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ORIGINAL ARTICLE

Investigation of the effects of different doses of sugammadex on kidney histopathology in rabbits with acute renal failure

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ABSTRACT

Objective: In our study, we hypothesised that using high doses, ie. 16 mg / kg sugammadex during general anesthesia after acute renal failure in rabbits would lead to a deteriorated renal histopathology due to the accumulation of rocuronium-sugammadex complex in the tubules. We aimed to investigate the effect of different doses of sugammadex (4 or 16 mg) on experimental kidney histopathology in rabbits with acute renal failure.

Methodology: Eight New Zealand white adult male rabbits were used in the study. The rabbits were divided into 2 groups of four. The first group received low dose (4 mg) sugammadex and the second group received high dose (16 mg) sugammadex. Rabbits were administered 20 mg / kg of cisplatin intravenously 4 hours before general anesthesia and an acute renal failure model was established. After general anesthesia was applied, V-GEL® Rabbıt was placed to all experimental animals to provide airway safety. All animals were manually ventilated using an anesthesia device. At the 25th min after induction, the rabbits in Group D received 4 mg / kg sugammadex iv, and the those in Group Y received 16 mg / kg sugammadex iv. At the end of the experiment, all experimental animals were sacrificed, and the kidneys were removed, and histopathologic examination was performed.

Results: At the end of our study all experimental animals were sacrificed. There was no statistically significant difference between findings in the kidneys of animals of Group Y and Group D on histopathologic evaluation.

Conclusion: The results of our study did not reveal any differences between the renal histopathological appearances of rabbits receiving 4 mg / kg or 16 mg /kg sugammadex IV.

Key words: Acute renal failure; Sugammadex; Rocuronium

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INTRODUCTİON

The use of neuromuscular blockers (NMBA) in steroids in general anesthesia is increasing due to the effects of rapid and easy endotracheal intubation and ventilation. Postoperative residual block resulting from the use of NMBA causes complications such as hypoventilation, airway obstruction, hypoxia and death.[1] Sugammadex is the first selective binding agent in the gamma-cyclodextrin structure, which contains eight glucose molecules, which reverses the NMBA effect in steroids. Sugammadex is easy to apply, its effect is potent and fast. Besides this, the side effect are minimal and its use is widespread for this reason.[2]

Sugammadex is not bound to plasma proteins or erythrocytes in human plasma (free form or rocuronium-bound forms).[3,4] It is assumed that sugammadex in is not metabolized or is considered to be metabolized very little. Sugammadex is discarded through the kidneys unchanged. In healthy adults, the half-time of sugammadex is 1.8 h. The majority (90%) of the administered dose of sugammadex is discarded within 24 h and 96% of the discarded portion is excreted by the urinary tract, particularly non-metabolised. For individuals with normal renal function, the sugammadex clearance is 84-138 mL / min.[5]

Cisplatin causes breaks in the replication and transcription of DNA. The most important side effect limiting the clinical use of cisplatin is nephrotoxicity.[6] In the early stages of nephrotoxicity, focal acute tubular necrosis develops histologically, involving distal and collecting tubules, dilatation of the tubules and formation of deposits. In the proximal tubules, especially in the S3 segment, typhoid-dependent nephrotoxicity is seen. Acute renal failure was observed after a single dose of cisplatin. It has been shown that tubular dysfunction develops early after cisplatin administration. One study reported that 25-35% of patients develop acute tubular necrosis after the first round of treatment and 20-25% develop dose-dependent cumulative renal insufficiency.[7,8]

We aimed to investigate the effect of different doses of sugammadex (4 mg and 16 mg) on experimental kidney histopathology in acute renal failure rabbit model.

METHODOLOGY

Ethics committee approval was received for this study from the ethics committee of Çanakkale Onsekiz Mart University School of Medicine. Eight New Zealand white (NZW) adult male rabbits (weights: 2.5-3 kg) were supplied by the Saki Yenilli Animal Production Center. Rabbits were housed in plastic cages throughout the experiment at 21 ± 2° C, 12 h light / 12 h dark photoperiod on a standard rabbit diet (Bil-Yem Ltd. Co., Ankara, Turkey)

The rabbits were divided into 2 random groups of four. The first group (Group Y) received low dose (4 mg) sugammadex and the second group (Group D) received medium dose (16 mg) sugammadex.

Anesthesia procedure:

The rabbits in both groups were fasted for 8 h overnight. Before general anesthesia, ketamine 10 mg / kg IM was injected to the rabbits (Group D, Group Y) for premedication. After 20 min of waiting, 2 mg / kg of propofol and 1 μg / kg of fentanyl IV were given to both groups for general anesthesia. Then rocuronium 0.6 mg / kg was administered. The V-GEL Rabbit (V-gel rabbit R-3 Docsinnovent® Ltd. London, UK) was then placed to all experimental animals to provide airway safety. All experimental animals were anesthetized with anesthesia Machine (Model M3000PK Parkland Scientific Lab and Research Equipment, Florida, USA) and manually ventilated. Anesthesia dosage was provided with 1 MAC isoflurane in 50% oxygen + 50% air mixture. The rabbits were manually ventilated by the same anesthesiologist at a pressure of about 15 cmH_2O (about 10 ml / kg), which would be about 40 per min, so that the number of breaths would be compatible with rabbit physiology. Blood gas were also collected and recorded at 10 s and 40 min before and after induction to evaluate the oxygenation of all rabbits (Blood Gas Analyzer - Gastat 600 Series, Techno Medica Co. Ltd., Yokohama, Japan). At the 25th min after induction, Group D rabbits were given 4 mg / kg sugammadex, Group Y rabbits were given 16 mg / kg sugammadex. At the end of the experiment, all experimental animals were sacrificed, and their kidneys were removed, and histopathologic examination was performed.

