VARYING INTENSITY OF THE M- AND N-EFFECTS IN POISONING WITH DIFFERENT ANTICHOLINESTERASE AGENTS

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It is accepted that a vast number of compounds, which share the basic property of being able to inactivate cholinesterase reversibly or irreversibly, are assigned to one group and termed anticholinesterase agents. The name of this group arose from the concept that the compounds that belonged to it all have the same mechanism of action, and it implies only quantitative differences in the effects of these agents, as the reason for greater or lesser anticholinesterase activity. Meanwhile, a number of authors have established rather substantial qualitative differences in the effects of these so-called anticholinesterase agents. Thus, proserine suppresses strychnine spasms in animals, while eserine facilitates them [21]. Proserine causes bronchospasm in cats primarily through excitation of the vagal ganglia, while armin acts on the cholinoreactive systems of the bronchi [3]. Phosphacol and tetraethylpyrophosphate lead to the death of animals, basically by producing a neuro-muscular block, while diisopropylfluorophosphate depresses the respiratory center [9]. There are also substantial differences in the antagonism of anticholinesterase agents with M- and N-cholinolytics. However, in the respective works [5, 8, 18, 22], the study of antagonism with cholinolytics was limited to 2-3 anticholinesterase agents.

In this work, we carried out a comparison of the effectiveness of atropine under conditions of poisoning with 6 compounds belonging to the group of anticholinesterase agents.

EXPERIMENTAL METHOD

The investigation was performed on 860 male mice, weighing 18-20 grams. Using atropine in dosages of 0.5 and 50.0 mg per kg of body weight, we determined its ability to prevent death of the animals subsequent to their injection with anticholinesterase compounds in dosages of one or several times the LD_{90}. All the compounds were injected subcutaneously; the atropine was given 10 minutes before the respective anticholinesterase agent. Atropine, as we know, is one of the most active and selective M-cholinolytics, and one of the most frequently used antidotes against intoxication with either reversible or irreversible cholinesterase inhibitors. The minimum centrally acting dose for mice is 0.5 mg/kg [1], and the dose of 50.0 mg/kg is the maximum non-toxic dose [4].

EXPERIMENTAL RESULTS

The results obtained are presented in the table, from which it follows that the effectiveness of atropine as an antidote is rather different for poisoning with the different anticholinesterase agents. While atropine did not manifest any sort of protective action, in either of the test dosages, against the poisoning with pyrophos, even when the mice were given only one LD_{90}, in the case of eserine poisoning the atropine, in a dose of 0.5 mg/kg, decreased the death rate of the animals with injection of three times the LD_{90}, and in a dose of 50.0 mg/kg, atropine decreased the lethalness of four times the LD_{90} of eserine. For a more graphic comparison of the effectiveness of atropine against poisoning with the different anticholinesterase agents, we expressed it in arbitrary units, designating the number of LD_{90}'s of each of the anticholinesterase agents at which atropine, both in the low and high doses (0.5 and 50.0 mg/kg), would no longer manifest a protective action. It was more convenient to assess the total effectiveness of atropine (in both doses) by multiplying the coefficients of effectiveness. In this case, the whole scale of coefficients is extended, and the differences in the antagonism of atropine with the different representatives of anticholinesterase agents

The Mortality of Mice Poisoned with Anticholinesterase Agents Under Conditions of Preliminary (by 10 minutes) Atropine Injection (Doses Presented in Milligrams per Kg of Body Weight)

