Review

THERAPEUTIC AND NEUROPROTECTIVE EFFICACY OF PHARMACOLOGICAL PRETREATMENT AND ANTIDOTAL TREATMENT OF ACUTE TABUN OR SOMAN POISONING WITH THE EMPHASIS ON PRETREATMENT DRUG PANPAL

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A good knowledge of the basic mechanisms of acute toxicity of organophosphorus compounds has lead to the development of specific antidotes able to counteract their acute toxic effects. Unfortunately, there are still some highly toxic organophosphorus compounds, called nerve agents, that are resistant to standard antidotal treatment.

Relatively unsatisfactory antidotal treatment of acute poisonings with some nerve agents has prompted studies of pretreatment possibilities that would increase the resistance of organisms exposed to nerve agents. Current protection against nerve agent poisoning is pyridostigmine, but its prophylactic efficacy is rather limited. To increase the effectiveness of pharmacological pretreatment of soman or tabun poisoning, a prophylactic mixture called PANPAL and consisting of pyridostigmine and two anticholinergic drugs – benactyzine and trihexyphenidyle was developed, produced and introduced into the Czech Army to protect soldiers against nerve agent exposure. This review describes the evaluation of the potency of PANPAL to counteract acute soman or tabun poisoning and to increase the therapeutic and neuroprotective efficacy of current post-exposure antidotal treatment in comparison with pyridostigmine given alone as pretreatment.

KEY WORDS: *acetylcholinesterase reactivators, anticholinergic drugs, functional observatory battery, mice, pyridostigmine, rats*

Standard antidotal treatment of poisoning with organophosphorous compounds, including nerve agents, usually consists of anticholinergic drugs (preferably atropine) and reactivators of acetylcholinesterase (AChE, EC 3.1.1.7). Atropine acts as an antagonist of acetylcholine at muscarinic cholinergic receptors and AChE reactivators, called oximes, restore the activity of nerve agent-inhibited AChE by their nucleophilic effect (1-3). Unfortunately, some nerve agents are relatively resistant to the therapeutic potency of commonly used antidotes. Tabun (ethyl N,N-dimethylphosphoramid cyanide) seems to be extraordinarily difficult to treat due to the existence of a free electron pair located on an amidic nitrogen that makes the nucleophilic attack of oximes almost impossible (4-6). Another resistant nerve agent is soman (pinacolyl methylphosphonofluoridate). It differs from other nerve agents in the very fast rate of aging of the phosphonylated enzyme that prevents oxime-induced reactivation of AChE (1, 7-8).

The relatively unsatisfactory treatment available for acute nerve agent poisonings has prompted studies of pretreatment possibilities that allow survival and increase resistance of organisms exposed to nerve agents. Currently used method of protection against nerve agent poisoning is the use of pyridostigmine bromide (9). The prophylactic effect of pyridostigmine can result from its reversible inhibition of AChE. It binds a small fraction of AChE in the periphery and reversibly shields it from irreversible inhibition by the nerve agents (10). However, pyridostigmine-induced increase in the level of acetylcholine (ACh) can itself cause symptoms of poisoning. Therefore, it would be useful to counteract the effects of the accumulated ACh using anticholinergic drugs. In addition, the combination of pyridostigmine with anticholinergic drugs allows the dose of pyridostigmine that is otherwise limited by symptoms caused by elevated levels of ACh to be increased and results in higher prophylactic efficacy than that observed for pyridostigmine alone (11-12). One of these mixtures developed for the Czech Army is PANPAL which combines pyridostigmine with benactyzine (BNZ) and trihexyphenidyle (THP) (13-14). This prophylactic antidotal combination has no side effects, as it has been demonstrated on volunteers; no statistically different changes were observed in the state of the volunteers' physiological functions (15).

