BCPT Basic & Clinical Pharmacology & Toxicology

Basic & Clinical Pharmacology & Toxicology, 2013, **113**, 280–285 Doi: 10.1111/bcpt.12089

Evaluation of the Effectiveness of Sugammadex for Verapamil Intoxication

Sule Ozbilgin[1], Mucahit Ozbilgin[2], Beyza Kucukoztas[1], Gonca Kamaci[3], Tarkan Unek[2], Bülent Serhan Yurtlu[1], Mehmet Ensari Güneli[3], Volkan Hanci[1] and Ali Gunerli[1]

[1]Department of Anesthesiology and Reanimation, School of Medicine, Dokuz Eylul University, Izmir, Turkey, [2]Department of General Surgery, School of Medicine, Dokuz Eylul University, Izmir, Turkey and [3]Department of Experienced Laboratory Animal Science, School of Medicine, Dokuz Eylul University, İzmir, Turkey

(Received 20 February 2013; Accepted 15 May 2013)

Abstract: Previous studies have shown that medications from the cyclodextrin family bind to verapamil. The aim of our study was to determine whether sugammadex could bind to verapamil and prevent the cardiovascular toxicity of that drug. Twenty-eight sedated Wistar rats were infused with verapamil at 37.5 mg/kg/h. Five minutes after the start of infusion, the animals were treated with a bolus of either 16 mg/kg, 100 mg/kg or 1000 mg/kg sugammadex. The control group was treated with an infusion without sugammadex. The heart rate and respiratory rate were monitored, and an electrocardiogram was recorded. The primary end-point was the time to asystole. The verapamil infusion continued until the animals arrested. The asystole time for the S16 group was significantly longer compared to those for the control and S1000 groups ($p < 0.05$). The asystole time for the S1000 group was significantly shorter than those for all of the other groups ($p < 0.05$). Reflecting these data, there was a near doubling of the mean lethal dose of verapamil from 13.57 mg/kg (S.D. ±8.1) in the saline-treated rats to 22.42 mg/kg (S.D. ±9.9) in the sugammadex 16 group ($p < 0.05$). However, for the sugammadex 1000 group, the mean lethal dose was found to be 6.28 ± 1.11 mg/kg. This dose is significantly lower than those for all of the other groups ($p < 0.05$). We found that treatment with 16 mg/kg sugammadex delayed verapamil cardiotoxicity in rats. However, 1000 mg/kg sugammadex accelerated verapamil cardiotoxicity in rats. Further studies must be conducted to investigate the interaction between verapamil and sugammadex.

Intoxication with medications is one of the most common reasons for patients to visit emergency departments. After motor vehicle accidents, intoxications are a substantial cause of mortality in young people [1]. Cardiovascular drugs are the second most common cause of mortality in drug 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 [2].

Calcium channel blockers are frequently used to treat hypertension and rhythmic dysfunction. However, these compounds frequently cause medication intoxication [3]. Their toxic/therapeutic ratio is relatively narrow, and serious toxicity may occur with therapeutic doses. Toxicity from calcium channel antagonists may occur with a therapeutic use or as a result of an accidental or intentional overdose. Overdoses of calcium channel antagonists are frequently life-threatening and represent an increasingly important source of drug-induced mortality [4].

Calcium channel blocker overdoses can cause hypotension, non-cardiogenic pulmonary oedema, sinus arrest, atrioventricular block, a reduction in cardiac output and hyperglycaemia [5–8]. To restore blood pressure, inotropic agents, pacemaker devices or intra-aortic balloon pumps may be used [9–11]. Case studies emphasize the advantages of ECMO and heart–lung machines [12,13].

There is no specific antidote for calcium channel blocker intoxication. For this reason, the delaying effects of various agents in calcium channel blocker poisoning have been investigated. These agents include intravenous lipid treatment, high-dose insulin and levosimendan [14–18]. However, a therapeutic antidote has not been found.

Cyclodextrins are molecules that are frequently used in the food and pharmaceutical industries. They are commonly used to convert lipophilic medications to hydrophilic forms [19,20]. Beta-cyclodextrin has been evaluated as an antidote for verapamil toxicity. Researchers have found that beta-cyclodextrin interacted with verapamil [21,22].

Sugammadex is a modified gamma-cyclodextrin that has recently entered trade use. Sugammadex has a distinctive molecular structure that allows it to encapsulate rocuronium, a neuromuscular blocker, and remove it from the muscle–nerve junction; it is used to selectively and quickly reverse neuromuscular blockage [23]. The affinity of sugammadex for verapamil is nearly 120–700 times less than that for rocuronium, but it is still known to interact with verapamil [24]. Although the interaction of beta-cyclodextrin with verapamil in animal models is known [21,22], there is no information available on the interaction between sugammadex and verapamil in a clinical setting.

