

The Effects of Sugammadex in Experimental Organophosphate Toxicity: comparison with atropine and pralidoxime treatment

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Abstract

Background

This study aimed to investigate the effect of sugammadex on the treatment of experimental acute organophosphate toxicity in rabbits and to compare it with pralidoxime (PAM) + atropine co-treatment.

Methods

Thirty-eight male New Zealand rabbits were randomized into five groups: control ($n = 6$), sham ($n = 8$), PAM + atropine ($n = 8$), sugammadex ($n = 8$), and sugammadex + PAM + atropine ($n = 8$). All groups except the control group were administered dichlorvos via orogastric tube at dose of 12 mg/kg. Subjects in the sham group received no treatment. Depending on the group, atropine (0.05 mg/kg) was administered intravenously (IV) as needed based on clinical findings, PAM was initially administered by IV bolus (30 mg/kg) followed by IV (15 mg/kg) every 4 hours, and sugammadex was administered by IV bolus (15 mg/kg) 5 minutes after dichlorvos administration. Blood samples were collected before and at 6, 12, and 24 hours after dichlorvos administration to measure erythrocyte acetylcholinesterase (AChE) activity. After 24 hours, all subjects were sacrificed, and tissue samples were collected from the brain, lung, and liver for histopathological examination and to measure AChE activity.

Results

At 12 hours, erythrocyte AChE activity was significantly higher in the sugammadex group than in the other groups ($p = 0.028$). At 6 and 24 hours, erythrocyte AChE activity was non-significantly higher in the sugammadex and PAM + atropine + sugammadex groups than in the PAM + atropine group. AChE activity in liver tissue was highest in the sugammadex and PAM + atropine + sugammadex groups. AChE activity in lung tissue was highest in the sugammadex group, and higher in the sugammadex and PAM + atropine + sugammadex groups than in the PAM + atropine group.

Conclusions

It has been observed that in the treatment of acute organophosphate toxicity, using sugammadex in combination with PAM and atropine may be beneficial on blood and tissue. Extensive experimental and clinical studies are warranted in this regard.

Introduction

Organophosphates (OPs) constitute an important group of pesticides widely used in agricultural production, agricultural areas, and gardens. Consequently, accidental OP exposure is very common, especially in developing countries. Exposure to OPs remains a critical issue, as they are used not only in

agriculture but also as chemical warfare agents. Although their sale and use are illegal in many countries, they are cheap and remain widely used and easily obtainable.

OP toxicity is a leading health problem worldwide. According to data from the World Health Organization (WHO), over 3 million individuals are hospitalized for OP poisoning annually. In some cases of OP exposure, poisoning progresses with severe clinical manifestations and results in death. Notably, 300,000 individuals die as a result of OP exposure annually. In severe OP poisoning cases, the mortality rate can reach up to 40%, even in well-equipped intensive care units [1, 2].

In acute poisoning, the OP irreversibly inhibits the enzyme acetylcholinesterase (AChE) at synapses, allowing acetylcholine to accumulate and, in turn, stimulate nicotinic and muscarinic acetylcholine receptors in the central and peripheral nervous systems. The clinical presentation of OP poisoning arises from the stimulation of these receptors. Today, OP intoxication is treated using pralidoxime (2-pyridine aldoxime methyl chloride [PAM]) as an atropine and antidote. However, research is also exploring new treatment options with fewer side effects [3].

One potential antidote is sugammadex, a drug used to selectively reverse the neuromuscular blockade caused by nondepolarizing aminosteroids such as vecuronium and rocuronium [4]. Therefore, this study aimed to compare the effect of sugammadex alone or in combination with 2-PAM and atropine in rabbits with acute OP poisoning.

Materials and Methods

Ethical Considerations

This study received approval from the Ethics Committee of the Experimental Medicine Research and Application Center at Selçuk University (approval number 41475755-2015/55). It was conducted at Selçuk University Experimental Medicine Research and Application Center.

Study Subjects and Procedure

Thirty-eight male New Zealand rabbits weighing 1700–3000 g were randomized into five groups: control ($n = 6$), sham ($n = 8$), PAM + atropine ($n = 8$), sugammadex ($n = 8$), and sugammadex + PAM + atropine ($n = 8$). All subjects were anesthetized by intramuscular injection of ketamine (50 mg/kg) and xylazine hydrochloride (Rompun®; 15 mg/kg). Next, the central ear artery and marginal ear vein were catheterized, and 2 mL of basal venous blood was collected in EDTA tubes to measure erythrocyte AChE activity before induction of OP toxicity, after which 5 mL of 0.9% serum was administered through the same vascular route. Then, the subjects were fitted with an orogastric feeding tube, and those not in the control group were administered the OP dichlorvos (2,2-dichlorovinyl dimethyl phosphate [DDVP]) at its median lethal dose (LD_{50} ; 12 mg/kg).