THE THERAPEUTIC EFFICACY OF PHARMACOLOGICAL PRETREATMENT AND CURRENT ANTIDOTAL TREATMENT OF SOMAN OR TABUN POISONINGS

The potency of pharmacological pretreatment with pyridostigmine alone or in combination with BNZ and THP to counteract acute tabun or soman poisoning and to increase the therapeutic efficacy of antidotal treatment of acute tabun or soman poisoning was evaluated in mice or rats by assessing the decrease in median lethal dose (LD_{50}) of tabun or soman. The LD_{50} values of tabun or soman and their 95 % confidence limits were assessed using a probit-logarithmic analysis of death occurring within 24 h after intramuscular (im) administration of tabun at five different doses with six experimental animals per dose (16). Pyridostigmine [5.82 mg kg^{-1} of body weight (b. w.)] alone or in combination with BNZ (70 mg kg^{-1} b. w.) and THP (16 mg kg^{-1} b. w.) was administered orally as solution in distilled water (0.2 mL per 100 g b. w. of rats or 10 g b. w. of mice) 60 or 120 min before im tabun or soman challenge, while antidotal treatment (oxime HI-6 or obidoxime at equieffective doses – 2 % of their LD_{50} in combination with atropine at 2 % of its LD_{50} and diazepam at the dose of 1 mg kg^{-1} b. w.) was carried out by im injection one minute following tabun administration. The dose of pyridostigmine used in our experiments caused a 40 % inhibition of erythrocyte AChE activity, determined by the Ellman's spectrophotometric method (17) using acetylthiocholine as substrate and 5,5'-dithio-bis(2-nitrobenzoic) acid as chromogen. The experimental doses of BNZ (10 % LD_{50}) and THP (2 % LD_{50}) were chosen to correspond human-relevant doses. The doses of oximes (HI-6 at 13.8 mg kg^{-1} b. w. for mice and 15.6 mg kg^{-1} b. w. for rats, obidoxime at 3.8 mg kg^{-1} b. w. for mice and 3.2 mg kg^{-1} b. w. for rats) and anticholinergic drug used (atropine at 8.4 mg kg^{-1} b. w. for mice and 25.2 mg kg^{-1} b. w. for rats) for the antidotal treatment correspond to human-relevant doses (2 % of their LD_{50}) (10). The efficacy of tested pretreatments to increase the resistance of experimental animals to acute toxicity of tabun or soman was expressed as protective ratio A and the efficacy of tested pretreatments to increase the therapeutical efficacy of antidotal treatment was expressed as protective ratio B.

Protective ratio A = (LD_{50} value of tabun or soman in pretreated mice or rats with or without antidotal treatment) / (LD_{50} value of tabun or soman in non-pretreated mice or rats without antidotal treatment).

Protective ratio B = (LD_{50} value of tabun or soman in pretreated mice or rats with antidotal treatment) / (LD_{50} value of tabun or soman in non-pretreated mice or rats with antidotal treatment).

The results summarized in Tables 1-4 (18-20) clearly demonstrate that pyridostigmine alone can not increase resistance to tabun or soman in the exposed mice. Pyridostigmine is only able to protect peripheral AChE from irreversible tabun- or soman-induced AChE phosphorylation, while tabun and soman can cross the blood-brain barrier and, thus, lead to centrally mediated seizure that can rapidly progress to epilepsy and contribute to brain damage (6). On the other hand, pyridostigmine was able to slightly increase the resistance of tabun-exposed rats because rats are more sensitive to tabun and peripheral effects of pyridostigmine seem to be sufficient to moderately decrease the acute toxicity of tabun in rats (18, 21).

In contrast to pyridostigmine given alone, PANPAL seems to be sufficiently effective in pretreatment of tabun- or soman-exposed mice and rats, because

Table 1 *The influence of pyridostigmine alone and PANPAL on the LD_{50} value of tabun in (a) mice and (b) rats. The time of pretreatment was 120 minutes. Numbers in brackets are the 95 % confidence limits of the LD_{50}. Statistical significance: *P<0.05 (between experimental animals with and without pretreatment), xP<0.05 (between experimental animals pretreated with pyridostigmine and with PANPAL). Data are from ref. No.18.*

Pretreatment	LD_{50} of tabun / μg kg-1	Protective ratio A
-----	275 (269-281)a	----
Pyridostigmine alone	277 (261-295)a	1.01a
PANPAL	701 (655-789)a*x	2.55a
-----	128 (121-136)b	----
Pyridostigmine alone	240 (220-262)b*	1.88b
PANPAL	285 (270-300)b*x	2.23b

Table 2 *The influence of pharmacological pretreatment on the potency of antidotal treatment to eliminate acute lethal effects of (a) tabun in rats and (b) soman in mice. The time of pretreatment was 120 minutes. Numbers in brackets are the 95 % confidence limits of the LD_{50}. Statistical significance: *P<0.05 (between non-pretreated and non-treated experimental animals and pretreated and/or treated experimental animals), xP<0.05 (between treated experimental animals with pretreatment and treated experimental animals without pretreatment). Data are from refs. No.18-20.*