Author for correspondence: Volkan Hanci, Dokuz Eylül Universitesi, Tip Fakültesi, Dokuz Eylül Universitesi Hastanesi, Poliklinikler binasi 3. Kat, Narlidere, İzmir, Turkey (fax +90 23 241 22846, e-mail: vhanci@gmail.com).

© 2013 Nordic Pharmacological Society. Published by John Wiley & Sons Ltd

The hypothesis of our study is that sugammadex, similar to beta-cyclodextrin, will have a delaying effect in a cardiotoxicity model induced by verapamil. To test this hypothesis, rats that were given verapamil infusions were administered sugammadex at doses of 16 mg/kg, 100 mg/kg and 1000 mg/kg, and the effects of sugammadex on verapamil cardiotoxicity were investigated.

Materials and Methods

After obtaining permission from the Dokuz Eylul University School of Medicine (DEUSM) Local Animal Experiments Ethical Committee (16.11.2012, number: 63/2012, Yõlmaz O), the research was carried out at the DEUSM Animal Experiment Laboratories. The study included 28 Wistar Albino rats that weighed between 250 and 400 g. The rats were housed in temperature-controlled (22–24°C) rooms that were lit on a daily schedule (12:12 hr light/dark) before the study. All of the rats were fed standard rat pellets. During the experimental period, the care of the laboratory animals was in accord with international guidelines.

The weights and ages of all of the rats were recorded. The rats were divided into four groups of seven rats: Group C, Group S16, Group S100 and Group S1000.

The rats were administered intraperitoneal 60 mg/kg ketamine for anaesthesia. All of the rats were monitored using electrocardiography (ECG), and their heart rate was tracked throughout the entire study. Using sterile techniques, all of the rats had a 24 G (Vasofix Safety FEP, Braun, Germany) cannula placed in the lateral tail vein for the administration of liquids and medications during the study. After catheterization, the rats were given a 1 ml normal saline infusion to replace the blood lost during the procedure. After the saline infusion, control heart rate values were taken. Oxygen was administered at a rate of 1 l/min through a nasal cannula.

A verapamil infusion of 37.5 mg/kg/hr was begun using an infusion pump through the lateral tail vein starting at time 0 (T0). This infusion rate was determined based on doses used in previous experimental studies on cardiotoxicity in rats [25]. The heart rate was recorded every minute until death. In the control group (Group C), the rats were given 12.4 ml/kg normal saline; the dose began 5 min. after verapamil was given (T5) and lasted for a period longer than 5 min. In the experimental groups, the rats were given 16, 100 and 1000 mg/kg sugammadex infused in 12 ml/kg normal saline volume; the dose began 5 min. after verapamil was given and lasted for a period longer than 5 min. The verapamil infusion continued until death. Rat death was defined on ECG as more than 1 min. of asystole or a lack of respiratory effort.

The sugammadex doses were determined by the doses used in previous experimental studies [26].

For all of the rats, the time between beginning the verapamil infusion and asystole was recorded in minutes (duration from T0 to the death of the rat). The total verapamil amount infused over this period and the average fatal verapamil dose (mg/kg) for each rat were recorded separately.

Statistical analysis. For statistical analysis, the program Statistical Package for Social Sciences 15 (SPSS 15.0, Chicago, IL, USA) was used. The distribution of the data was examined using the Kolmogorov–Smirnov test. To evaluate the significance of the comparisons between groups, the Kruskal–Wallis and Mann–Whitney *U*-tests were used. Statistical significance was accepted as $p < 0.05$.

Results

The mean baseline ages, weights, heart rates and respiratory rates were similar between the controls and all of the treatment groups (S16, S100 and S1000) (table 1).

The T5 heart rates for the control, S16, S100 and S1000 groups were 339.85 ± 30.55, 341.70 ± 46.99, 337.71 ± 32.24 and 347.86 ± 28.37, respectively. At the end of the sugammadex infusion (T5), there was no significant difference in the heart rates between the saline- and sugammadex-treated groups ($p > 0.05$).

The asystole time of the S16 group was significantly longer compared to those of the control and S1000 groups ($p < 0.05$). The asystole time for the S1000 group was significantly shorter than those for any of the other groups ($p < 0.05$) (table 2, fig. 1).