After DDVP administration, no treatment was given to the Sham group. Depending on the group, atropine (0.05 mg/kg) was administered intravenously (IV) as needed based on clinical findings, PAM was initially administered by IV bolus (30 mg/kg) followed by IV (15 mg/kg) every 4 hours, and sugammadex was administered by IV bolus (15 mg/kg) 5 minutes after orogastric DDVP administration.

Venous blood samples were collected in EDTA tubes at 6, 12, and 24 hours after DDVP administration to re-measure erythrocyte AChE, and at corresponding time points in the control group, with 5 mL of 0.9% serum administered after each blood collection. After 24 hours, all subjects were sacrificed by administering at a dose of 100 mg/kg pentobarbital IV, and tissue samples were collected from the liver, lung, and brain for histopathological examination and to measure AChE activity.

Biochemical Methods

Tissue and Erythrocyte Homogenization

Tissue samples with a wet weight of 1 g were cut into small pieces with clean surgical scissors while ensuring they remained cold and placed in a glass tube. Next, 2 mL of ice-cold phosphate buffer was added to the tissue, the tube was placed in an ice-filled plastic container, and the tissue was homogenized for 30 seconds at 16,000 rpm. Then, homogenates were centrifuged at 1500 g for 5 minutes, and total protein and AChE levels were measured in the supernatants.

Erythrocyte membranes were disrupted by ultrasonication. Briefly, 100 μ L of whole blood was mixed with 1 mL of phosphate. Homogenates were centrifuged at 1500 g for 5 minutes, and total protein and AChE levels were measured in the supernatants.

Total Protein Qualification

Total protein content was measured using the Bradford (Coomassie brilliant blue G-250) method, which is based on the interaction of organic dyes with acidic and basic groups in proteins, producing a blue color, and is very sensitive (5–100 μ g protein/mL). Briefly, 100 mg of Coomassie brilliant blue G-250 was dissolved in 50 mL of 95% ethanol, and then 55 mL of 88% phosphoric acid was added. Next, this solution was mixed with 985 mL of distilled water and filtered. Then, a fixed volume of the samples was mixed with 5 mL of Coomassie solution and incubated for 5 minutes. Finally, the reaction was transferred to a glass or polystyrene cuvette, and the absorbance was measured at 595 nm in a spectrophotometer. When required, glass cuvettes were immersed in 0.1 M hydrochloric acid and then washed with water and acetone before use. Protein concentrations were determined against a standard series of known bovine serum albumin concentrations.

Statistical Analysis

Statistical analyses were conducted using SPSS Statistics (version 31.0; IBM Corp., Armonk, NY, USA), and graphs were created using GraphPad Prism (version 10; GraphPad Software, Boston, MA, USA). A $p < 0.05$ was considered statistically significant. Continuous variables were assessed for homogeneity of variances across groups using Levene’s test and normality using the Shapiro–Wilk test, histograms, skewness/kurtosis, and Q–Q plots. Continuous variables are presented as the mean $\pm$ standard deviation if normally distributed, and as the median (interquartile range [IQR]: minimum–maximum) if non-normally distributed. Categorical variables are presented as frequencies (percentages). Data were compared across groups using the Kruskal–Wallis H test or analysis of variance (ANOVA), followed by post-hoc Bonferroni tests. Relationships between dependent variables at different time points were examined using repeated-measures ANOVA followed by post-hoc Dunnett’s T3 or Bonferroni tests.

Results

Table 1. Comparison of erythrocyte AChE activities across experimental groups.

Time Point	AChE Activity (mIU/mL)					p^*
	Sham ($n = 8$, 21.05%)	Control ($n = 6$, 15.79%)	Sugammadex ($n = 8$, 21.05%)	PAM + Atropine ($n = 8$, 21.05%)	PAM + Atropine + Sugammadex ($n = 8$, 21.05%)	
	Mean $\pm$ SD					
0-hour	947.58 $\pm$ 103.70	940.94 $\pm$ 40.80	994.96 $\pm$ 114.4	929.38 $\pm$ 156.84	874.58 $\pm$ 59.53	0.201 [§]
6-hour	876.00 $\pm$ 151.85	847.33 $\pm$ 176.18	846.17 $\pm$ 52.60	873.67 $\pm$ 178.41	1026.25 $\pm$ 138.55	0.139 [§]
12-hour	894.21 $\pm$ 88.84	864.78 $\pm$ 95.64	992.33 $\pm$ 110.70	857.48 $\pm$ 102.54	861.50 $\pm$ 70.88	0.028[¶]
24-hour	1012.67 $\pm$ 160.46	864.44 $\pm$ 199.62	884.88 $\pm$ 58.33	960.67 $\pm$ 245.60	978.10 $\pm$ 154.60	0.384

Abbreviations: AChE = Acetylcholinesterase; PAM = 2-pyridine aldoxime methyl chloride (pralidoxime); SD = standard deviation.

[§] Since variances were not homogeneous across groups, Welch’s correction was applied.

[¶] Eta-squared (η^2) = 0.260.

*One-way ANOVA (with 1000 bootstraps).

