PHARMACOKINETIC STUDIES ON THREE REACTIVATORS OF CHOLINESTERASE

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Introduction

The drug therapy on intoxication with organophosphoric compounds (OPC) included mainly combination of cholinesterase reactivators and cholinolytics (4). A variety of bispyridinium mono- and dioximes have been synthesized over several years in order to improve the treatment of poisoning with highly toxic organophosphates. The "H"-oximes (HI-6 and HLo-7) synthesized by Prof. Hagedorn are the most popular now.

Some of the pyridine-heterocyclic oximes, synthesized in Military Medical Academy, Sofia have good protective effect against OPC intoxication. Very important is their anticonvulsive action (3).

In our previous studies (2) was demonstrated that pharmacokinetic of some H-oximes was changed after OPC intoxication. We suggest that the drug monitoring of oximes was needed. The pharmacokinetics of most of the newer oximes has not been studied. Only limited information is available with regard to plasma concentration of oximes in experimental animals (1, 2, 5). The pharmacokinetics of newly oximes is important to discuses the possible mechanisms of there antidotal action.

The OBJECTIVES of this study were to study the pharmacokinetics of two new reactivators on cholinesterase - BT93 (RD-2) and BT93(I) (RD-4)-Reg. № 101073/1996 (Bg) and BT 93(2,2) - bis(2--hydroxyiminomethyl-pyridinium-1-methyl)ether diiodide (as referent compound) in plasma after i.m. administration in rats.

Materials and Methods

The reactivates of inhibited cholinesterase - RD-2, RD-4 and BT 93(2,2) was synthesized in the Laboratory of Experimental Toxicology at Military Medical Academy, Sofia.

The reactivators were administrated i.m. to albino rats line "Wistar" (n = 120) in dose $0.5x10^{-3}$ M/kg b.w. = 36.0 mg/kg, 36.0 mg/kg and 27.0 mg/kg b.w. for RD-2, RD-4 and BT93(2,2), respectively.

Serial blood samples were collected in heparinized tubes at 8 time intervals after reactivator's injection - 10., 20., 30., 45., 60., 90., 120., and 150. min. Plasma was deproteinized with 0.6 M trichloracetic acid (1:1) and centrifuged at 10000 rpm for 10 min at 4 °C.

An HPLC-method for analysis was used. The Perkin-Elmer liquid chromatography system consisted of a Series 410 quarterpump, injector Rheodine 7125 with 20 μL loop, UV/VIS spectrophotometric detector LC-5, operated at 308 and 300 nm, and computer integrator LCI-100. A 125x4.6 mm LiChrospher 100 RP-18 column was used. Eluting solvent, delivered at 1.5 mL/min, consisted of 90% 0.1 M phosphate buffer, adjusted to pH 3.0 with trimethylamin, 10% acetonitrile and cyclamat natrium 0.02 mol/l. The retention time was 1.7 min.

The plasma concentration-time profile for each reactivator was fitted to one-compartment (i.m.) pharmacokinetics model with computer program PKCALC and REGRESS-PC (6).

Results and Discussion

The plasma concentration estimates were shown on Table 1. Parameters for i.m. administration was averaged and was used to draw the best fit line. Pharmacokinetic estimates of RD-2, RD-4 and BT93(2,2) were shown on Table 2.

The concentration-time profiles of RD-2, RD-4 and BT93(2,2) after i.m. administration fit a one--compartment model. Essential differences in absorption and elimination rates between RD-2, RD-4 and BT93(2,2) were found after this route of application (Table 2). The first two oximes were slower absorbed and eliminated than BT93(2,2). The apparent volume of distribution for RD-2 and RD-4 was found greater than BT93(2,2). The clearance of RD-2 was higher.

The pharmacokinetics data received with RD-2 and RD-4 are more close to this obtained from us with HI-6 (2).

A very important result is that the time of the semi-elimination of RD-2 and RD-4 is longer that the time of BT93(2,2), TMB-4 and toxogonine - 57.0 and 92.8 min vs. 21.7, 28.3 and 19.9 min respectively. This is practically analogical with thedata of HI-6 (72.5 min).

Table 1

Plasma concentration (μg/mL) of RD-2, RD-4 and BT93(2,2) administered i.m. to rats

	RD-2 36.0 mg/kg b.w. (n = 5)	RD-4 36.0 mg/kg b.w. (n = 5)	BT93(2,2) 27.0 mg/kg b.w. (n = 5)
time (min)	SM ± SE	SM ± SE	SM ± SE
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
10	9.2 ± 0.8	6.0 ± 0.8	19.0 ± 2.6
20	9.4 ± 0.8	8.6 ± 1.2	29.4 ± 0.5
30	9.5 ± 0.6	10.4 ± 1.3	20.4 ± 1.6
45	9.5 ± 0.7	11.4 ± 0.9	12.8 ± 0.6
60	8.4 ± 0.6	8.7 ± 1.3	6.1 ± 1.3
90	5.9 ± 0.6	8.6 ± 0.7	1.8 ± 0.2
120	3.6 ± 0.1	4.0 ± 0.4	0.7 ± 0.1
150	1.6 ± 0.2	2.7 ± 0.7	0.5 ± 0.1

Table 2

Pharmacokinetic estimates of RD-2, RD-4 and BT93(2,2) administered i.m. to rats

Parameter	Dimension	RD-2 36.0 mg/kg b.w. (n = 5)	RD-4 36.0 mg/kg b.w. (n = 5)	BT93(2,2) 27.0 mg/kg b.w. (n = 5)
k_A	min^{-1}	0.12	0.07	0.32
k_B	min^{-1}	2.6	2.4	3.74
$t_{1/2\ (beta)}$	min^{-1}	57.0	92.8	21.7
MRT	min^{-1}	90.1	135.9	38.1
t_{max}	min^{-1}	30.0	45.0	20.0
C_{max}	μg/mL	9.5	11.4	29.4
V_d	mL	2992	3216	966
Plasma Cl	mL/min.kg	33.2	23.7	25.3
AUC(total)	μg/min/mL	1084	1521	1066

The data obtained for the plasma clearance show that substances (RD-2, RD-4) pass quickly from blood into the organs. The seemingly large volume of distribution of RD-2 and RD-4, mean that they are more concentrated in extravascular tissue.

The therapeutic effective dose of H-oximes was claimed to be 4 μg/ml (5) and was retained with RD-2 and RD-4 for more than 2 hours after i.m. rout of administration. The slow rate of absorption, distribution and elimination of RD-2 and RD-4 give some explanation of its better prophylactic effectiveness in OPC intoxication (3).

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