Pretreatment	Treatment	LD_{50} of tabun / μg kg^{-1}	Protective ratio A	Protective ratio B
----	----	128 (121-136)a	---	---
----	Obidoxime, atropine, diazepam	382 (340-430)a*	2.98a	---
Pyridostigmine	Obidoxime, atropine, diazepam	412 (350-487)a*	3.22a	1.08a
PANPAL	Obidoxime, atropine, diazepam	990 (820-1180)a*x	7.73a	2.59a
---	---	108 (102-115)b	---	---
---	Obidoxime + atropine + diazepam	179 (167-192)b*	1.66b	---
Pyridostigmine	Obidoxime + atropine + diazepam	420 (386-456)b*x	3.89b	2.34b
PANPAL	Obidoxime + atropine + diazepam	509 (458-565)b*x	4.71b	2.84b

Table 3 *The influence of pyridostigmine alone and PANPAL on the LD_{50} value of soman in mice. Numbers in brackets are the 95 % confidence limits of the LD_{50}. Statistical significance: *P<0.05 (between experimental animals with or without pretreatment), xP<0.05 (between experimental animals pretreated with pyridostigmine alone or PANPAL). Data are from refs. No.19-20.*

Pretreatment	Time of pretreatment / min	LD_{50} of soman / μg kg^{-1}	Protective ratio A
----	----	108 (102-115)	----
Pyridostigmine alone	60	109 (93-128)	1.01
PANPAL	60	356 (301-421)*x	3.30
Pyridostigmine alone	120	113 (97-131)	1.04
PANPAL	120	383 (348-420)*x	3.54

Table 4 *The influence of pharmacological pretreatment on the potency of antidotal treatment to eliminate acute lethal effects of soman in mice. Numbers in brackets are the 95 % confidence limits of the LD_{50}. Statistical significance: *P<0.05 (between non-pretreated and non-treated experimental animals and pretreated and/or treated experimental animals), xP<0.05 (between treated experimental animals with pretreatment and treated experimental animals without pretreatment). Data are from refs. No.19-20.*

Pretreatment	Time of pretreatment / min	Treatment	LD_{50} of soman / μg kg^{-1}	Protective ratio A	Protective ratio B
----	-	-	108 (102-115)	-	-
----	-	HI-6 + atropine	218 (202-236)*	2.02	-
Pyridostigmine	60	HI-6 + atropine	258 (238-280)*	2.39	1.18
PANPAL	60	HI-6 + atropine	449 (356-566)*x	4.16	2.06
Pyridostigmine	120	HI-6 + atropine	199 (162-243)*	1.84	0.91
PANPAL	120	HI-6 + atropine	391 (336 - 455)*x	3.62	1.80

it can protect them from tabun doses as high as 2.5xLD_{50} and protect mice from soman doses reaching 3.5xLD_{50}. This effect of PANPAL is probably caused not only by pyridostigmine-induced protection of peripheral AChE from irreversible inhibition by nerve agents, but also by the anticholinergic drugs BNZ and THP, which induced a decrease in the overstimulation of peripheral and central cholinergic nervous systems (19). Moreover, PANPAL seems to be very effective in enhancing the efficacy of antidotal treatment to protect experimental animals poisoned with tabun or soman. Rats or mice pretreated by PANPAL and treated by current antidotes can survive poisoning with soman or tabun administered at doses as high as 4xLD_{50} to 7xLD_{50} (11-12, 18-19). Pyridostigmine is also able to increase the therapeutic efficacy of currently used antidotal mixtures (22-23), but pyridostigmine-induced increase in the therapeutic efficacy of antidotal treatment is significantly lower in comparison with PANPAL, because pyridostigmine alone is not able to prevent the effects of nerve agents on the central nervous system (18-19).