Although the difference between the sugammadex and PAM + atropine groups was only marginally significant ($p = 0.090$), the effect size in the ANOVA was large ($\eta^2 = 0.260$), and 12-hour erythrocyte AChE activities were higher in the Sugammadex group than in the other groups. Therefore, sugammadex may

be a promising agent for increasing plasma AChE activity and thus have clinically noticeable effects in treating OP poisoning. The presented post-hoc tests used Bonferroni correction to increase robustness and better control for familywise error (strict control over type 1 error); however, when this pairwise comparison was performed using a post-hoc test with weaker type 1 error control (Fisher's least significant difference test), it was significant ($p = 0.046$), supporting this proposition. Since Bonferroni correction provides more robust control over familywise errors and yields more reliable adjustments, it was used in cases where variances were homogeneously distributed, and our results have been reported using Bonferroni correction.

The timeline of erythrocyte AChE activity in each group, along with comparisons across time points within each group, is shown in Figure 2. Erythrocyte AChE activity did not differ significantly across time points in the sham, control, and PAM + atropine groups (all $p > 0.05$). However, it did differ significantly across time points in the sugammadex and PAM + atropine + sugammadex groups ($p = 0.008$ and 0.020 , respectively). In the PAM + atropine group, although erythrocyte AChE activities generally increased after 6 hours, they did not differ significantly across or between time points. In the sugammadex group, erythrocyte AChE activity was lower at 6 hours than at the other time points and was significantly lower than at 0 and 12 hours (both $p = 0.030$). In contrast, in the PAM + atropine + sugammadex group, erythrocyte AChE activity was higher at 6 hours than at the other time points and was significantly higher than at 12 hours ($p = 0.040$). Across groups, erythrocyte AChE activity at 6 hours was highest in the PAM + atropine + sugammadex group (1026.25 ± 138.55 mIU/mL).

Tissue AChE Activity

Unstandardized (U/L) and standardized (U/g protein) AChE activities in brain, lung, and liver tissues were compared within and across experimental groups (Tables 2 and 3, and Figure 3). In all five experimental groups, AChE activity was highest in the liver tissue and lowest in the brain tissue (Table 2). Generally, AChE activities differed significantly across tissues (all $p < 0.001$). Unstandardized AChE activity (U/L) did not differ significantly across groups in brain, lung, and liver tissue. However, AChE activity standardized to total protein content (U/g protein) did differ significantly across groups in brain and lung tissues ($p = 0.030$). In brain tissue, standardized AChE activity remained higher in the control group than in the other groups and was significantly higher compared with the sham group ($p = 0.020$). In lung tissue, although standardized AChE activity remained higher in the control group than in the other groups ($p = 0.030$), it did not differ significantly between groups.

Table 2. Comparison of unstandardized (U/L) and standardized (U/g protein) AChE activities in the brain, lung, and liver in each experimental group.

Group	Tissue	Unstandardized AChE Activity (U/L)	Standardized AChE Activity (U/g protein)
Sham	Brain	262.9 (202.4–491.3)	1.63 (1.09–3.19)
	Lung	518.5 (393.6–840.7)	3.41 (2.23–4.21)
	Liver	2799.9 (1155.8–3611.1)	22.13 (9.71–110.39)
Control	Brain	550.6 (306.9–878.8)	3.95 (2.65–5.07)
	Lung	547.1 (459.6–855.4)	7.74 (2.90–15.74)
	Liver	1691.5 (1238–5203.5)	26.78 (22.58–66.61)
Sugammadex	Brain	346.9 (250.8–466.2)	2.10 (1.46–2.64)
	Lung	706.7 (522.4–800.9)	4.56 (3.40–9.00)
	Liver	4222.8 (2733.2–6465.0)	25.70 (14.77–45.27)
PAM + Atropine	Brain	335.6 (192.9–523.3)	1.99 (1.03–3.12)
	Lung	567.4 (427.3–666.9)	3.76 (2.36–4.60)
	Liver	2273.1 (874.2–5680.0)	17.99 (9.74–36.85)
PAM + Atropine + Sugammadex	Brain	410 (323.5–474.9)	1.94 (1.71–2.87)
	Lung	665.1 (538.9–1029.3)	4.12 (2.96–7.20)
	Liver	4456.2 (164.0–6807.0)	23.51 (17.13–41.13)

Data are presented as the median (IQR).

Abbreviations: AChE = acetylcholinesterase; 2-PAM = 2-pyridine aldoxime methyl chloride (pralidoxime).

Unstandardized and standardized AChE activities are compared across tissues within each group (Table 3 and Figure 3). In the Sham group, both unstandardized and standardized AChE activities were significantly higher in liver tissue than in brain and lung tissues. In the control group, while unstandardized AChE activity was higher in liver tissue than in brain and lung tissue, standardized AChE activity differed significantly only between brain and liver tissues. In the Sugammadex group, while unstandardized AChE activities differed significantly between all tissues, standardized AChE activities differed significantly only between brain and liver tissues. In the PAM + atropine group, both unstandardized and standardized AChE activities were significantly higher in liver tissue than in brain and lung tissues. Finally, in the PAM + atropine + sugammadex group, both unstandardized and standardized AChE activities differed significantly only between brain and liver tissues.

