ARAŞTIRMA

Cilt 63, No 1,2,3 S : 157 - 164
Türk Hij Den Biyol Derg 2006

A COMPARISON OF NEUROPROTECTIVE EFFECTS OF NEWLY DEVELOPED OXIMES WITH TRIMEDOXIME IN TABUN-POISONED RATS

Jiri KASSA[1] **Gabriela KUNESOVA[1]** **Kamil KUCA[1]**

ABSTRACT

The neuroprotective effects of newly developed oximes (K027, K048) or trimedoxime in combination with atropine (atropine, K027/atropine, K048/atropine and trimedoxime/atropine mixtures) on rats poisoned with tabun at a lethal dose (270 μg/kg i.m.; 120% of LD50 value) were studied. The tabun-induced neurotoxicity was monitored using a functional observational battery and an automatic measurement of motor activity. The neurotoxicity of tabun was monitored at 24 hours and 7 days following tabun challenge. The results indicate that atropine alone is not able to protect the rats from the lethal effects of tabun. Six non-treated tabun-poisoned rats and five tabun-poisoned rat treated with atropine alone died within 24 hours. On the other hand, atropine combined with all tested oximes allows most tabun-poisoned rats to survive within 7 days following tabun challenge. All three oximes tested combined with atropine seem to be sufficiently effective antidotes for a decrease in tabun-induced neurotoxicity in the case of lethal poisonings although they are not able to eliminate tabun-induced neurotoxicity completely. Due to their neuroprotective effects, all tested oximes appear to be more suitable oximes for the antidotal treatment of acute tabun exposure than currently used oximes (pralidoxime, obidoxime, HI-6).

Key Words: Tabun, atropine, trimedoxime, neuroprotective effects, warfare agents

TABUNLA ZEHİRLENEN SIÇANLARDA YENİ GELİŞTİRİLEN OKSİMLERİN NÖROPROTEKTİF ETKİLERİNİN TRİMEDOKSİM İLE BİR KARŞILAŞTIRMASI

ÖZET

Yeni geliştirilen oksimler veya trimedoksimin atropin (atropin, K027/atropin, K048/atropin ve trimedoxime/atropin karışımları) ile beraber uygulanması, öldürücü dozda (270 μg/kg i.m.; LD50 değerinin %120si) tabun ile zehirlenen ratlarda nöroprotektif etkileri çalışılmıştır. Tabunla oluşturulan nörotoksisite, fonksiyonel izleme bataryası ve otomatik motor aktivite ölçümleri kullanılarak izlenmiştir. Tabun nörotoksisitesi tabun uygulamasını takiben 7 gün, 24 saat boyunca takip edilmiştir. Sonuçlar, sadece atropin uygulamasının sıçanları tabunun öldürücü etkisinden korumadığını göstermiştir. Tabunla zehirlenen ve tedavi uygulanmayan 6 sıçan ile tabunla zehirlenen ve atropin uygulanan 5 sıçanın 24 saat içinde öldüğü gözlenmiştir. Diğer taraftan, atropinle birlikte test edilen oksimlerin, zehirlenen sıçanların çoğunun tabun uygulama sonrasını izleyen 7 gün boyunca yaşamasını sağladığı görülmüştür. Üç oksim de tabunla indüklenen nörotoksisiteyi tamamiyle düzeltmemekle beraber öldürücü dozlardaki tabun zehirlenmelerinde nörotoksisiteyi yeterli düzeyde azaltan etkili antidotlardır. Nöroprotektif etkilerinden dolayı test edilen tüm oksimlerin, akut tabun zehirlenmelerinde günümüzde kullanılan oksimlerden (pralidoxime, obidoxime, HI-6) daha uygun olduğu görülmektedir.

Anahtar Kelimeler: Tabun, atropin, trimedoksim, nöroprotektif etkiler, kimyasal ajanlar

[1]Department of Toxicology, Faculty of Military Health Sciences, University of Defense, Hradec Kralove, Czech Republic
Yazışma Adresi: Dr.Kamil KUCA, Department of Toxicology, Faculty of Military Health Sciences, University of Defense, Czech Republic
Tel: +420 973 251 523 Fax: +420 495 518 094 e-posta: kucakam@pmfhk.cz

INTRODUCTION

Tabun (O-ethyl-N,N-dimethyl phosphoramidocyanidate) belongs to highly toxic organophosphorus compounds misused as chemical warfare agents for military as well as terroristic purposes. It differs from other highly toxic organophosphates by its chemical structure and by the fact that commonly used antidotes (atropine in combination with an oxime) are not able to sufficiently eliminate tabun-induced acute toxic effects (Cabal and Bajgar 1999).