In the S16 group, six rats lived to the 25th min., whereas only one rat lived longer than 25 min. in the verapamil group. In the S1000 group, all of the rats expired before the 15th min. (figs 1–4).

Reflecting these data, there was a near doubling of the mean lethal dose of verapamil from 13.57 mg/kg (S.D. ±8.1) in the

Table 1.

Baseline characteristics (mean ± S.D.).

Group	Control (n = 7)	S16 (n = 7)	S100 (n = 7)	S1000 (n = 7)	*p*-value
Age (days)	202 ± 56.49	212 ± 59.49	225 ± 54.73	174 ± 31.93	0.271
Weight (g)	301.428 ± 35.50	310.71 ± 42.44	311.28 ± 34.35	280.85 ± 17.52	0.244
Heart rate (beats/min.)	382.42 ± 31.75	386.28 ± 22.70	373.85 ± 27.16	385.57 ± 26.95	0.623
Respiratory rate (breaths/min.)	85.28 ± 14.55	84.28 ± 14.81	85.85 ± 13.50	87.42 ± 13.16	0.948

$p < 0.05$, compared with Group 1000, Mann–Whitney *U*-test.
$p < 0.05$, compared with Group 16, Mann–Whitney *U*-test.

Table 2.

Comparison of time to death and lethal dose of verapamil between groups

Group	Control (n = 7)	S16 (n = 7)	S100 (n = 7)	S1000 (n = 7)	*p*-value
Time to death (min.)	22.57 ± 12.88*†	33.28 ± 16.17*	25.28 ± 16.50*	10.14 ± 1.77	0.001
Lethal dose of verapamil (mg/kg)	13.57 ± 8.10*†	22.42 ± 9.96*	16.00 ± 10.03*	6.28 ± 1.11	0.001

*$p < 0.05$, compared with Group 1000, Mann–Whitney *U*-test.
†$p < 0.05$, compared with Group 16, Mann–Whitney *U*-test.

© 2013 Nordic Pharmacological Society. Published by John Wiley & Sons Ltd

control group to 22.42 mg/kg (S.D. ±9.9) in the S16 group ($p < 0.05$; fig. 2). However, the mean lethal dose was 6.28 ± 1.11 mg/kg for the S1000 group. This dose was significantly lower than those for all of the other groups ($p < 0.05$).

The heart rate decreased over time during the verapamil infusion; however, the rate of decrease was significantly slower in the S16 group compared with that in the control group. In addition, the heart rate in the S1000 group decreased at a significantly faster rate than did those in all of the other groups ($p < 0.05$) (fig. 3,4).

The ECG revealed that the dominant rhythm was sinus bradycardia, with some of the rats developing slow atrial fibrillation, junctional or idioventricular rhythms or varying degrees of heart block.

In the arterial blood gas analyses of the control rats, none showed respiratory acidosis, hypoxia or hypercarbia. Spontaneous ventilation was adequate for most of the experiment. In all of the animals, the terminal event was respiratory arrest, most often preceded by primary apnoea and then gasping respirations.

Discussion

The results concerning the effectiveness of various doses of sugammadex on animal models of verapamil-induced cardiotoxicity indicated that 16 mg/kg sugammadex delayed cardiotoxicity, whereas a 1000 mg/kg dose of sugammadex hastened cardiotoxicity.

Verapamil is a potent calcium channel blocker and is used to treat hypertension, ischaemic heart disease and supraventricular tachyarrhythmia [27,28]. Overdoses of verapamil may cause hypotension, sinus arrest, atrioventricular block, a reduction in cardiac output and hyperglycaemia [6,8,28,29]. There

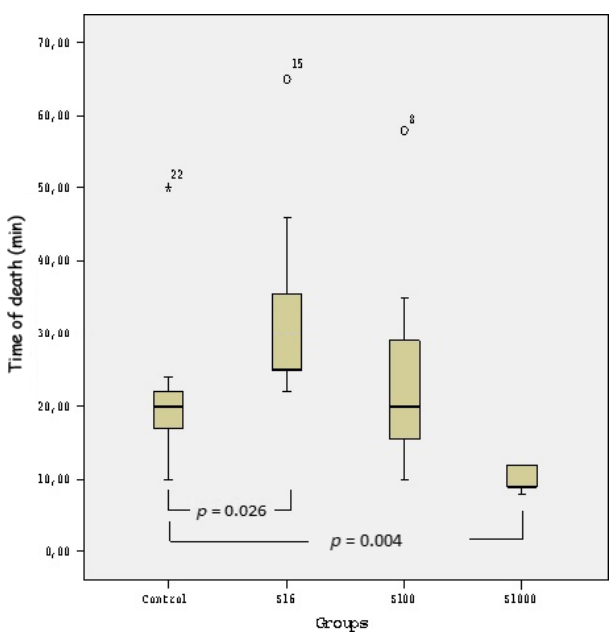


Fig. 1. Box-and-whisker plot of time of death by sugammadex (S16, S100, S1000) and control group status. Median indicated by black line, and upper and lower quartiles indicated by box edges.