Table 3. Comparisons of unstandardized (U/L) and standardized (U/g protein) AChE activities across the brain, lung, and liver in each experimental group.

	Sham			p[*]
	Brain	Lung	Liver	
Unstandardized AChE Activity (U/L)	262.9 ^a (202.4–491.3)	518.5 ^a (393.6–840.7)	2799.9 ^b (1155.8–3611.1)	<0.001
Standardized AChE Activity (U/g protein)	1.63 ^a (1.09–3.19)	3.41 ^a (2.23–4.21)	22.13 ^b (9.71–110.39)	<0.001
Control				
	Brain	Lung	Liver	
Unstandardized AChE Activity (U/L)	550.6 ^a (306.9–878.8)	547.1 ^a (459.6–855.4)	1691.5 ^b (1238–5203.5)	0.025
AChE Activity (U/g protein)	3.95 ^a (2.65–5.07)	7.74 (2.90–15.74)	26.78 ^b (22.58–66.61)	0.015
Sugammadex				
	Brain	Lung	Liver	
Unstandardized AChE Activity (U/L)	346.9 ^a (250.8–466.2)	706.7 ^b (522.4–800.9)	4222.8 ^c (2733.2–6465.0)	<0.001
Standardized AChE Activity (U/g protein)	2.10 ^a (1.46–2.64)	4.56 (3.40–9.00)	25.70 ^b (14.77–45.27)	<0.001
PAM + Atropine				
	Brain	Lung	Liver	
Unstandardized AChE Activity (U/L)	335.6 ^a (192.9–523.3)	567.4 ^a (427.3–666.9)	2273.1 ^b (874.2–5680.0)	<0.001
Standardized AChE Activity (U/g protein)	1.99 ^a (1.03–3.12)	3.76 ^a (2.36–4.6)	17.99 ^b (9.74–36.85)	<0.001
PAM + Atropine + Sugammadex				
	Brain	Lung	Liver	
Unstandardized AChE Activity (U/L)	410 ^a (323.5–474.9)	665.1 (538.9–1029.3)	4456.2 ^b (164.0–6807.0)	0.004
Standardized AChE Activity (U/g protein)	1.94 ^a (1.71–2.87)	4.12 (2.96–7.20)	23.51 ^b (17.13–41.13)	

Abbreviations: AChE = acetylcholinesterase; PAM = 2-pyridine aldoxime methyl chloride (pralidoxime).

Note: Data are presented as the median (IQR). Superscript letters (^a, ^b, and ^c) denote the significance of differences: differences were not significant if marked by the same letter (or no letter), and were significant if marked by different letters (post-hoc Bonferroni test).

**Kruskal–Wallis H test.*

Tissue Histology

Histological examination of brain, lung, and liver tissues using hematoxylin–eosin staining revealed inflammation and congestion in the portal area of the liver in the sham and PAM + atropine groups (Pictures 1 and 2). However, no pathological findings were observed in the liver tissue of the control, sugammadex, and sugammadex + PAM + atropine groups (Picture 3). In the control group, neuronal cell appearance and integrity appeared normal in the brain tissue. No changes in neuron size were observed (Pictures 4 and 5). In the other groups, neurons were slightly smaller, and shrunken neurons with pyknotic nuclei were observed (Pictures 6 and 7).

Discussion

Today, the standard pharmacological treatment for acute OP toxicity is atropine and PAM. Nucleophilic pyridine aldoxime reactivators (PAM and obidoxime), which reverse the nicotinic and muscarinic effects of OP toxicity and reactive AChE, can be administered intramuscularly or IV. In this context, PAM is administered especially to patients with signs of neuromuscular dysfunction, muscle weakness, cholinergic toxicity, and delayed neurotoxicity. For adults, the WHO recommends administering PAM as an initial IV bolus of at least 30 mg/kg, followed by IV infusion at 8 mg/kg/hour. When given as an IV bolus, PAM should be administered slowly over at least 30 minutes, as rapid administration can cause cardiac arrest [5]. Atropine is used to eliminate cholinergic activation and has no accepted maximum dosage. During treatment, dosing and administration are determined based on clinical findings, such as decreased bronchial secretions and salivation, disappearance of bradycardia, blood pressure rising above 80 mmHg, disappearance of bronchospasm, and improvement in oxygenation. Excessive atropine administration can result in antimuscarinic toxicity, which presents as tachycardia, hyperthermia, urinary retention, loss of bowel sounds, ileus, and delirium [5, 6].