Tabun is able to cause centrally mediated seizure activity that can rapidly progress to status epilepticus and contribute to profound brain damage. The exposure of experimental animals to tabun in convulsions-induced doses may result in irreversible lesions in the central nervous system that can be manifested as behavioral effects in convulsing survivors (Jokanovic 1993). Therefore, the ability of antidotes to counteract the acute neurotoxic effects of tabun and prevent tabun-poisoned organisms from irreversible lesions in the central nervous system is very important for the successful antidotal treatment of acute tabun poisonings.

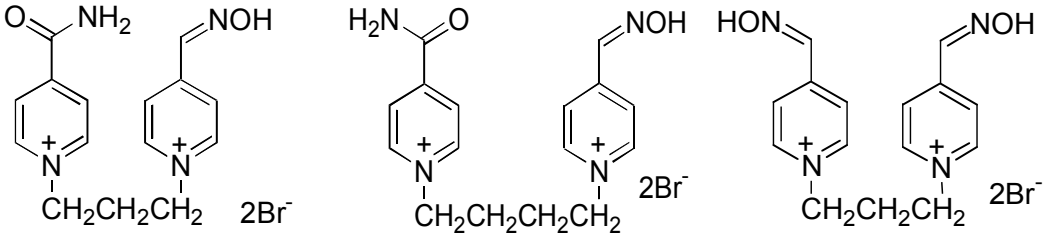
As the ability of currently used monopyridinium (e.g. pralidoxime) and bispyridinium oximes (e.g. obidoxime, HI-6) to eliminate toxic effects of tabun is generally rather low (Kassa et al. 2005), the replacement of commonly used oximes (pralidoxime, obidoxime) as well as H oximes (the oxime HI-6) with a more effective oxime has been a long-standing goal for the treatment of tabun poisoning (Dohnal et al. 2005). New asymmetric bispyridinium oximes, called K027 [1-(4-hydroxyiminomethyl pyridinium)-3-(4-carbamoylpyridinium) propane dibromide] and K048 [1-(4-hydroxyiminomethyl pyridinium)-3-(4-carbamoylpyridinium) butane dibromide] were synthesized at our Department of Toxicology (Kuca et al. 2003a,b) (Figure 1) to improve the efficacy of antidotal treatment in reactivating tabun-inhibited AChE and eliminating tabun-induced acute lethal toxic effects. In addition, another oxime called trimedoxime (1,3-bis (4-hydroxyiminomethyl pyridinium) propane dibromide) (Figure 1) was chosen for testing its neuroprotective efficacy against tabun in this study.

The aim of this study was to evaluate the neuroprotective effects of a currently available oxime trimedoxime and newly developed oximes (K027, K049) in combination with an anticholinergic drug atropine in tabun-poisoned rats.

MATERIAL AND METHODS

Animals

Male albino Wistar rats weighing 180-220g were purchased from Konárovice (Czech Republic). They were kept in an air-conditioned room and allowed to access to standard food and tap water add libitum. The rats were divided into groups of eight animals (N=8). Handling of the experimental animals was done under the supervision of the Ethics Committee of the Faculty of Military Health Sciences in Hradec Kralove (Czech Republic).



K027 **K048** **Trimedoxime**

Figure 1. Chemical structures of oximes studied

Table 1. Functional observational battery (FOB)

