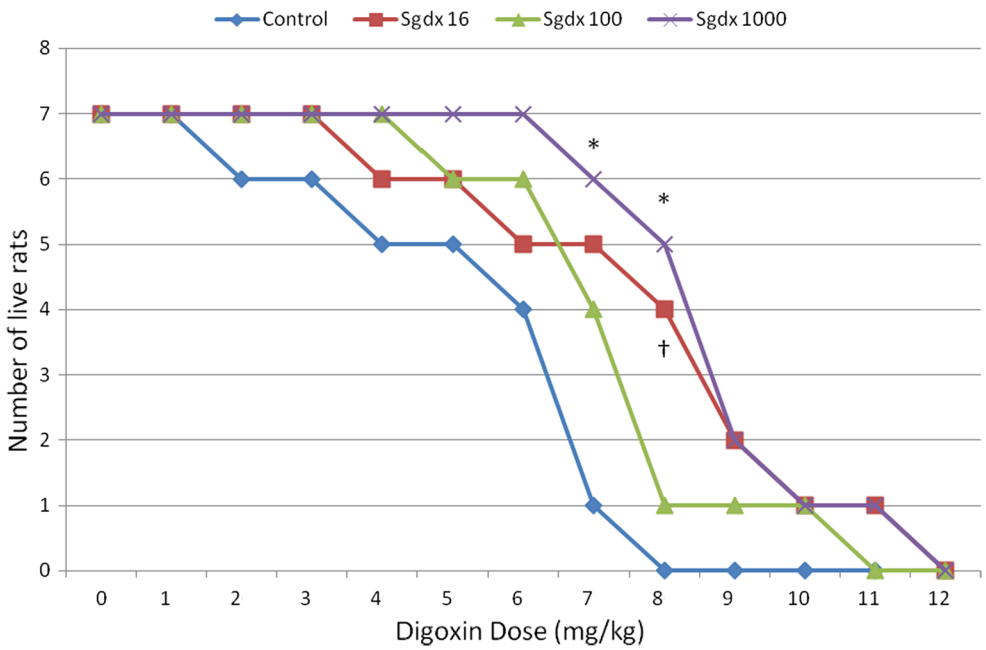


Fig. 3 Dose–response curves for sugammadex and control groups. *$p < 0.05$ compared with group Sgdx1000, Chi-squared test. †$p < 0.05$ compared with group Sgdx1000, Chi-squared test

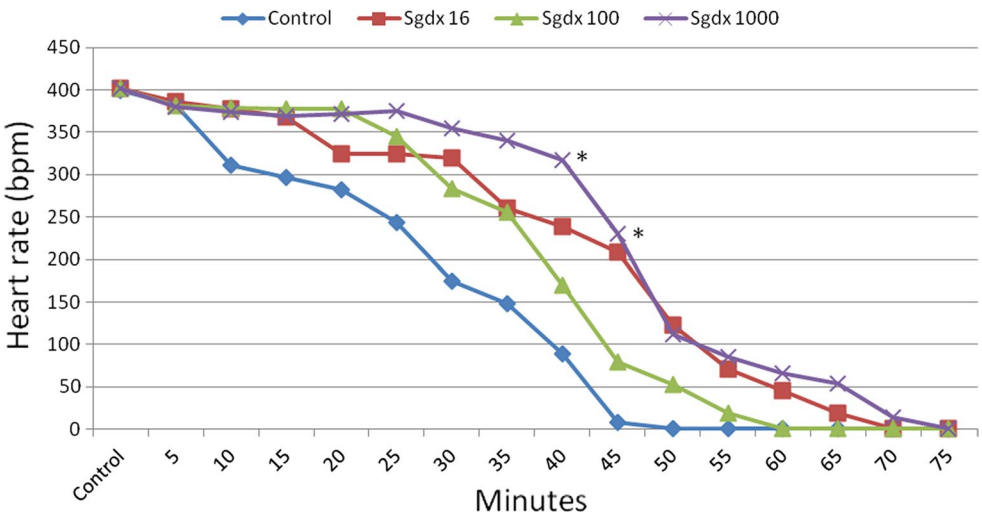


Fig. 4 Heart rate versus time for control and sugammadex groups. *$p < 0.05$ compared with group Sgdx1000, Mann–Whitney *U*-test

In patients developing a life-threatening AV block, a temporary pacemaker can be inserted. In these patients, the pacemakers should not be removed until the intrinsic heart rate ensures hemodynamic stability [3, 13, 14]. In life-threatening digoxin toxicity, it has been demonstrated that the effectiveness of Fab antibodies is high. Fab antibodies are used particularly in resistant arrhythmias, hemodynamic instability and in the presence of hyperkalemia. The inhibitory effects of different digoxin-binding antibodies administered in different doses on digoxin intoxication have been investigated [18, 28–30]. Although these specific antibodies are effective in the treatment of severe poisonings, they have the disadvantages of being expensive and difficult to obtain [15, 16]. Several studies have been conducted to evaluate the effects of different drugs on digoxin-intoxicated animal models [16].

Oubaassine et al. [16] suggested that glucose–insulin infusion improved survival in an acute digoxin-intoxicated rat model and delayed abnormalities in cardiac conduction and thus insulin had cardioprotective effects on acute digoxin toxicity. It has been reported that the result can significantly be improved with glucose–insulin infusion in case specific digoxin antibodies are not immediately available [16]. In this study, lethal doses of digoxin in rats treated with glucose–insulin infusion before the digoxin toxicity were found to be higher. Similarly, in our study, lethal doses of digoxin were determined to be higher in the group treated with sugammadex 1000 mg/kg.