is no known antidote to verapamil, and intoxication with this drug may cause multiorgan failure [6,28]. Treatment typically includes preventing gastrointestinal system absorption and a symptomatic approach. Bay K 8644 and 4-aminopyridine show promise as potential antidotes, but these compounds are currently still experimental [30].

The first step in treating patients with calcium channel antagonist toxicity should be to maintain an adequate airway, ventilation, oxygenation and haemodynamic support, as is the case for all serious poisonings. Due to the depressed mental state or evolving ARDS of the patients, endotracheal intubation and mechanic ventilation are frequently required in cases of serious poisoning with these agents. The essential elements in intensive care unit management include close monitoring of cardiac rhythms, vital signs, respiratory status and urine output [6]. Many modalities are typically employed to treat the cardiovascular system impairments associated with these agents. Calcium, glucagon, sympathomimetics, insulin, inamrinone, pacing and mechanical cardiac assistance devices have been used. For a patient who sustains a cardiac arrest, the pathophysiological changes induced by calcium channel antagonists are potentially completely reversible despite prolonged resuscitations. They should be treated aggressively using a supportive approach [6].

Therefore, the effectiveness of various agents to delay cardiotoxicity during calcium channel blocker poisoning is under investigation. The use of intravenous lipid treatment, high-dose insulin and levosimendan for delaying the cardiotoxicity from calcium channel blocker poisoning has been studied, and these agents have been observed to possess variable efficacies [14–16,25,31–36]. Research continues to identify an effective and, if possible, specific antidote for verapamil intoxication.

Various cyclodextrins have been used to transform lipophobic agents into lipophilic compounds in the drug industry. These molecules are ‘donut-like’ due to their circular 3-D structure with sugar rings (D-glucopyranose units) forming an empty cut cone or hydrophobic cavity and a hydrophilic outer structure. The negative load hydroxyl groups cause the molecule to be water soluble. The internal alpha 1–4 bonded carbon atoms create a lipophilic cavity. Consequently, the water-soluble molecule surrounds a lipophilic core. This structure possesses the appropriate size to encapsulate lipophilic medications and increases their water solubilities. Non-covalent thermodynamic interactions create an inclusion complex. The cavity size is larger than that in alpha-, beta- or gamma-cyclodextrin and is 0.8 mm. Thermodynamic, Van der Waals, hydrophobic, hydrogen and load-transfer interactions strengthen the formation of the inclusion complex (host–guest complex). The inclusion complex encapsulates a lipophilic molecule [19].

Limited previous research has shown that cyclodextrin has an antagonist effect, due to its molecular characteristics, and may be useful to reverse verapamil toxicity [21,22]. In the literature, there are only two studies that examine cyclodextrin as an antidote for verapamil toxicity [21,22]. Both are experimental. Initially, Mottram *et al.* [21] induced intoxication in rats using verapamil and found that the group treated with

