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SHORT COMMUNICATION

Comparative Evaluation of Carbamates as Prophylactic Agents against Organophosphate Intoxication in Rats

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ABSTRACT

Investigates the effects of two well-known carbamates, physostigmine and pyridostigmine against organophosphorous compound and nerve gas toxicity. Physostigmine pretreatment for 30 min enhanced the survival time of rats against DFP intoxication whereas it did not have any effect with sarin poisoning. However, pyridostigmine pretreatment did not produce any significant effect on survival time either against DFP or sarin intoxication. Treatment with atropine along with carbamates further enhanced significantly the survival time against DFP poisoning.

1. INTRODUCTION

The prophylaxis with physostigmine and atropine varies in effectiveness in different animal species[1]. Physostigmine has a short duration of action and is known to cross the blood-brain barrier in rats[2] and dogs[3]. Whereas, pyridostigmine has a longer duration of action and cannot cross the blood-brain barrier[4].

In the present investigation, the effects of two well-known carbamates, physostigmine and pyridostigmine, have been compared as prophylactic agents against organophosphorous compound (OPC) and nerve gas toxicity by means of survival time measurements.

2. MATERIALS AND METHODS

Male albino rats of Wistar strain (body weight 125+10 g), fed on Gold Mohur laboratory animal feed at the rate of 17 g per rat per day, were divided into five groups consisting of six subgroups each. There were five animals in each subgroup. Group I was the control in which animals were administered 2, 4 and 8 LD_{50} doses of diisopropyl phosphorofluoridate (DFP) (subgroups 1-3) and methyl isopropyl phosphonofluoridate (sarin), (subgroups 4-6). The survival times were measured or observed up to 24 hr in each case. For the measurement of survival times, the time of administration of DFP or sarin was considered as zero time. Fresh aqueous solutions of DFP (LD_{50} 3.3 mg/kg, sc) and sarin (LD_{50} 203.4 μg/kg, sc) were prepared each time before administration. The purity of DFP and sarin used were established by IR spectroscopic analysis.

A maximum sign-free dose[5,6] of an aqueous solution of physostigmine and pyridostigmine (0.1 mg/kg, im) were administered to each animal 30 min prior to the challenge dose of DFP or sarin in their respective subgroups in groups II and III and their survival times were noted.

To each of the animals of groups IV and V of Table 1, an additional dose of atropine (10 mg/kg, ip), prepared in distilled water, was administered within 30 s of OPC treatment, with other details remaining exactly the same as described for groups II and III.

3. RESULTS AND DISCUSSION

Gordon, *et al*[6], on the basis of studies of protection of animals against poisoning with OPCs by carbamate

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Table 1 Effect of treatment with physostigmine, pyridostigmine and atropine on survival time of rats intoxicated with DFP and sarin

Group	Treatment	Survival time (min)					
		DFP (mg/kg)			Sarin (mg/kg)		
		6.6 ($2LD_{50}$)	13.2 ($4LD_{50}$)	26.4 ($8LD_{50}$)	0.406 ($2LD_{50}$)	0.812 ($4LD_{50}$)	1.624 ($8LD_{50}$)
I.	Nil	47.6±3.70	25.0±2.60	14.2±0.38	6.6±0.50	5.4±0.25	3.2±0.11
II.	Physostigmine	>24 hr	>24 hr	25.8±0.68	7.8±1.20	5.4±0.25	4.6±13
III.	Pyridostigmine	16.4±0.50	9.0±0.45	8.0±0.45	5.4±0.25	4.6±0.25	2.8±0.22
IV.	Physostigmine + atropine	>24 hr	>24 hr	>24 hr	4.3±0.19	4.4±0.25	4.4±0.12
V.	Pyridostigmine + atropine	>24 hr	>24 hr	>24 hr	4.2±0.12	4.5±0.22	4.2±0·12

pretreatment, found that the dose of carbamate is not critical; the protection being essentially constant for doses ranging from 0.5 to 4 times the maximum sign-free dose.

In the present study, group I in Table 1, shows that in all the doses tested (2, 4 and 8 LD_{50}), the survival times are more against DFP challenge than against sarin, and followed a reciprocal relationship with concentration. It is not surprising, as the sarin is 16.2 times more toxic than DFP as calculated from their LD_{50} values.

In group II, when an additional drug physostigmine was administered 30 min prior to the challenge doses of OPCs, the survival times against DFP challenge, in all doses, were drastically increased ($P < 0.001$ as compared to the corresponding subgroups in control group I), because of the protective action of physostigmine on DFP toxicity. However, the same increase was not possible against sarin challenge, at these doses, probably due to quicker dealkylation or 'ageing' of enzyme-inhibitor complex, caused by greater toxicity of sarin[7].

In group III, under similar pretreatment with pyridostigmine followed by intoxication by OPCs, there was a significant decrease in survival times in all the doses ($P < 0.001$ for DFP and $P < 0.05$ for sarin as compared to corresponding subgroups in control group I). This indicates that under similar conditions pyridostigmine does not have as much protective action as physostigmine. Also, the doses of sarin/DFP seem to be too high for effective action of pyridostigmine.

In groups IV and V, when atropine, an additional cholionolytic and antimuscarinic agent, was used as an after-treatment drug against OPC poisoning along with respective carbamate pretreatment, the survival time figures increased greatly in case of DFP ($P < 0.001$ as compared to corresponding subgroups in control group I) but not in case of sarin challenge. The protective action of atropine against OPC toxicity has been widely studied[8].

Indeed, studies on rodents and non-human primates have shown that combination of pyridostigmine prophylaxis with atropine and pyridine-2-aldoxime methiodide (P-2AM) therapy can protect against several multiples of a normally lethal dose of *Soman*[6,7].

It is concluded from the present study, that physostigmine is a better prophylactic agent against intoxication by OPCs than pyridostigmine and may prove useful at times of chemical warfare.

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