In OP toxicity, PAM is effective if administered before AChE undergoes an irreversible secondary dealkylation (i.e., aging reaction). If PAM is administered after AChE has aged, it has no effect. Generally, PAM is not stored in large quantities in hospital pharmacies. In the event of OP toxicity, it is distributed from antidote centers established in different locations. The PAM transfer process can sometimes be prolonged, leading to delays in treatment and rendering the therapy ineffective due to AChE aging. Particularly when OPs are used as chemical warfare agents during wars or terrorist attacks, hundreds or even thousands of OP toxicity cases may be encountered. In such scenarios, hospitals and antitoxin

storage centers will face a shortage of PAM to treat all cases. Thus, ongoing research aims to develop different antidotes for OP toxicity that are more effective, easier to use, and simpler to store [7].

No published study has investigated the effects of sugammadex in the treatment of acute OP toxicity. However, studies have evaluated adding certain drugs and prodrugs to PAM and atropine in the treatment of OP toxicity. For example, Felipe et al. found greater healing of the cardiorespiratory system in rats with acute OP intoxication cotreated with PAM and atropine, which better restored chemoreflex bradycardic dysfunction [8]. Similarly, Liu et al. found that continuous micropump infusion of PAM and atropine was more effective than intermittent bolus injection therapy in the treatment of acute OP intoxication [9].

Neuromuscular blockers help during surgery by relaxing the skeletal muscles. They are also used in numerous interventions, including rapid serial intubation and mechanical ventilation, as well as to facilitate other therapies. Following numerous randomized placebo-controlled trials, sugammadex has begun to be used to reverse the effects of aminosteroid neuromuscular blockers, such as rocuronium, within 2 minutes [4, 10-13]. Honing et al. reported that sugammadex significantly reduced residual neuromuscular blockade and reversed the effects of aminosteroid neuromuscular blockers, with no serious adverse reactions, compared with neostigmine [4]. However, no published study has investigated the effect of sugammadex in the treatment of acute OP toxicity.

Lagadec et al. investigated the effects of cotreatment with atropine sulfate and PAM on short-term recovery, brain waves, and behavioral patterns in a mouse model of OP toxicity induced by administering a single sublethal dose ($LD_{50} = 0.63 \text{ mg/kg}$) of subcutaneous sarin [14]. They found that cotreatment with atropine sulfate and PAM alleviated sarin-related encephalopathy, stabilized brain oscillations, and reduced anhedonic behavior. However, they noted that despite this treatment, mice with sublethal (non-convulsive) sarin toxicity exhibited impaired working memory associated with disrupted theta oscillations during tasks, as well as disturbed sleep architecture and anxiety-like behaviors. They concluded that cotreatment with atropine sulfate and PAM provides only partial neuroprotective effects in sarin toxicity and is ineffective in preventing long-term neurobehavioral complications.

Due to the limited blood-brain barrier penetration of oxime-based antidotes such as PAM, obidoxime, and asoxime, and their limited efficacy across a broad spectrum of OPs, non-oxime reactivators have been investigated as alternatives. In vitro studies with non-oxime group reactivators (amodiaquine, scopolin, and Mannich phenol derivatives) have shown that adjusting the inhibitor-activator dose is challenging, as these compounds are also potent AChE inhibitors themselves and have narrow therapeutic windows. Furthermore, non-oxime reactivators exhibit severe cytotoxicity in liver tissue and blood. These studies found that non-oxime reactivators show variable effects on different OP-AChE complexes, and only a few were more effective than oxime reactivators in vitro [15].

In a meta-analysis examining the safety and efficacy of adjuvant therapies in OP toxicity, patients treated only with atropine were compared to those treated with atropine plus oxime, fresh frozen plasma,

magnesium sulfate (MgSO_4), N-acetyl cysteine (NAC), or glycopyrrolate in terms of survival rate, complication rate, and duration of mechanical ventilation. It revealed that oxime treatment was associated with increased mortality, higher rates of cardiac dysrhythmia, and adverse outcomes. Thus, further studies are needed to evaluate the clinical benefits of MgSO_4 and NAC, while hemoperfusion therapy appears promising [16].

Our study compared the effectiveness of sugammadex in the treatment of acute OP toxicity with that of cotreatment with PAM and atropine in a rabbit model. The findings demonstrated that sugammadex positively affected erythrocytes and tissues in rabbits with acute OP toxicity. Notably, erythrocyte AChE activity was significantly higher in the sugammadex group than in the PAM + atropine group after 12 hours, supporting the potential of sugammadex in the treatment of OP toxicity. In addition, although not statistically significant, erythrocyte AChE activity after 6 and 12 hours was highest in the PAM + atropine + sugammadex group, further supporting the therapeutic effect of sugammadex. Altogether, these results support the potential use of sugammadex, either alone or in combination with PAM and atropine, in the treatment of acute OP toxicity.