© 2013 Nordic Pharmacological Society. Published by John Wiley & Sons Ltd

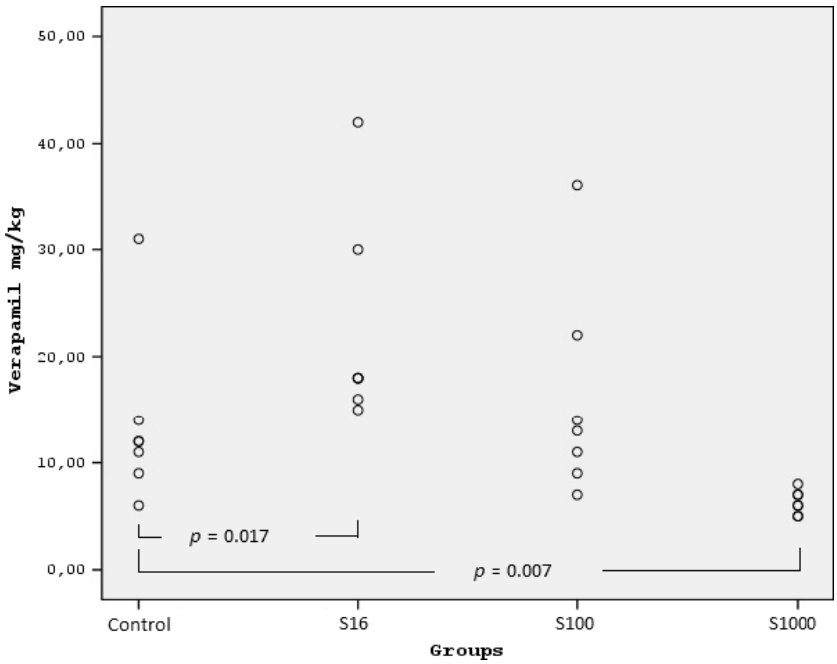


Fig. 2. Dot plot of lethal dose of verapamil by sugammadex (16 mg/kg, 100 mg/kg, 1000 mg/kg) and control groups status.

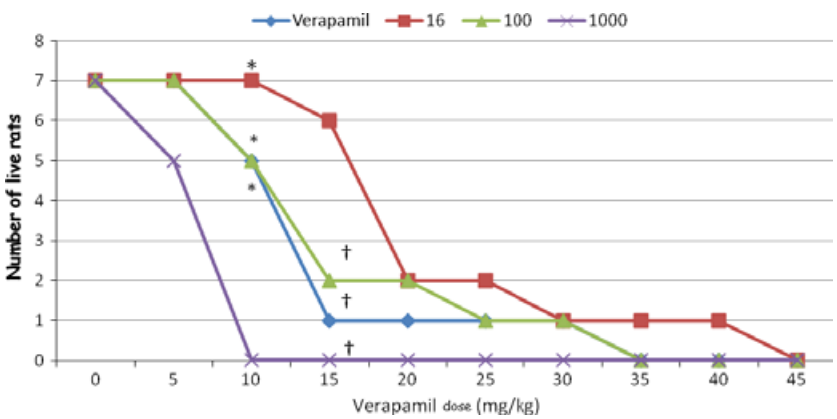


Fig. 3. Dose–response curves for sugammadex and control groups. *$p < 0.05$, compared with Group 1000, chi-squared test. †$p < 0.05$, compared with Group 16, chi-squared test.

2.25 g/kg sulphobutylether-b-cyclodextrin (SBE-CD) did not exhibit any differences in heart rate, asystole and apnoea times compared to the control group; in fact, contrary to their hypothesis, 2.25 g/kg SBE-CD increased the verapamil toxicity. They emphasized the need to conduct further studies to elucidate the mechanism of increased toxicity and later performed a second dose-linked study [22]. In the group given a 1:4 ratio of verapamil to SBE-CD concentration infusion, a delay in the asystole time was observed compared to the control group, and this difference was found to be significant (21.2 min. compared to 17.6 min.). There were no significant differences between the groups in terms of the heart rate, inhalations and apnoea time. Together with the evidence that a 1:4 verapamil/SBE-CD concentration was the most effective model, other than at this dose, there were no significant differences in the asystole time improvements [22].

However, these experimental models all used beta-cyclodextrin. There are no studies on gamma-cyclodextrin (gamma-CyD, a molecule used in the trade) as an antidote or as a potential source of medication interactions.

Sugammadex has a modified gamma-cyclodextrin structure with a wider cavity distinct from that of beta-cyclodextrin and is the only example of a molecule used in anaesthetic practice as a binding molecule for selective neuromuscular agents. Human and animal studies on the deep neuromuscular blockage caused by sugammadex and rocuronium have revealed that reversal occurs without muscle weakness [37]. In recent years, the use of this agent in anaesthetic practice has become popular for this reason. Because it provides quick and problem-free recovery, it has become an agent that is favoured by anaesthetists, and the use of sugammadex has increased in anaesthesia management.