Establishing kidney failure in rabbits:

Cisplatin was administered intravenously at a dose of 20 mg / kg four hours before the administration of general anesthesia to the rabbits and an acute renal failure model was established. Before and after this procedure, blood was taken to evaluate kidney function, to confirm kidney failure.

Histopathological evaluation:

At the end of the experiment, all experimental animals were sacrificed, and their kidneys were removed, and fixated in 10% neutral formalin. After routine procedures for histopathologic examination, paraffin blocks were stained with hematoxylin and eosin for examination. Four micrometer thick sections were taken and examined under light microscopy. Histopathological evaluation was performed on all animals. Histopathologic examination evaluated proximal tubule injury, interstitial hemorrhage, congestion, presence of fibrin and glomerular damage.

Statistical analysis:

Kruskal-Wallis variant analysis test (ANOVA) was used for statistical evaluation. Group D and Group Y were crossed with Mann-Whitney U Test (Table 1). The p values less than 0.05 were considered statistically significant.

RESULTS

At the end of our study all experimental animals were sacrificed. There was no statistically significant difference in the histopathological evaluation between Group Y and Group D in terms of proximal

Table 1: Histopathological results of experimental groups [Data given as n (%)]

Finding	Group D	Group Y	P
Proximal Tubule Injury	1 (25)	2 (50)	> 0.005
Interstitial Bleeding	1 (25)	1 (25)	> 0.005
Congestion	2 (50)	2 (50)	> 0.005
The presence of fibrin	1 (25)	1 (25)	> 0.005
Glomerular Damage	0/0	1 (25)	> 0.005

tubule injury, interstitial hemorrhage, congestion, fibrinosis, or glomerular injury. The results are shown in Table 1.

Table 2: Values of urea, creatinine before and after experiment in experimental groups

	Urea Pre-test / Post-test	Creatinine Pre-test / Post-test
Group D	38 / 49	1,07 / 1,42
Group Y	36 / 54	1,02 / 1,64

Urea and creatinine values before and after the experiment were found in order to evaluate the renal failure caused by cisplatin during the experiment. The results are shown in Table 2.

DISCUSSION

In this study, we observed that there was no difference between kidney functions histopathologically and biochemically in experimental animals using 4mg / kg or 16 mg / kg sugammadex in rabbits developed acute renal failure model.

Clearance of sugammadex is 84-138 mL / min for individuals with normal renal function. The release of sugammadex or rocuronium complex with sugammadex significantly decreases normal renal function [creatinine clearance (CCl) > 80 mL / min] in patients with severe renal insufficiency (CCl < 30 mL / min). Reduced creatinine clearance prolongs the half-life and mean duration of action. This does not change the efficacy of sugammadex in patients and no recurrence occurs. Sugammadex shows a decreasing variability in plasma concentration in patients with severe renal insufficiency, especially those in need of dialysis. Thus, the use of sugammadex in patients with severe renal insufficiency is not common.[9] The sugammadex is taken up in the central cavity to trap the side chain rocuronium, while the chain end is electrostatically bound to the negative carboxyl atoms of the rocuronium-positive nitrogen atoms. As a result of this binding, the amount of rocuronium and vecuronium bound to the nicotinic receptors in the neuromuscular junction is reduced. The resulting sugammadex and rocuronium complex is inactive and is eliminated from the body by the pharmacokinetic properties of sugammadex.[10,11] Clinical side effects on sugammadex-related liver and kidney function have not been reported in Phase 2 and 3 studies.[12]

In the early stages of renal involvement, focal acute tubular necrosis develops, leading to dilatation and sediment formation in the tubules affecting histologically distal and collecting tubules.[13] Although studies have shown that rocuronium-sugammadex complex does not have an adverse effect on renal function in both healthy individuals and chronic renal failure patients, we think that this condition has not been adequately studied in patients with acute renal failure. In our study, our hypothesis was that when we used 16 mg / kg sugammadex in rabbits we received in general anesthesia after acute renal failure, the renal histopathology was more likely to be deteriorated due to the accumulation of rocuronium-sugammadex complex in the tubules. However, in our study we did not observe any histopathological or biochemical difference between the two groups.

Although the mechanisms underlying the nephrotoxic effect of cisplatin have not yet been fully elucidated, studies have shown that oxidative stress plays an important role. It has been shown that the use of cisplatin increases reactive oxygen species, which leads to DNA damage and lipid peroxidation in membranes. For this purpose, experimental studies have been carried out to reduce or prevent the nephrotoxic effect of cisplatin with certain antioxidant substances.[14,15]

Parlakpınar and colleagues[16] observed dilated tubules in the kidney, faint glomeruli, edema, and areas of focal inflammation in the interstitium during their cisplatin-induced kidney injury studies. Ozyurt and colleagues in a similar study[17] observed vacuolization, cellular swelling, and spillage of excess tubular epithelium, especially in the proximal tubule. İşeri and colleagues[18] described cisplatin nephrotoxicity with severe glomerular congestion, degeneration, dilatation of Bowman's cavity, and degeneration of tubular cells. In our study, proximal tubule injury, congestion, interstitial bleeding, and glomerular injury were also observed in both study groups. However, there was no significant difference between the two groups in terms of kidney damage.

CONCLUSION

In our study there was no difference in terms of histopathological and biochemical aspects between the two groups of animals taking either 4 mg or 16 mg sugammadex, in terms of kidney damage. We believe that sugammadex can be safely used at different doses

in patients with acute renal failure, but controlled human studies are needed to further confirm this finding.

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Author Contributions:

OO: Concept, Design, Supervision, Analysis and/or Interpretation, Critical Review

ME: Supervision, Resources, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Search, Writing Manuscript, Critical Review

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