In our study, when AChE activity in brain, lung, and liver tissues was compared, it was lowest in brain tissue across all experimental groups. This finding may indicate that sugammadex, which has a high molecular weight, has limited ability to cross the blood–brain barrier, similar to PAM and atropine, and therefore has little or no effect on the central nervous system symptoms of OP toxicity. Although the difference was not significant, AChE activity in brain tissue was higher in the PAM + atropine + sugammadex group than in both the PAM + atropine and sugammadex groups. Similarly, although the difference was not significant, AChE activity in lung tissue was highest in the sugammadex group, followed by the PAM + atropine + sugammadex group. Additionally, AChE activity in liver tissue was also highest in the sugammadex and PAM + atropine + sugammadex groups. Therefore, these findings support that sugammadex exerts positive effects at the tissue level in acute OP toxicity and may enhance the effects of PAM and atropine.

Altogether, the observed effects of AChE activity in blood and tissue samples support sugammadex as a potential therapeutic drug for acute OP poisoning, which warrants further investigation in this context. Nonetheless, our study had some limitations, the most notable being that subjects were not followed for more than 24 hours and that cardiopulmonary physiological parameters were not monitored.

Conclusions

This study demonstrated that sugammadex has curative effects on erythrocytes and liver tissue in acute OP toxicity, and it can be used in combination with atropine and PAM. When used alone in the treatment of OP toxicity, sugammadex exerted a greater healing effect than co-treatment with PAM and atropine, especially at the tissue level. Therefore, sugammadex may be a promising potential drug for treating acute OP poisoning. However, it requires further comprehensive experimental and clinical research.

Abbreviations

OPs	Organophosphates
OP	Organophosphate
PAM	Pralidoxime (2-pyridine aldoxime methyl chloride)
DDVP	Dichlorvos (2,2-dichlorovinyl dimethyl phosphate)
IV	Intravenous
AChE	Acetylcholinesterase
WHO	World Health Organization

Declarations

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Author contrubitions

AB: Conceptualization, Data collection, Formal analysis, Writing manuscript.

HK: Data collection, Formal analysis, Writing manuscript.

MA: Data collection, Formal analysis

SA: Biochemical analysis, Formal analysis

CU: Pathological investigation, Formal analysis

Fi: Data collection, Statical analysis

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Data availability

The data used to support the study's results will be provided by the corresponding author upon request.

Ethics approval and consent to participate

This study received approval from the Ethics Committee of the Experimental Medicine Research and Application Center at Selçuk University (approval number 41475755-2015/55). The experimental study was initiated immediately at Selçuk University Experimental Medicine Research and Application Center after approval. All procedures were conducted in accordance with institutional and national guidelines for the care and use of laboratory animals, consistent with the European Directive 2010/63/EU. All data reported in this manuscript are original and have not been previously published.

Competing interests

The authors declare no competing interests.