© 2013 Nordic Pharmacological Society. Published by John Wiley & Sons Ltd

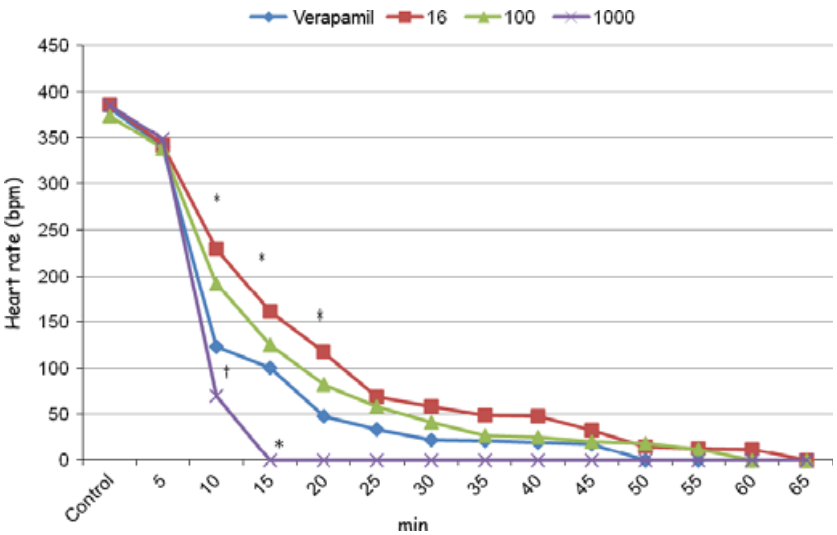


Fig. 4. Heart rate *versus* time for control and sugammadex groups. *$p < 0.05$, compared with Group 1000, Mann–Whitney *U*-test. †$p < 0.05$, compared with Group 16, Mann–Whitney *U*-test. Min., Minute.

For the cases in which sugammadex is used, it is important to know whether it might interact with previously taken medications. Apart from the rocuronium/sugammadex interaction, this compound interacts in various forms from the perspectives of both pharmacokinetics and pharmacodynamics. Sugammadex may cause the precipitation of protamine, amiodarone and dobutamine [38]. Additionally, sugammadex may interact with over 40 lipophilic, steroidal and non-steroidal medications. These medications include propofol, thiopental, fentanyl, remifentanil, vancomycin, gentamicin, salbutamol, aminophylline, atropine, ephedrine, phentolamine, verapamil, cortisone and hydrocortisone [39]. Although sugammadex has an affinity for verapamil, that is, up to 120–700 times lower than that for rocuronium, it still binds to verapamil [24]. However, no experimental or clinical studies on the interaction between sugammadex and verapamil were found in the literature.

In our study on the cardiotoxicity caused by verapamil, similar to studies using beta-cyclodextrin, the group given a 16 mg/kg dose of sugammadex with verapamil showed longer asystole times than did the control group. Our study showed that a 16 mg/kg dose of sugammadex caused the development of cardiovascular toxicity to be delayed. Again, similar to studies using beta-cyclodextrin, the 1000 mg/kg sugammadex group showed significantly shorter asystole times compared to those of the control, S16 and S100 groups; 1000 mg/kg sugammadex hastened the cardiotoxicity caused by verapamil.

Cyclodextrins have been used at various doses in experimental studies on rats [21]. Tomak *et al.* [27,40,41] used various doses of sugammadex, including 16 mg/kg, 96 mg/kg and 100 mg/kg, in their studies. The beta-cyclodextrin sulphobutylether-b-cyclodextrin (SBE-CD) was used at 2.25 g/kg dose to treat verapamil toxicity [21]. Similar to the doses used in these previous experiments, we used 16 mg/kg, 100 mg/kg and 1000 mg/kg. We included a 1000 mg/kg dose because sugammadex interacts with verapamil with an affinity 120–700 times less than that for rocuronium. In a preliminary study before the main experiment, 1000 mg/kg sugammadex was given to rats, and they were observed for 1 hr; no respiratory depression or asystole was observed in any individual, so we determined that a 1000 mg/kg dose of sugammadex was appropriate for use in our model.

There are some limitations of this study. The possible effect of ketamine, used for anaesthetic purposes in our rats, on haemodynamic changes is one limitation. However, there are no anaesthetics that are devoid of haemodynamic effects. Another limitation is that mechanical ventilatory support was not provided to the rats. Similar to many experimental studies, the present study used spontaneous respiration of the animals [42,43]. This study is also limited with respect to an explanation for the observed controversial findings in groups S16 and S1000. This result was possibly due to mechanical factors between the sugammadex and verapamil molecules, but at this moment, this issue remains speculative.

In conclusion, this study showed that the effects of various doses of sugammadex in a rat model of cardiotoxicity caused by a 16 mg/kg dose of verapamil delayed verapamil cardiotoxicity and that a 1000 mg/kg dose hastened cardiotoxicity. Future studies should investigate the mechanisms of the relationship between verapamil and sugammadex.

Financial support

The authors have no financial interests related to this work.

Conflict of Interest

The authors report no conflict of interests.

References

1 Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS), 2009, http://www.cdc.gov/injury/wisqars/ (last accessed on 1 May 2013).