THE NEUROPROTECTIVE EFFICACY OF PHARMACOLOGICAL PRETREATMENT AND CURRENT ANTIDOTAL TREATMENT OF TABUN POISONING

The neuroprotective efficacy of pharmacological pretreatment and its influence on the neuroprotective potency of antidotal treatment of rats poisoned with nerve agents can be assessed using a procedure known as Functional Observational Battery (FOB) which includes 40 measurements of sensory, motor and autonomic nervous functions. Some parameters are scored, others measured in absolute units (24-26). First measurements are made while the animal is in the home cage. The observer evaluates the posture, palpebral closure and involuntary motor movements of each animal. Each rat is then removed from the home cage and briefly held in the hand. Exploratory activity, piloerection and other skin abnormalities are noted too. Salivation and nose secretion are also registered and scored. Then the rats are placed on a flat surface, which serves as an open field. A timer is started for three minutes during which the frequency of rearing responses is recorded. At the same time, gait characteristics are noted and ranked and arousal, stereotypy and bizarre behaviour and abnormal posture are evaluated. At the end of the third minute, the number of faecal boluses and urine pools on the absorbent pad is registered. Reflex testing is also used, 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. The responsiveness to a pinch on the tail and the ability of pupils to constrict in response to light are then assessed. These measurements are followed by the measurements of forelimb and hindlimb grip strength, body weight, rectal temperature and finally hindlimb landing foot splay. This battery of tests takes about 6-8 minutes per rat. The observer of the behaviour does not know the experimental design. After the FOB, motor activity data are collected using an apparatus for testing spontaneous motor activity of laboratory animals (constructed at the Faculty of Military Health Sciences, Hradec Kralove, Czech Republic). The animals are placed in the measuring cage for 10 minutes and their movements (total, horizontal and vertical activity) recorded. Data collected with the FOB and motor activity assessment include categorial, ordinal and continuous values. Statistical analyses of the results are performed on a PC with a special interactive program, NTX (24). The categorial and ordinal values are formulated as contingency tables and evaluated consecutively by the chi-square test of homogeneity, concordance-discordance test and Kruskal-Wallis test, respectively. The continual data are assessed by successive statistical tests: CI for Delta, Barlett test for equality of variance, Williams test and test for distribution functions (27). The differences are considered significant when $P<0.05$.

The potency of PANPAL was evaluated using the FOB in tabun-poisoned rats at 24 hours following tabun challenge (28). Pyridostigmine (5.82 mg kg^{-1} b. w.) in combination with BNZ (70 mg kg^{-1} b. w.) and THP (16 mg kg^{-1} b. w.) was administered orally as solution in distilled water (0.2mL per 100 g b. w.) 120 min before im tabun challenge at a dose corresponding to the LD_{50} value (280 μg kg^{-1} b. w.). Antidotal treatment (obidoxime in combination with atropine) was carried out by im injection 1 min following tabun administration. The doses of obidoxime (3.2 mg kg^{-1} b. w.) and anticholinergic drug atropine (25.2 mg kg^{-1} b. w.) correspond to human-relevant doses (2 % of their LD_{50}) (10). The evaluated markers of tabun-induced neurotoxicity in experimental animals were compared to the parameters obtained from control rats, administered with saline instead of tabun and antidotes at the same volume (0.1 mL per 100 g b. w.).

Table 5 summarises the results of the evaluation of tabun-induced neurotoxicity at 24 hours following

Table 5 *The influence of PANPAL pretreatment on tabun-induced markers in rats 24 hours following tabun challenge. Markers No.1-30 are based on the Functional observation battery described in the text. n is the number of rats, SD is the standard deviation. Control rats received only saline. Asterisks indicate values statistically different from the control. Statistical significance: *P<0.05; **P<0.01; ***P<0.001. Data are from ref. No 28.*