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Figures

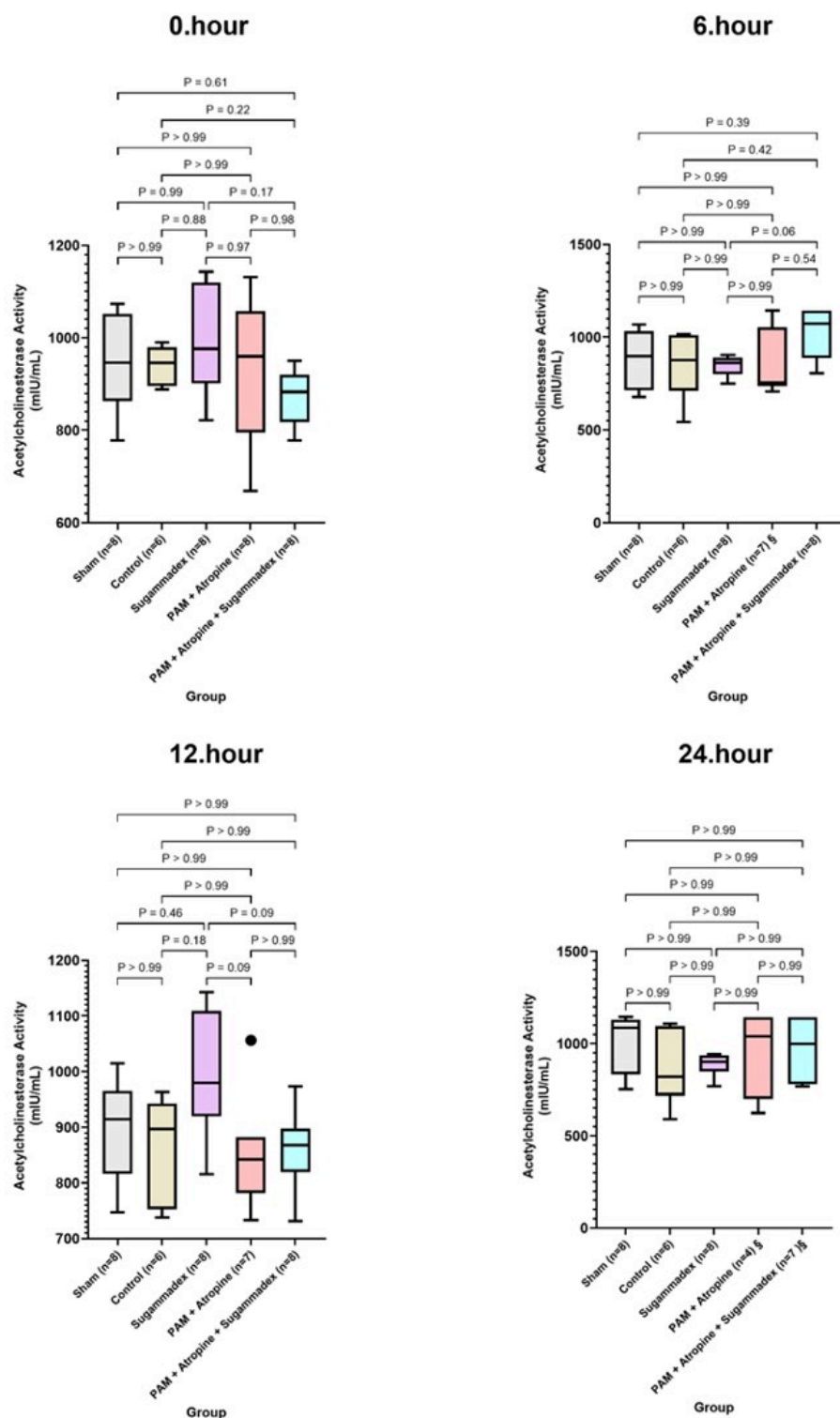


Figure 1

Summary of pairwise comparisons of erythrocyte AChE activities (mIU/mL) between the five experimental groups at 0, 6, 12, and 24 hours. [§] One or more subjects died in the marked group at that time point. Pairwise comparisons were performed using Dunnett's T3 test at 0 and 6 hours and using the Bonferroni test at 12 and 24 hours.