Although cases of digoxin toxicity have been significantly decreased in the last few decades due to a decrease in the use of digoxin, monitoring of serum levels, improved dose-finding methods and learning and awareness of drug interactions, it is still a life-threatening condition for at-risk patients [14]. Therefore, careful monitoring of digoxin use, clinical indicators and arrhythmias seen in digitalis toxicity can reduce mortality and morbidity and can lead to effective treatment [14]. However, attempts to find an effective antidote treatment model to be used for digoxin intoxication still continues.

Cyclodextrins are agents commonly used in the pharmaceutical and food industries. Cyclodextrin molecules are especially used to convert lipophilic agents into hydrophilic ones. The 3-dimensional structure of cyclodextrins with its sugar ring molecules resembles a hollow truncated cone or a ring having a hydrophobic cavity and a hydrophilic outer structure. Thus, the water-soluble molecule surrounds the lipophilic core. With this structural arrangement, it encapsulates the appropriately sized lipophilic drugs and promotes water solubility. Through the thermodynamic noncovalent interaction, inclusion complexes are formed. Thermodynamics, van der Waals, hydrophobic interactions, hydrogen and charge transfer interactions contribute to the formation of the inclusion complex. The inclusion complex is an encapsulated lipophilic molecule [25]. In the literature, there are studies in which cyclodextrins are used as an antidote. Based on the fact that the sulfobutylether-b-cyclodextrin (SBE-CD) molecule pharmacologically binds verapamil in rat models, Mottram et al. carried out two dose-dependent studies of verapamil intoxication [31, 32]. However, all these are β-cyclodextrin molecules.

Sugammadex is a modified gamma cyclodextrin molecule and was introduced into the clinical neuromuscular pharmacology recently. Due to its special molecular structure, sugammadex is used for the selective and rapid reversal of neuromuscular blockade since it removes rocuronium, a neuromuscular blocker, from a neuromuscular junction by encapsulating it. However, there is only one antidote study conducted with sugammadex [24]. In that study, the effectiveness of sugammadex administered in different doses on verapamil-induced cardiotoxicity in rats had been evaluated. It was determined that 16 mg/kg dose of sugammadex delayed verapamil cardiotoxicity, and 1000 mg/kg dose

of sugammadex accelerated verapamil cardiotoxicity. This result was possibly due to mechanical factors between the sugammadex and verapamil molecule. In that study, survival durations were found to be 22.57 ± 12.88, 33.28 ± 16.17, 25.28 ± 16.50 and 10.14 ± 1.77 min in control, Sgdx16, Sgdx100 and Sgdx1000 mg groups, respectively. In this digoxin intoxication model, survival durations were determined as 33.14 ± 12.91, 47.42 ± 17.03, 42.00 ± 10.06 and 52.28 ± 11.49 min, respectively. The only statistical difference was determined between control and Sgdx 1000 mg groups in the latter study. This result of current experiment and previous sugammadex-verapamil intoxication study might seem conflicting; however, there are certain differences between the studies. For example, studied molecules and their effects on the corresponding cardiac tissues are opposite (negative and positive inotropy, respectively), so it may not be surprising to end up with various outcomes. Lipid sink theory and transient rise in plasma concentrations of drugs might have encountered for this findings.

In this current study, it had been found that the mean lethal dose of digoxin to induce death of rats was higher in Sgdx 1000 mg group in comparison with the other groups. On the other hand, the mean intracardiac digoxin level after the death of animals was similar between all of the groups. Thus, this finding may reflect mechanism of action of sugammadex. Then, we hypothesize that sugammadex might have encapsulated digoxin molecules from the plasma.

Nonetheless, the current therapy for digoxin intoxication is the use of Fab anticors which may not be readily available everywhere [33]. Sugammadex is a molecule that is increasingly consumed for the reversal of neuromuscular block at the operating theatres, and it is readily available at most of the institutions. Results of our experiment demonstrate that there is an interaction between sugammadex and digoxin and application of sugammadex increases the survival duration in digoxin-intoxicated rats. Clinical implications of this finding are not clear at the moment, but its potential does exist whenever Fab anticors are not readily available.

With a similar opinion, Yurtlu [34] and Turan [35] et al. have evaluated the utility of intravenous lipid emulsion in digoxin toxicity model. The latter study added DigiFab to the experiments and searched and compared the protective effects of intravenous lipid emulsion and DigiFab on digoxin toxicity. Both intravenous lipid emulsion and DigiFab were found to be protective for digitalis toxicity. Indeed, both drugs were not statistically different in their protective duration against the intoxication. On contrary, in this current study, sugammadex was administered after the development of digoxin toxicity, so our observations might be the result of sugammadex encapsulating free digoxin molecules.

There are some limitations of this study. One of limitations is the fact that mechanical ventilatory support was not provided to the rats. Absence of respiratory support might have affected the cardiac asystole duration in the rats. Second, we did not have quantified data on the type of arrhythmias observed before death of animals. So, it is not apparent the death of animals has occurred from digitalis toxicity-induced cardiac conduction defect. Third, since sugammadex was not compared to DigiFab in another group, we cannot make any comment on the relative efficiency of sugammadex at intoxicated animals.

In conclusion, this study demonstrated that 1000 mg/kg dose of sugammadex delayed digoxin cardiotoxicity in rats. Future studies should investigate the mechanisms of the relationship between digoxin and sugammadex and the possibility of reversal after asystole.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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