© 2013 Nordic Pharmacological Society. Published by John Wiley & Sons Ltd

2 Bronsteõn AC, Spyker DA, Cantõlena LR, Rumack BH, Dart RC. 2011 Annual Report of the American Association of Poison Control Centers ' National Poison Data System (NPDS): 29th Annual Report. Clin Toxicol 2012;**50**:911–1164.
3 Yalçõn Ş, Güntekin Ü, Sezen Y, Nacar H, Dalyan A. Yavaş Salõnõmlõ Verapamil İntoksikasyonu. Bidder Tõp Bilimleri Dergisi 2010;**2**:29–31.
4 Olson KR. Poisoning and Drug Overdose 3rd edn, Appleton &Lange Stamford, Connecticut 1999, Calcium antagonists Benowittz NL 119–23.
5 Dustan HP. Calcium channel blockers. Potential medical benefits and side effects. Hypertension 1989;**13**:137–40.
6 Jeffrey B. Cardiovascular. In: Jeffrey B, Kevin W, Keith K Burkhart (eds). Critical Care Toxicology:Diagnosis and Management of the Critically Poisoned Patient, Vol III, Edition 1, 2004, 393–441.
7 Brass BJ, Winchester-Penny S, Lipper BL. Massive verapamil overdose complicated by noncardiogenic pulmonary edema. Am J Emerg Med 1996;**14**:459–61.
8 Mégarbane B, Karyo S, Abidi K, Delhotal-Landes B, Aout M, Sauder P *et al.* Predictors of mortality in verapamil overdose: usefulness of serum verapamil concentrations. Basic Clin Pharmacol Toxicol 2011;**108**:385–9.
9 Liang CW, Diamond SJ, Daniel SH. Lipid rescue of massive verapamil overdose: a case report. J Med Case Rep 2011;**5**:399.
10 Kimura Y, Okamura M, Harioka T, Hara T, Nakasato A, Ishiyama T *et al.* Suspected diltiazem intoxication resulting in repeated asystole after the induction of anesthesia. Masui 2012 Jan;**61**:104–7.
11 Janion M, Stepień A, Sielski J, Gutkowski W. Is the intra-aortic balloon pump a method of brain protection during cardiogenic shock after drug intoxication? J Emerg Med 2010 Feb;**38**:162–7.
12 Daubin C, Lehoux P, Ivascau C, Tasle M, Bousta M, Lepage O *et al.* Extracorporeal life support in severe drug intoxication: a retrospective cohort study of seventeen cases. Crit Care 2009;**13**: R138.
13 Rygnestad T, Moen S, Wahba A, Lien S, Ingul CB, Schrader H *et al.* Severe poisoning with sotalol and verapamil. Recovery after 4 h of normothermic CPR followed by extra corporeal heart lung assist. Acta Anaesthesiol Scand 2005 Oct;**49**:1378–80.
14 Young AC, Velez LI, Kleinschmidt KC. Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. Resuscitation 2009;**80**:591–3.
15 Montiel V, Gougnard T, Hantson P. Diltiazem poisoning treated with hyperinsulinemic euglycemia therapy and intravenous lipid emulsion. Eur J Emerg Med 2011;**18**:121–3.
16 French D, Armenian P, Ruan W, Wong A, Drasner K, Olson KR *et al.* Serum verapamil concentrations before and after Intralipid® therapy during treatment of an overdose. Clin Toxicol (Phila) 2011;**49**:340–4.
17 Zhanna L, Robert S. Hoffman response to: 'Intravenous Fat Emulsion Therapy: Can It be Tried Without Sufficient First-Line Treatment Modalities?' Basic Clin Pharmacol Toxicol 2012;**111**:3
18 Litonius E, Niiya 1T, Neuvonen PJ, Rosenberg PH. Antidotal effect of intravenous lipid emulsion in experimental amitriptyline intoxication despite significant entrapment of amitriptyline. Basic Clin Pharmacol Toxicol 2012;**110**:378–83.
19 Challa R, Ahuja A, Ali J, Khar RK. Cyclodextrins in drug delivery: an updated review. AAPS Pharm SciTech 2005;**6**:329–57.
20 Valentõno JS, Quanren H. Cyclodextrins. Toxicologic Pathol 2008;**36**:30–42.
21 Mottram AR, Bryant SM, Steven E. Effect of cyclodextrin infusion in a rat model of verapamil toxicity. Am J Therap 2011;**18**:371–4.
22 Mottram AR, Bryant SM, Steven E. Dose-dependent response to cyclodextrin infusion in a rat model of verapamil toxicity. West J Emerg Med 2012;**13**:63–7.
