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THE ACTION OF NN'-TRIMETHYLENEBIS (4-HYDROXYIMINOMETHYLPYRIDINIUM BROMIDE) (TMB-4) ON ACUTE LETHAL ANTICHOLINESTERASE POISONING IN MICE

by

M. Milošević, V. Vojvodić and V. Milošević

Institute of Pharmacology, Medical Faculty, Belgrade

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Poziomek, Hackley and Steinberg (1958) and, independently, Hobbiger, O'Sullivan and Sadler (1958) have recently described a series of NN'-polymethylenebis(4-hydroxyiminomethyl-pyridinium) compounds, which are potent reactivators of cholinesterases inhibited by organophosphate anticholinesterases. The most effective compound in this series NN'-trimethylenebis(4-hydroxyimino-methyl-pyridinium bromide) (TMB-4) was reported to be an effective agent in protecting animals from the lethal poisoning by methylphosphonofluoridate (Sarin), DFP and TEPP (Bay, Krop and Yates, 1958; Berry, Davies and Green, 1959; Hobbiger and Sadler, 1959).

In this paper additional experiments are described, carried out to estimate the antagonism of TMB-4 toward some other organo-P-compounds. A number of specific nonphosphorus anticholinesterases are included as well.

METHOD

The animals used were adult white mice of both sexes weighing 16 to 22 g. The fresh solutions of the following anticholinesterases were used: 0,0-diethyl-0-p-nitrophenylphosphate (Parathion, E 605), 0,0-diethyl-0-p-nitrophenylphosphorothionate (Paraoxon, E 600), bis-dimethylaminofluorophosphin-oxide (Dimefox), 0,0-dimethyl-0-(2-ethyl-mercaptoctyl) thiophosphate (Metasystox, Methyldemeton), 0,0-dimethyl-I-hydroxy-2, 2,2-trichlorethyl-phosphonate (Dipterex), octamethyl-pyrophosphoramide (Ompa, Schradan), neostigmine (Prostigmine), Physostigmine (Eserine), 1,5-bis(N-allyl-NN-dimethyl-4-ammonium-phenyl)pentane-3-one dibromide (BW284C51) and N p chlorophenyl-N-methylcarbamate of m-hydroxy-phenyltrimethyl ammonium bromide (Ro-2-1250).

All compounds were dissolved in distilled water except Parathion and Metasystox which were dissolved in propylenglycole. The solutions of anticholinesterases and TMB-4 were adjusted so that 0,01 ml per gram of body weight was injected. TMB-4 (25 and 50 mg/kg) was administered intraperitoneally one minute after subcutaneous injection of the poison. Final readings of results were recorded after 24 hours.

RESULTS AND DISCUSSION

The results are summarized in Table I.

Table 1.

The Effect of TMB-4 on the Toxicity of Anticholinesterases
(Results are number of mice surviving for 24 hours/number of mice injected)

Compound mg/kg	Controls	TMB-4 mg/kg	
		25	50
Paraoxon (E 600)			
0.75	2/6	6/6	—
1.0	0/6	—	6/6
Parathion (E 605)			
17.6	2/6	6/6	6/6
35.2	0/6	—	4/6
Metasystox			
11.5	2/6	6/6	—
23.0	0/6	—	6/6
46.0	0/6	—	5/6
Dimefox			
2.5	1/6	—	—
5.0	0/6	0/6	6/6
Dipterex			
750	3/6		
1000	0/6	3/6	5/6
OMPA (Schradan)			
20	3/6	5/6	5/6
40	0/6	1/6	1/6
Neostigmine			
0.5	1/6	—	
0.75	0/6	6/6	—
1.0	0/6	—	5/6
Eserine			
2.0	1/6	—	5/6
5.0	0/6	—	6/6
Ro-2-1250			
0.25	2/6		
0.5	0/6	—	6/6
1.0	0/6	—	0/6
BW-284 C 51			
0.25	3/6	—	—
0.5	1/6	1/6	0/6

The present experiments show that a single dose of 25 to 50 mg/kg of TMB-4 was effective in protecting mice from the lethal poisoning by Paraoxon (E 600), Parathion (E 605) and Metasystox. In mice poisoned by lethal doses of Dimefox and Dipterex some degree of protection was obtained only with a large dose of TMB-4. No satisfactory protection could be obtained by TMB-4 in animals poisoned by OMPA. However, TMB-4 was effective in protecting mice poisoned by some anticholinesterases which do not give phosphorylated enzyme, such as neostigmine, eserine and, partly, by the Ro-2-1250. These results are in line which the results of Hobbiger and Sadler (1959) who found that TMB-4 displayed the distinct antagonism against neostigmine toxicity. Thus it may be concluded that TMB-4 may reverse cholinesterase inhibition by a more general mechanism than displacement of phosphoryl group. However, no protection was obtained with TMB-4 against lethal poisoning by the BW284C51.

These experiments, as well as those of the investigators cited, suggest that TMB-4 may be superior to pyridine-2-aldoxime methiodide (PAM -2) which has hitherto proved to be the most potent reactivator of cholinesterases inhibited by organo-P-compounds. (For review see Davies and Green, 1959.)

CONCLUSION

TMB-4 was effective in protecting mice from the lethal poisoning by Paraoxon, Parathion, Metasystox, neostigmine, eserine and, partly, by the Ro-2-1250, Dimefox and Dipterex. No satisfactory protection could be obtained by TMB-4 in mice poisoned by OMPA and BW284C51.

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Sadržaj

DJELOVANJE TMB-4 NA AKUTNO LETALNO TROVANJE MIŠEVA ANTIKOLINESTERAZAMA

TMB-4 pokazao se uspješnim u zaštiti miševa, koji su otrovani letalnim dozama paraoksona, parationa, metasistoksa, neostigmina, eserina, a djelomično i RO-2-1250, dimefoksa i ditereksa. Njegovo djelovanje, međutim, ne pruža dovoljnu zaštitu miševa otrovanih OMPA-om i BW284C51.

Zavod za farmakologiju Medicinskog fakulteta, Beograd

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