		Controls	PANPAL + Tabun + Atropine + Obidoxime	PANPAL + Tabun	Tabun + Atropine + Obidoxime	Tabun
No	Marker	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
1	posture	1.90±0.88	2.30±0.95	1.60±0.97	1.80±0.92	2.57±1.13
2	catch difficulty	2.10±0.32	1.70±0.48	1.70±0.48	1.30±0.48***	2.00±1.91***
3	ease of handling	2.10±0.32	1.70±0.48	1.70±0.48	1.60±0.52	1.43±0.79***
4	muscular tonus	0.00±0.00	-0.50±0.53**	-0.7±0.48***	-0.2±0.42	-1.00±0.82***
5	lacrimation	0.00±0.00	0.40±1.26	0.00±0.00	1.20±1.93	2.29±2.14*
6	palpebral closure	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.32	1.86±1.07*
7	endo-exophthalmus	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
8	piloerection	0.00±0.00	0.00±0.00	0.00±0.00	0.10±0.32	1.00±1.41*
9	skin abnormalities	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	1.00±1.41*
10	salivation	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.71±0.49***
11	nose secretion	0.00±0.00	0.00±0.00	0.00±0.00	0.60±1.26	2.57±1.13***
12	exploratory activity	11.60±6.57	1.90±2.08***	3.30±0.00***	6.00±3.59*	2.43±2.51***
13	urination	0.00±0.00	0.20±0.63	0.00±0.00	1.00±3.16	2.86±7.56
14	defecation	0.80±1.23	1.10±1.60	0.30±0.48	0.00±0.00	0.00±0.00
15	clonic movements	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.43±0.79*
16	tonic movements	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.86±1.46*
17	gait disorder	0.00±0.00	0.70±0.82*	1.20±1.40**	0.30±0.48	4.29±3.09***
18	gait score	1.00±0.00	1.60±0.70*	1.80±0.42***	1.60±0.97*	3.43±0.53***
19	mobility score	1.00±0.00	1.30±0.48	1.40±0.70	1.00±0.00	2.29±1.38**
20	arousal	3.70±0.95	3.30±0.67	2.70±1.49*	3.70±0.67	2.86±1.46
21	tension	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
22	stereotypy	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.29±0.76
23	bizarre behavior	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
24	approach response	1.90±0.32	1.70±0.48	1.60±0.52	2.40±0.52	1.00±0.00***
25	touch response	1.10±0.32	1.30±0.48	1.20±0.42	1.40±0.70	1.14±0.38
26	click response	2.00±0.00	2.20±0.48	2.20±0.42	2.20±0.42	2.14±0.69
27	tail-pinch response	2.00±0.00	1.90±1.20	1.50±0.71	1.80±0.42	1.71±0.49
28	pupil size	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	- 0.86±0.90**
29	pupil response	1.00±0.00	0.85±0.24	1.00±0.00	1.00±0.00	0.57±0.45*
30	fall from vertical position	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	3.86±2.79**
31	landing foot splay (cm)	94.80±15.75	87.30±17.70	84.35±16.55	82.1±10.06*	43.00±30.25***
32	forelimb grip strength (kg)	2.26±0.74	2.34±0.63	2.68±0.47	2.05±0.51	1.43±1.20***
33	hindlimb grip strength (kg)	1.04±0.20	0.29±0.89	0.89±0.22	0.76±0.12***	0.74±0.65***
34	fore and hindlimb grip strength (kg)	5.63±0.72	4.73±0.61**	5.22±0.55	4.63±0.63***	2.64±1.79***
35	food receiving (%)	100.00±0.00	100.00±0.00	95.00±5.27*	100.00±0.00	50.00±0.00***
36	body weight (g)	221.90±16.43	223.10±12.68	221.80±7.41	216.40±10.45	193.57±14.36**
37	rectal temperature (°C)	37.61±0.42	37.84±0.41	37.87±0.24	37.20±0.36*	37.22±0.20*
38	activity horizontal (No/10 min)	78.00±44.56	12.70±13.35***	40.90±27.82*	23.30±24.21***	3.00±6.03***
39	activity vertical (No/10 min)	320.70±90.60	115.20±78.17***	200.60±104.41*	156.9±81.38***	38.57±50.22***
40	total motor activity (No/10 min.)	398.70±130.20	127.90±89.22***	241.50±129.77*	180.20±102.40***	41.57±55.79***
		n=10	n=10	n=10	n=10	n=7

tabun poisoning (28). Three non-treated tabun-poisoned rats died within 24 hours following tabun administration. All tabun-poisoned rats, treated and/or pretreated, survived till the end of the experiment. The evaluation of tabun-induced neurotoxic signs at 24 hours following intoxication showed a significant change in 29 observed parameters. Tabun caused abnormal behaviour of rats during catching (extreme excitation or, on the other hand, considerable passivity). Behaviour was passive in tabun-poisoned rats during handling, animals were hypotonic. Tabun also caused an increase in miosis, lacrimation, palpebral closure, salivation, nose secretion and skin as well as fur abnormalities. The exploratory activity in the open field was significantly decreased. Clonic as well as tonic movements appeared, gait and mobility were impaired. Tabun affected animal response to approaching objects and pupil response to light as well. Rats' forelimb and hindlimb grip strength as well as the distance between hindpaws after a jump significantly diminished, and their spontaneous horizontal and vertical motor activity, body weight and body temperature decreased (28).