MARKER	Scored values only									
	-2	-1	0	1	2	3	4	5	6	7
POSTURE				sitting or standing	rearing	asleep	flattened	lying on side	crouched over	head bobbing
CATCH DIFFICULTY				passive	normal	defense	flight	escape	aggrression	
EASE OF HANDLING				very easy	easy	moderately difficult	difficult			
MUSCULAR TONUS	atonia	hypotonia	normal	hypertonia	rigidity	fasciculations				
LACRIMATION			none	slight	severe	crusta	coloured crusta			
PALPEBRAL CLOSURE					open drooping	slightly drooping	half-way shut	completely	ptosis	
ENDO-EXOPHTHALMUS			endo	normal	exo					
PILOERECTION			no	yes						
SKIN ABNORMALITIES			normal	pale	erythema	cyanosis	pigmented	cold	injury	
SALIVATION			none	sllight	severe					
NOSE SECRETION			none	slight	severe	coloured				
CLONIC MOVEMENTS			normal	repetitive movements of mouth and jaws	nonrhythmic quivers	mild tremors	severe tremors	myoclonic jerks	clonic convulsions	
TONIC MOVEMENTS			normal	contraction of extensors	opisthotonus	emprostho-tonus	explosive jumps	tonic convulsions		
GAIT			normal	ataxia	overcompen-sation of hindlimbs movements	feet point outwards from body	forelimbs are extended	walks on tiptoes	hunched body	body is flattened against surface
GAIT SCORE				normal	slightly impaired	somewhat impaired	totally impaired			
MOBILITY SCORE				normal	slightly impaired	somewhat impaired	totally impaired			
AROUSAL (level of unprovoked activity)				very low	sporadic	reduced	normal	enhanced	permanent	
TENSION			none	partial (ears)	stupor					
TENSION			none	partial (ears)	stupor					
STEREOTYPY			none	head weaving	body weaving	grooming	circling	others		
BIZARRE BEHAVIOR			none	head	body	self-mutilation	abnormal movements	others		
APPROACH RESPONSE				no reaction	normal	slow reaction	energetic reaction	exaggerated reaction		
TOUCH RESPONSE				no reaction	normal	slow reaction	energetic reaction	exaggerated reaction		
CLICK RESPONSE				no reaction	normal	slow reaction	energetic reaction	exaggerated reaction		
TAIL - PINCH RESPONSE				no reaction	normal	slow reaction	energetic reaction	exaggerated reaction		
PUPIL SIZE		miosis	normal	mydriasis						
PUPIL SIZE		miosis	normal	mydriasis						
PUPIL RESPONSE			no reaction	normal reaction						
RIGHTING REFLEX				normal	slightly uncoordin	lands on side	lands on back			

Chemicals

Tabun was obtained from Military Technical Institute in Brno (Czech Republic) and was 95% pure. Its purity was assayed by acidimetric titration. Trimedoxime and newly developed oximes (K027, K048) of 98.5% purity were synthesized at the Department of Toxicology of the Faculty of Military Health Sciences in Hradec Kralove (Czech Republic). Its purity was analysed using HPLC. All other drugs and chemicals of analytical grade were obtained commercially and used without further purification. All substances were administered intramuscularly (i.m.) at a volume of 1 mL/kg body weight (b.w.).

In vivo experiments

Tabun was administered at a lethal dose (270 μg/kg b.w. - 120% LD_{50}). One minute following tabun challenge, the rats were treated with atropine (21 mg/kg b.w.) alone or in combination with trimedoxime, K027 or K048 at equimolar doses corresponding to 10 μmol/kg b.w. The control rats were administered with saline instead of tabun and antidotes at the same volume. The neurotoxicity of tabun was monitored using the functional observational battery (FOB) at 24 hours and 7 days following tabun poisoning. The evaluated markers of tabun-induced neurotoxicity in experimental animals were compared with the parameters obtained from control rats.

The functional observational battery consists of 47 measurements of sensory, motor and autonomic nervous functions. Some of them are scored, the others are measured in absolute units (Frantik and Hornychova 1995, Hornychova and 1995) (Table 1). Data collected with the functional observational battery include categorial, ordinal and continuous values. Their statistical analyses were performed on a PC with a special interactive programme NTX (Frantik and Hornychova 1995).