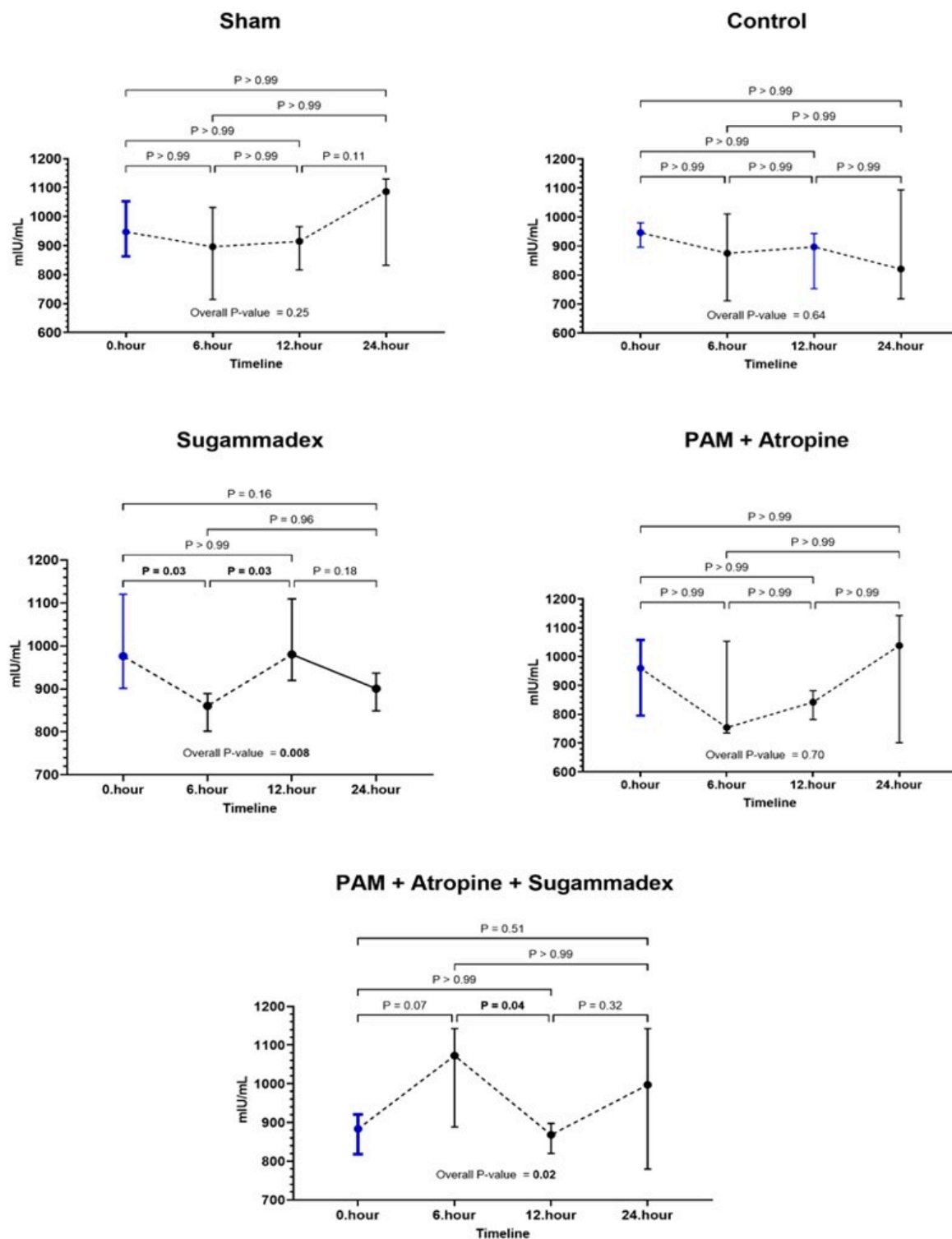


Figure 2

Erythrocyte AChE activity across time points in each experimental group and pairwise comparisons between time points. The overall p -values were derived from repeated-measures ANOVA, with a Greenhouse–Geisser adjustment applied in the sham group. The data are presented as the mean $\pm$ SD, and post-hoc pairwise comparisons were conducted using the Bonferroni test.

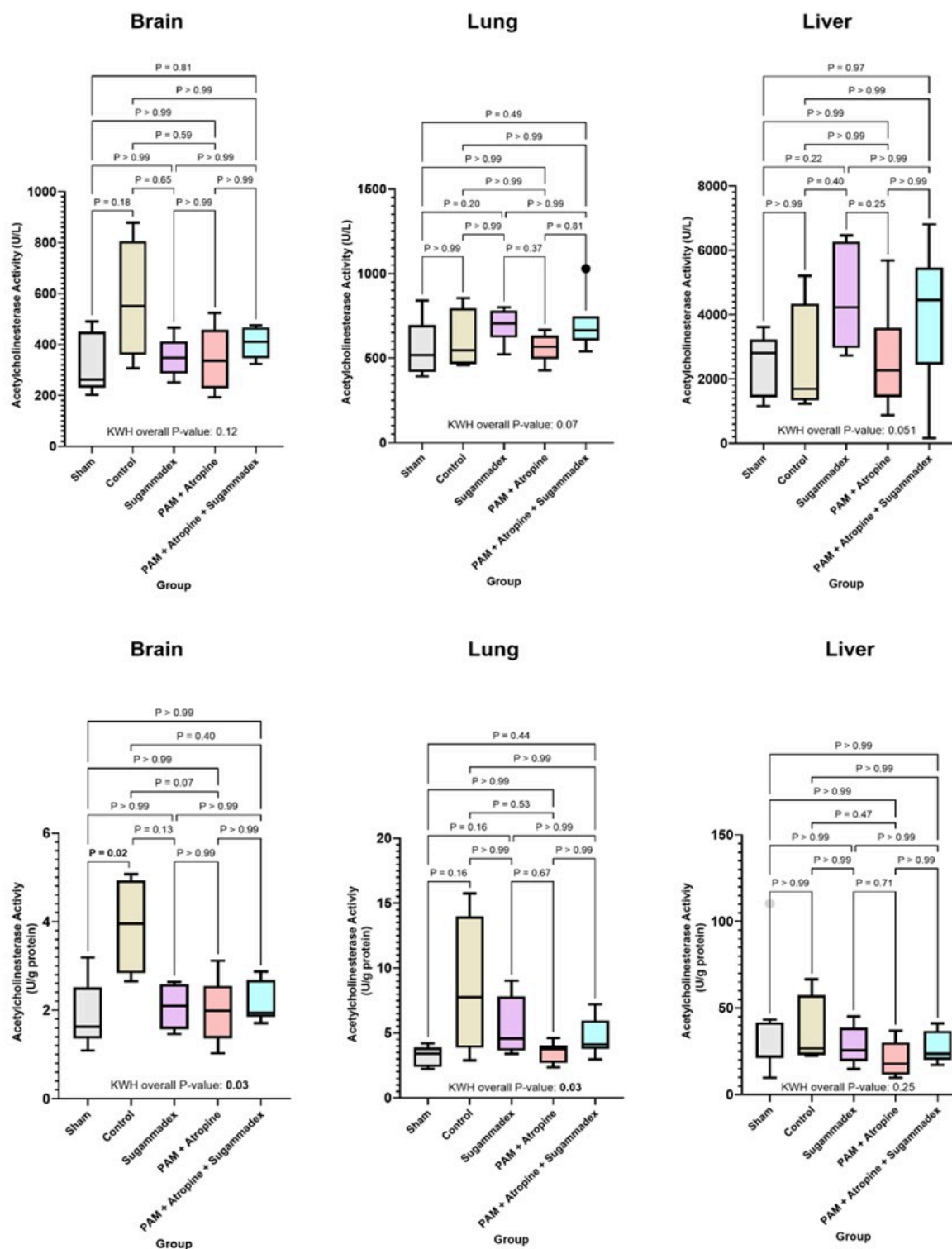


Figure 3

Comparisons of unstandardized (U/L) and standardized (U/g protein) AChE activities in the brain, lung, and liver across groups. The *p*-values were derived from Kruskal–Wallis *H* tests (KWH) with post-hoc pairwise Dunn’s tests.

Supplementary Files

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