Index	Pyrophos $LD_{90}=1.25$			Mercaptophos $LD_{90}=7.25$			Phosphacol $LD_{90}=0.74$			Proserine $LD_{90}=0.53$			Armin $LD_{90}=0.58$			Eserine $LD_{90}=1.10$		
Dose of atropine	0	0.5	50	0	0.5	50	0	0.5	50	0	0.5	50	0	0.5	50	0	0.5	50
Dose of anticholinesterase agent:																		
$LD_{90}\times1$	90	90	85	90	100	45	90	90	0	90	32	9	90	50	0	90	0	0
M	7	10	8	5		11	7	10		4	7	4	1	11		7		
$LD_{90}\times2$	—	—	—	—	—	100	—	—	70	—	100	100	—	90	30	—	30	0
M	—	—	—	—	—	—	—	—	15	—	—	—	—	10	15	—	15	—
$LD_{90}\times3$	—	—	—	—	—	—	—	—	100	—	—	—	—	—	38	—	70	0
M									—						9		15	—
$LD_{90}\times4$	—	—	—	—	—	—	—	—	—	—	—	—	—	—	60	—	100	50
M															16			17
$LD_{90}\times5$	—	—	—	—	—	—	—	—	—	—	—	—	—	—	90	—	—	80
M															10			13
Relative effectiveness of atropine		1	1		1	2		1	3		2	2		2	5		4	5
		1			2			3			4			10			20	

becomes more pronounced. As a result of this scheme, we obtained the following relative indices for the effectiveness of atropine: with intoxication by pyrophos – 1, mercaptophos – 2, phosphacol – 3, proserine – 4, armin – 10, eserine – 20. According to the obtained indices (see the last line of the table), all the compounds tested can be divided into two groups. Pyrophos, mercaptophos, phosphacol and proserine belong to one of them – anticholinesterase substances which cause a poisoning that is unaffected or slightly affected by atropine, while armin and eserine belong to the other – against which atropine is a manifest antagonist.

Such a significant difference in atropine effectiveness associated with poisoning by equitoxic doses of different anticholinesterase agents is not compatible with the concept of an exclusively anticholinesterase action by the substances of this group. These differences are too great to be explained by certain variations in the sensitivity of cholinesterase, related to different cholinoreactive systems, to the inhibitors [13, 16], especially since even in one system the acting strength of the substances was not proportional to the degree of cholinesterase inhibition caused by them [11]. This fact, as well as the data of a number of authors on the absence of a parallel relationship between toxicity and activity of the anticholinesterase agents [7, 10], compel the conclusion that the reason for the differences in the effects of these compounds is their capacity (or perhaps the capacity of certain of them) to exert not only an anticholinesterase, but also a non-anticholinesterase, action. Since the most probable variant of these substances' non-anticholinesterase action is their ability to elevate the sensitivity of cholinoreactive systems to actylcholine [2, 12], the difference in the effects of the anticholinesterase agents might be caused by the fact that some of them sensitize predominantly the M-cholinoreactive systems, while the others – the N-cholinoreactive systems. This hypothesis [6] is supported by the work of Mason [17], who showed that proserine sensitizes the sympathetic ganglia to nicotine, while eserine does not possess this property. It must be postulated that certain qualitative peculiarities in the effects of the anticholinesterase agents may also be caused by a difference in the intensity of their presynaptic action [15, 19], and with the use of very large doses – by a difference in the intensity of cholinomimetic action of these agents [14].

Despite the impossibility, at this time, of drawing a final conclusion as to the reason for the differences in effects between the individual representatives of the so-called anticholinesterase agents, it is beyond doubt that these differences depend on varying participation of the M- and N-cholinoreactive systems during their action. It may be postulated that of the compounds tested, pyrophos and mercaptophos, and also, though to a lesser degree, phosphacol and proserine, cause excitation predominantly of the N-cholinoreactive systems, and thus, poisoning by these compounds is poorly prevented, or not at all prevented, by atropine. At the same time, armin and eserine cause excitation predominantly of the M-cholinoreactive systems, and atropine is thus a very effective antidote for poisoning by these agents.

SUMMARY

As it was seen from the experiments on mice, atropine was a very effective antidote in eserine and armine poisoning but its efficacy was low in pyrophos, mercaptophos, phosphacol and proserine poisoning. It is supposed that these differences were caused by the preponderant excitation of the M-cholinoreactive body systems in poisoning with the agents of the first group and a preponderant excitation of the N-cholinoreactive body systems in poisoning with the substances belonging to the second group.

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