RESULTS AND DISCUSSION

The results of the experiments related to the measurement of tabun-induced neurotoxicity at 24h and 7d following tabun poisoning are summarized in Table 2 and 3. The observation of neurotoxic signs indicated that many functional disorders of poisoned organisms outlasted at least 24 hours not only in non-treated tabun-poisoned rats but also in tabun-poisoned rats treated with atropine alone. Tabun caused passive behavior of rats during handling and catching, enophthalmus and an increase in lacrimation, salivation and nose secretion at 24 h following its administration. The exploratory activity was significantly decreased, gait and mobility were severely impaired and tonic convulsions were observed. In addition, no reaction during a reflex testing consisting of recording each rat`s response to the frontal approach of the blunt end of a pen, a touch of the pen to the posterior flank and an auditory clic stimulus was observed. No responsiveness to a pinch on the tail and the ability of pupils to constrict in response to light were demonstrated either. A significant decrease in the distance between hindpaws after a jump, forelimb and hindlimb grip strength, food receiving, body temperature and spontaneous horizontal as well as vertical motor activity were also observed at 24 h following tabun challenge (Tab. 2).

All three oximes tested in combination with atropine were able to eliminate some tabun-induced signs of neurotoxicity observed at 24 hours following tabun challenge with the exception of a passive behavior of rats during handling and catching, ataxia, a decrease in the ability of pupils to constrict in response to light, forelimb and hindlimb grip strength, food receiving and spontaneous horizontal as well as vertical motor activity (Tab. 2).

Practically all tabun-induced neurotoxic signs in tabun-poisoned rats non-treated or treated with atropine alone were observed at 7 days following tabun administration, too. While trimedoxime and K027 in combination with atropine were able to eliminate almost all signs of tabun-induced neurotoxicity, tabun-poisoned rats treated with K048 in combination with atropine showed the passive behavior of rats during handling and

Table 2. The values of tabun-induced neurotoxic markers measured at 24 hours following tabun challenge by the functional observational battery (No 1-11, 14-36 - scored values, No 12-13, 37-47 - values in absolute units)