All three combinations of protection against tabun poisoning (PANPAL pretreatment, antidotal treatment and the combination of PANPAL pretreatment with antidotal treatment) brought marked improvement in most parameters. Pretreated tabun-poisoned rats only showed higher rearing in the open field and a decrease in ingested food in comparison with control rats. Animals treated with atropine in combination with obidoxime without pretreatment showed passive behaviour during catching, lower activity (in the open field as well as in the special apparatus for testing spontaneous motor activity), higher gait score, a decrease in the distance between hindpaws after a jump, and lower hindlimb grip strength and body temperature in comparison with the control group. Rats pretreated by PANPAL and treated by atropine in combination with obidoxime showed the best protection from tabun-induced neurotoxicity compared to other groups 24 hours after tabun challenge. The combination of PANPAL pretreatment and antidotal treatment was able to eliminate most of the tabun-induced signs of neurotoxicity (save for hypotony, reduced activity and some gait abnormalities) (28). The results clearly demonstrate the potency of PANPAL to eliminate some tabun-induced neurotoxic effects and to increase neuroprotective efficacy of current antidotal treatment compared to antidotal treatment without pharmacological pretreatment. PANPAL is therefore suitable for pharmacological pretreatment of tabun exposure and in combination with common antidotal treatment it is able to counteract tabun-induced acute neurotoxicity. Similar results were obtained with experimental soman poisoning (29). The beneficial effects of PANPAL against acute neurotoxicity of nerve agents are probably based on the protection of central cholinergic receptors caused by centrally acting anticholinergic drugs (BNZ and THP) as well as on the protective properties of pyridostigmine bromide against irreversible AChE inhibition caused by nerve agents (8, 14).

CONCLUSION

In conclusion, the addition of anticholinergic drugs to pyridostigmine in pre-treatment is useful not only for enhancing resistance to tabun or soman, but also for eliminating the side effects of pyridostigmine, especially the effects of accumulated ACh. Generally, pyridostigmine at the common dose (30 mg pyridostigmine tablet three times a day) is thought to produce no significant side effects, but when it was taken by 10 asthmatic soldiers during Operation Desert Storm, seven experienced worsening of the asthma symptoms (30, 31). It was demonstrated that exposure to physiologically relevant doses of pyridostigmine leads to neurobehavioral deficiences and region-specific alterations in AChE and cholinergic receptors (32). On the other hand, peripherally acting carbamate with centrally acting anticholinergics may also results in side effects. Nevertheless, PANPAL was clinically examined at doses recommended for humans (pyridostigmine 35 mg, BNZ 8 mg, THP 6 mg, two times a day) and no health problems or side effects were found during clinical and laboratory observation of the volunteers (14-15).

The combination of pyridostigmine with anticholinergic drugs such as PANPAL has definite advantages over pyridostigmine alone in the pretreatment of nerve agent poisoning and deserves to be considered as replacement for the currently used pretreatment of nerve agent poisoning (pyridostigmine alone), especially where there is a threat of exposure to soman or tabun, because common antidotes can not treat well acute tabun or soman poisoning due to the low reactivating potency of all currently available oximes (1, 7, 33). Therefore, PANPAL has been licensed, produced and introduced into the Czech Army to protect our soldiers from the threat of exposure to nerve agents.

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Sažetak

TERAPIJSKA I NEUROPROTEKTIVNA DJELOTVORNOST PROFILAKSE I PRIMJENE PROTUOTROVA U LIJEČENJU AKUTNOG OTROVANJA TABUNOM ODNOSNO SOMANOM S POSEBNIM OSVRTOM NA PROFILAKSU PANPAL-om

Uvid u osnovne mehanizme akutnog otrovanja organofosfornim spojevima omogućio je razvoj specifičnih protuotrova koji su u stanju poništiti akutno toksično djelovanje otrova. Nažalost još postoje veoma toksični organofosforni spojevi poznati kao živčani otrovi, a koji su otporni na liječenje standardnim protuotrovima.

Relativno slabi rezultati dosadašnjeg liječenja akutnog otrovanja živčanim otrovima potaknuli su istraživanje mogućnosti profilakse koja bi povećala otpornost izloženih organizama. Dosada se u te svrhe rabio piridostigmin, ali je njegovo profilaktičko djelovanje prilično ograničeno. Kako bi se povećala djelotvornost profilakse protiv trovanja somanom odnosno tabunom, u oružanim snagama Češke Republike razvijena je kombinirana profilaksa pod nazivom PANPAL, a koja obuhvaća piridostigmin i dva antikolinergika, benaktizin i triheksifenidil. Svrha joj je bolje zaštititi vojnike kod izlaganja živčanim otrovima. Ovaj pregledni rad opisuje testiranje djelotvornosti PANPAL-a protiv akutnog otrovanja somanom odnosno tabunom te poboljšanje terapijskoga i neuroprotektivnog djelovanja kod akutnog otrovanja tabunom odnosno somanom u odnosu na isključivu primjenu piridostigmina kao uobičajene profilakse kod trovanja živčanim agensima.

KLJUČNE RIJEČI: *acetilkolinesteraza, antikolinergici, miševi, piridostigmin, reaktivatori; štakori*

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