23 Sacan O, White PF, Tufanogullari B, Klein K. Sugammadex reversal of Rocuronium-Induced neuromuscular blockade: a comparison with Neostigmine–Glycopyrrolate and Edrophonium–Atropine. Anesth Analg 2007;**104**:569–74.
24 Srivastava A, Hunter JM. Reversal of neuromuscular block. Br J Anaesth 2009;**103**:115–29.
25 Tebbutt S, Harvey M, Nicholson T. Intralipid prolongs survival in a rat model of verapamil toxicity. Acad Emerg Med 2006;**13**:134–9.
26 Tomak Y, Yõlmaz A, Bostan H, Tümkaya L, Altuner D, Kalkan Y *et al.* Effects of sugammadex and rocuronium mast cell number and degranulation in rat liver. Anaesthesia 2012 Oct;**67**:1101–4.
27 Monteiro PF. Calcium channel antagonists: role in acute coronary syndromes therapy. European Heart J, ISSN 0195-668X, 08/2006, Cilt 27, 381.
28 Cardiac & Cardiovascular Systems. Calcium Antagonists. Ehud Ehud and Franz H. Messerli. Progress in Cardiovascular Diseases, ISSN 0033-0620, 07/2004, Vol 47, Edit: 1, 34–57.
29 Engebretsen KM, Kaczmarek KM, Morgan J. And. Holger J S - High dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clinical Toxicol 2011;**49**:277–83.
30 Hofer CA, Smith JK, Tenholder MF. Verapamil intoxication: a literature review of overdoses and discussion of therapeutic options. Am J Med 1993 Oct;**95**:431–8.
31 Perez E, Bania TC, Medlej K, Chu J. Determining the optimal dose of intravenous fat emulsion for the treatment of severe verapamil toxicity in a rodent model. Acad Emerg Med 2008;**15**:1284–9.
32 Bania TC, Chu J, Perez E, Su M, Hahn IH. Hemodynamic effects of intravenous fat emulsion in an animal model of severe verapamil toxicity resuscitated with atropine, calcium, and saline. Acad Emerg Med 2007;**14**:105–11.
33 Kurola J, Leppikangas H, Magga J, Lindgren L, Kiviniemi V, Rutanen J, Ruokonen E. Effect of levosimendan in experimental verapamil induced myocardial depression. Scand J Trauma, Resus Emerg Med 2010;**18**:12.
34 Graudins A, Najafi J, Rur-Sc P. Treatment of experimental verapamil poisoning with levosimendan utilizing a rodent model of drug toxicity. Clinical Toxicol 2008;**46**:50–6.
35 Abraham MK, Scott SB, Meltzer A, Barrueto F. Levosimendan does not improve survival time in a rat model of verapamil toxicity. J Med Toxicol 2009;**5**:3–7.
36 Agoston S, Maestrone E, van Hezik EJ, Ket JM, Houwertjes MC, Uges DR. Effective treatment of verapamil intoxication with 4-aminopyridine in the cat. J Clin Invest 1984 May;**73**:1291–6.
37 Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. Anesth Analg 2007;**104**:575–81.
38 Hanci V, Kiraz HA, Ömür D, Ekin S, Uyan B, Yurtlu S. Precipitation in Gallipoli: Sugammadex/Amiadoron & Sugammadex/Dobutamin & Sugammadex/Protamin. Brazillian J Anesthesiol 2013;**63**:163–4.
39 Zhang M-Q. – Drug-specific cyclodextrins: the future of rapid neuromuscular block reversal? Drugs Future 2003;**28**:347–54.
40 Kalkan Y, Bostan H, Tumkaya L, Tomak Y, Bostan M, Yilmaz A, Turut H, Temiz A, Yalçin A, Turan A. The effect of rocuronium, sugammadex, and their combination on cardiac muscle and diaphragmatic skeletal muscle cells. J Anesth 2012 Dec;**26**:870–7.
41 Kalkan Y, Tümkaya L, Bostan H, Tomak Y, Yõlmaz A. Effects of sugammadex on immunoreactivity of calcineurin in rat testes cells after neuromuscular block: a pilot study. J Mol Histol 2012; **43**:235–41.
42 Tanaka K, Oda Y, Funao T, Takahashi R, Hamaoka N, Asada A. Dexmedetomidine decreases the convulsive potency of bupivacaine. and levobupivacaine in rats: involvement of α-2 adrenoceptor for controlling convulsions. Anesth Analg 2005;**100**: 687–96.
43 Rosen MA, Thigpen JW, Shnider SM, Foutz SE, Levinson G, Koike M. Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 1985;**64**:1089–109.

© 2013 Nordic Pharmacological Society. Published by John Wiley & Sons Ltd