24 hours		Controls		A+K027		A+Trimedoxime		A+K048		Atropine		Tabun	
No	*Marker*	*x/M*	*-/+s*	*x/M*	*-/+s*	*x/M*	*-/+s*	*x/M*	*-/+s*	*x/M*	*-/+s*	*x/M*	*-/+s*
1	posture	1.00		3.00		3.00		3.00		**7.00***		**7.00***	
2	catch difficulty	2.00		**1.00***		**1.00***		**1.00***		**1.00***		**1.00***	
3	ease of handling	2.00		**1.00***		**1.00***		**1.00***		**1.00***		**1.00***	
4	muscular tonus	0.00		**´-1.00***		**´-2.00***		**´-2.00***		**´-2.00***		**´-2.00***	
5	lacrimation	0.00		0.00		0.00		0.00		**4.00***		**4.00***	
6	palpebral closure	1.00		1.00		1.00		1.00		**5.00***		**5.00***	
7	endo/exophtalmus	0.00		0.00		0.00		0.00		**´-1.00***		**´-1.00***	
8	fur abnormalities	0.00		0.00		0.00		0.00		**7.00***		**7.00***	
9	skin abnormalities	0.00		0.00		0.00		0.00		**3.00***		**3.00***	
10	salivation	0.00		0.00		0.00		0.00		**2.00***		**2.00***	
11	nose secretion	0.00		**3.00***		0.00		**3.00***		**3.00***		**3.00***	
12	rearing	15.50	4.540	**0.830***	0.980	**5.00***	7.640	**4.670***	3.780	**1.67***	1.530	**4.00***	0.00
13	urination	1.880	3.720	3.500	6.120	3.00	5.130	0.00	0.00	11.330	16.170	3.00	0.00
14	defecation	0.00		0.00		0.00		0.00		0.00		0.00	
15	hyperkinesis	0.00		0.00		0.00		0.00		**7.00***		**7.00***	
16	tremors	0.00		0.00		0.00		0.00		**5.00***		**5.00***	
17	clonic movements	0.00		0.00		0.00		2.00		**2.00***		**2.00***	
18	tonic movements	0,00		0.00		0.00		0.00		**5.00***		**5.00***	
19	gait	0.00		1.00		1.00		7.00		**7.00***		**7.00***	
20	ataxia	0.00		**1.00***		**1.00***		**2.00***		**2.00***		**2.00***	
21	gait score	0.00		0.00		0.00		2.00		**2.00***		**2.00***	
22	mobility score	1.00		3.00		2.00		**4.00***		**4.00***		**4.00***	
23	arousal (GSC)	1.00		**2.00***		**2.00***		**4.00***		**4.00***		**4.00***	
24	activity	4.00		**1.00***		1.00		1.00		**1.00***		**1.00***	
25	tension	0.00		0.00		0.00		0.00		0.00		0.00	
26	vocalisation	0.00		0.00		0.00		0.00		0.00		0.00	
27	stereotypy	0.00		0.00		0.00		0.00		0.00		0.00	
28	bizzare behavior	0.00		0.00		0.00		0.00		0.00		0.00	
29	approach response	2.00		**1.00***		**1.00***		**1.00***		**1.00***		**1.00***	
30	touch response	2.00		**1.00***		**1.00***		**1.00***		**1.00***		**1.00***	
31	click response	2.00		3.00		**3.00***		**2.00***		**1.00***		**1.00***	
32	tail-pinch response	2.00		1.00		2.00		**1,00***		**1.00***		**1.00***	
33	pupil size	0.00		**´-2.00***		2.00		**´-2.00***		**´-2.00***		**´-2.00***	
34	pupil response	1.00		**0.00***		**0.50***		**0.00***		**0.00***		**0.00***	
35	RRF	1.00		2.00		1.00		2.00		**7.00***		**7.00***	
36	RRV	1.00		1.00		1.00		1.00		**4.00***		**4.00***	
37	landing foot splay (mm)	107.380	21.270	67.380	45.050	**71.19***	29.620	64.50	42.010	29.250	41.280	**9.63***	27.220
38	forelimb grip strength (kg)	6.480	1.030	**4.05***	0.480	**4.71***	0.480	**4.12***	1.290	**4.10***	0.44	**2.40***	0.00
39	hindlimb grip strength (kg)	1.190	0.16	**0.50****	0.15	**0.56***	0.13	**0.55***	0.29	**0.47***	0.06	**0.40***	0.00
40	grip strength of all limbs (kg)	19.880	3.820	**10.470***	2.970	**9.760***	4.630	**10.67***	4.630	**6.03***	0.31	**12.80***	0.00
41	food receiving (%)	100.00	0.00	**18.50***	12.220	**36.25***	16.420	**23.13***	16.680	**12.50***	23.150	**0.63***	1.770
42	body weight (g)	254.00	17.670	277.670	23.520	281.430	17.650	**277.83***	14.150	232.670	22.480	265.00	0.00
43	body temperature (°C)	37.260	0.26	**36.13***	0.35	36.960	0.37	**36.68***	0.45	**34.67***	0.40	**36.10***	0.00
44	respiration	0.00		0.00		0.00		0.00		´-2.00		**´-2.00***	
45	vertical activity	259.00	68.110	**65.67***	45.460	**33.00***	51.070	**37.33***	53.460	**8.00***	0.00	0.00	0.00
46	horizontal activity	54.130	41.360	**3.33***	5.920	**6.86***	18.140	3.00	5.200	2.00	0.00	0.00	0.00
47	total motor activity	313.130	98.10	**51.75***	53.740	**34.88***	64.360	**15.13***	37.360	**1.25***	3.540	0.00	0.00
		n=8		n=6		n=7		n=6		n=3		n=3	

Statistical significance: * $p < 0.05$;
** $p < 0.01$;
*** $p < 0.001$ (comparison with the control values)

Table 3. The values of tabun-induced neurotoxic markers measured at 7 days following tabun challenge by the functional observational battery (No 1-11, 14-36 - scored values, No 12-13, 37-47 - values in absolute units)

7 days		Controls		A+K027		A-Trimedoxime		A+K048		Atropine		Tabun	
No	*Marker*	*x/M*	*-/+s*	*x/M*	*-/+s*	*x/M*	*-/+s*	*x/M*	*-/+s*	*x/M*	*-/+s*	*x/M*	*-/+s*
1	posture	1.00		1.00		3.00		**7.00***		**7.00***		**7.00***	
2	catch difficulty	2.00		**2.00***		2.00		**1.00***		**1.00***		**1.00***	
3	ease of handling	2.00		2.00		2.00		**1.00***		**1.00***		**1.00***	
4	muscular tonus	0.00		0.00		0.00		´-2.00		**´-2.00***		**´-2.00***	
5	lacrimation	0,00		0.00		0.00		0.00		**4.00***		**4.00***	
6	palpebral closure	1.00		1.00		1.00		1.00		**5.00***		**5.00***	
7	endo/exophtalmus	0.00		0.00		0.00		0.00		**´-1.00***		**´-1.00***	
8	fur abnormalities	0.00		0.00		0.00		0.00		**7.00***		**7.00***	
9	skin abnormalities	0.00		0.00		0.00		0.00		**3.00***		**3.00***	
10	salivation	0.00		0.00		0.00		0.00		**2.00***		**2.00***	
11	nose secretion	0.00		0.00		0.00		0.00		**3.00***		**3.00***	
12	rearing	4.500	3.780	4.170	5.230	4.290	4.790	5.670	6.660	11.00	9.540	10.00	0.00
13	urination	0.00		0.00		0.00		0.00		0.00		0.00	
14	defecation	0.00		0.00		0.00		2,00		0.00		0,00	
15	CLO	0.00		0.00		**3.00***		0.00		**7.00***		**7.00***	
16	TRE	0.00		0.00		**2.00***		0.00		**5.00***		**5.00***	
17	clonic movements	0.00		0.00		0.00		0.00		**2.00***		**2.00***	
18	tonic movements	0.00		0.00		0.00		0.00		**5.00***		**5.00***	
19	gait	0.00		0.00		**1.00***		**7.00***		**7.00***		**7.00***	
20	ataxia	0.00		0.00		**1.00***		**2.00***		**2.00***		**2.00***	
21	gait score	0.00		0.00		0.00		0.00		**2.00***		**2.00***	
22	mobility score	1.00		1.00		1.00		4.00		**4.00***		**4.00***	
23	arousal (GSC)	1.00		1.00		2.00		**4.00***		**4.00***		**4.00***	
24	ACT	4,00		1.00		1.00		**1.00***		**1.00***		**1.00***	
25	tension	0.00		0.00		0.00		0.00		0.00		0.00	
26	VOC	0.00		0.00		0.00		0.00		0.00		0.00	
27	stereotypy	0.00		0.00		0.00		0.00		0.00		0.00	
28	bizzare behavior	0.00		0.00		0.00		0.00		0.00		0.00	
29	approach response	2.00		1.00		1.00		**1.00***		1.00		**1.00***	
30	touch response	2.00		2.00		2.00		**1.00***		**1.00***		**1.00***	
31	click response	2.00		3,00		2.00		1.00		**1.00***		**1.00***	
32	tail-pinch response	2.00		**1.00***		**2.00***		**1.00***		**1.00***		**1.00***	
33	pupil size	0,00		**´-2.00***		0,00		2.00		**´-2.00***		**´-2.00***	
34	pupil response	1.00		**0.00***		**0.50***		**0.00***		**0.00***		**0.00***	
35	RRF	1.00		1.00		1.00		7.00		**7.00***		**7.00***	
36	RRV	1.00		1.00		1.00		4.00		**4.00***		**4.00***	
37	landing foot splay (mm)	113.250	22.190	73.50	49.20	86.630	37.80	44.290	55.70	34.00	47.160	14.130	39.950
38	forelimb grip strength (kg)	7.560	1.080	6.100	1.240	**5.90***	0.950	5.870	1.540	5.770	0.640	6.800	0.00
39	hindlimb grip strength (kg)	1.420	0.320	0.980	0.190	1.190	0.410	1.130	0.210	0.970	0.120	1.00	0.00
40	grip strength of all limbs (kg)	20.690	4.00	15.730	3.820	17.30	2.950	19.970	7.870	18.830	3.810	14.20	0.00
41	food receiving (%)	100.00		100.00		100.00		100.00		**0.00***		**0.00***	
42	body weight (g)	279.250	14.020	**312.00***	25.00	**306.43***	17.740	**332.33***	31.50	254.670	28.150	258.00	0.00
43	body temperature (°C)	37.10		37.30		37.30		37.10		37.30		37.10	
44	RES	0.00		0.00		0.00		0.00		**´-2.00***		**´-2.00***	
45	vertical activity	186.630	79.00	313.170	173.750	214.290	137.490	250.330	142.150	115.00	27.620	38.00	0.00
46	horizontal activity	33.00	28.790	50.830	29.180	33.710	32.840	25.670	21.220	6.670	9.870	18.00	0.00
47	total motor activity	219.630	100.930	273.00	236.580	217.00	164.680	118.290	175.020	45.630	64.670	7.00	19.80
		n=8		n=6		n=7		n=6		n=3		n=3	

Statistical significance: see Table 2.

catching and the impairment of gait and mobility (Tab. 3).

Our results demonstrate that newly developed oximes (K027, K048) as well as trimedoxime appear to be more effective to eliminate tabun-induced acute neurotoxicity in rats than previously tested oximes although they are not able to completely eliminate tabun-induced signs of neurotoxicity in the case of lethal tabun poisoning either. Thus, they seem to be more promising oximes for the antidotal treatment of lethal tabun poisonings than currently used oximes such as pralidoxime, HI-6 and obidoxime. Trimedoxime, relatively weak reactivator of soman-inhibited AChE, is promising reactivator of tabun-inhibited AChE according to previously published data (Cabal et al. 2004). The reason for its relatively high efficacy is probably a special chemical structure of its molecule. The stereochemical arrangement of oximes can play a role in the difference in therapeutic efficacy of oximes against tabun (Cabal and Bajgar 1999, Patocka et al. 2005). Both newly developed oximes (K027, K048) seem to be promising reactivators of tabun-inhibited AChE too (Kuca and Kassa 2003, Kuca and Kassa 2004), nevertheless, the differencies of reactivating efficacy between newly developed (K027, K048) and currently available (obidoxime, trimedoxime) oximes is not so high to think about replacement of currently used oximes by them for the treatment of acute tabun poisonings (Kassa et al. 2005).

The study was supported by the grant of Ministry of Defence (Czech Republic) - MO0FVZ 0000501.

REFERENCES

1. Cabal J, Bajgar J. Tabun – reappearance 50 years later (in Czech). Chem. Listy, 1999; 93: 27-31.
2. Cabal J, Kuca K, Kassa J. Specification of the structure of oximes able to reactivate tabun-inhibited acetylcholinesterase. Pharmacol. Toxicol. 2004; 95: 81-6.
3. Dohnal V, Kuca K, Jun D. Prediction of a new broad-spectrum reactivator capable of reactivating acetylcholinesterase inhibited by nerve agents. J Appl. Biomed. 2005; 3:139-45.
4. Frantik E, Hornychova M. Clustering of neurobehavioral measures of toxicity. Homeostasis, 1995; 36: 19-25.
5. Hornychova M, Frantik E, Kubat J, Formanek J. Neurotoxicity profile of supermethrin, a new pyrethroid insecticide. Cent. Eur. J. Publ. Health, 1995; 3: 210– 8.
6. Jokanovic M. Anticholinesterase activity and delayed neurotoxic effects of tabun in hens. Vojvosanit. Pregl. 1993; 50: 451-6.
7. Kassa J, Cabal J, Kuca K. A comparison of the efficacy of currently available oximes against tabun in rats. Biologia 60/Suppl. 2005; 17: 77-9.
8. Kuca K, Bielavsky J, Cabal J, Bielavska M. Synthesis of a potential reactivator of acetylcholinesterase 1-(4-hydroxyiminomethylpyridinium)-3-(carbamoylpyridinium)-propane dibromide. Tetrahedron Lett. 2003; 44: 3123-5.
9. Kuca K, Bielavsky J, Cabal J, Kassa J. Synthesis of a new reactivator of tabun inhibited acetylcholinesterase. Bioorg. Med. Chem. Lett. 2003; 13: 3545-7.
10. Kuca K, Kassa J. A comparison of the ability of a new bispyridinium oxime - 1 - (4-hydroxyiminomethylpyridinium)-4-(4-carbamoylpyridinium)butane dibromide and currently used oximes to reactivate nerve agent-inhibited rat brain acetylcholinesterase by in vitro methods. J. Enzyme Inhib. Med. Chem. 2003; 18: 529–35.
11. Kuca K, Kassa J. In vitro reactivation of acetylcholinesterase using the oxime K027. Vet. Hum. Toxicol. 2004; 46: 15-8.
12. Patocka J, Cabal J, Kuca K, Jun D. Oxime reactivation of acetylcholinesterase inhibited by toxic phosphorus esters: in vitro kinetics and thermodynamics. J. Appl. Biomed. 2005; 3: 91-9.