INFLUENCE OF PRETREATMENT OF CARBAMATES ON DYNAMIC PULMONARY MECHANICS IN RATS EXPOSED TO SARIN AEROSOLS

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Abstract: The effect of pretreatment of two carbamates, pyridostigmine and physostigmine on dynamic pulmonary mechanics has been studied in rats exposed to sarin aerosols. Sign-free dose of pyridostigmine (0.075 mg/kg, i.m.) or physostigmine (0.1 mg/kg, i.m.) did not significantly alter the parameters of the dynamic pulmonary mechanics 20 min after treatment. However, sarin (51.2 mg/m³, for 15 min) depressed the respiratory rate, air flow and minute volume and enhanced the transthoracic pressure and tidal volume. Pretreatment with carbamates 20 min prior to sarin exposure significantly modified or counteracted the above induced changes. It is concluded that the protective effect of carbamates is mainly due to the correction of respiratory changes caused by sarin aerosols in rats.

Key words: sarin carbamates dynamic pulmonary mechanics

INTRODUCTION

Carbamates are reversible inhibitors of cholinesterase enzyme and have been proved to be effective prophylactic agents against organophosphate intoxication (1-3). The prophylactic efficacy of two carbamates, physostigmine and pyridostigmine, have been established against parenterally administered organophosphorus compounds (4-6). Inhalation is one of the major route of entry of organophosphorus compounds into the body and through this route organophosphorus compounds as vapour or aerosol may interact directly or indirectly with the receptors or enzymes in the pulmonary system and may alter the dynamic pulmonary mechanics. Since reports on the efficacy of carbamates on changes in dynamic pulmonary mechanics caused by organophosphorus nerve agents are sparse, an attempt has been made to investigate the influence of pretreatment of carbamates on dynamic pulmonary mechanics in rats exposed to sarin aerosols.

METHODS

Adult male albino rats of Wistar strain weighing 160-180 gm were used in the present study. They are provided food and water ad libitum except overnight fasting before their use in the experiments. The animals were anaesthetized with urethane (1.6 gm/kg, i.p.) and dissected for the placement of tracheal cannula. Oesophageal catheter was inserted in the oesophagus upto thorax. The animals were mounted in plethysmograph and the parameters of dynamic pulmonary mechanics viz. air flow, tidal volume, minute volume, air way resistance, dynamic compliance, respiratory rates and transthoracic pressure were recorded at every 3 min interval on data logger of Pulmonary Mechanics Analyser (Model-6, Programme-1, Buxco Electronics, West Germany). After stabilization (30 min) the animals were exposed to sarin (isopropyl methyl phosphonofluoridate, 97% pure as checked by chromatographic analysis) aerosol (51.2% mg/m³, nominal concentration) for 15 min as described earlier (15) and again all the parameters were recorded for 20 min. Ninety percent of the particles of the generated aerosols were within the respirable range (<3.0 µ diameter) as monitored by Royco Particle Monitor (Model 225), USA. In another set of experiment, the animals were injected with sign-free dose of pyridostigmine (0.075 mg/kg, i.m.) (4) obtained from Roche, F. Hoffman - LaRoche & Co. Ltd.
Switzerland or physostigmine (0.1 mg/kg, i.m.) (2) purchased from Sigma Chemical Co. USA and all the parameters were recorded upto 20 min. Thereafter these animals were exposed to sarin aerosols for 15 min and combined effects were recorded for 20 min. The control animals were injected equal volume of saline, exposed to fresh filtered air under similar conditions and recordings were made for 20 min. The data were analysed statistically using Student’s 't' test.

RESULTS

The effect of pyridostigmine or physostigmine alone, sarin aerosol alone, pretreatment with pyridostigmine or physostigmine followed by sarin exposure on the dynamic pulmonary mechanics are depicted in Table I. The values of air flow, transthoracic pressure, tidal volume, compliance, air way - resistance, minute volume and respiratory rate in control animals are 3.34±0.30 ml/sec, 2.85±0.20 cm. of water, 0.78±0.10 ml, 0.48±0.05 ml/cm of water, 0.53±0.10 cm of water/ml/sec, 67.50±5.50 ml/min and 88.40±6.60 respiration/min respectively. Maximum sign free doses of pyridostigmine or physostigmine alone at 20 min did not significantly alter the parameters of pulmonary dynamic mechanics. However, animals were exposed to sarin aerosols for 15 min showed, decrease in air flow, minute volume, and respiratory rate (10.7, 25.5 and 30.2%, respectively) and elevation in transthoracic pressure (30.1%) and tidal volume (12.8%). Pretreatment with either pyridostigmine or physostigmine protected against sarin induced depression in air flow, minute volume and respiratory rate and the augmentation in transthoracic pressure.

DISCUSSION

Sarin being organophosphate compound may interact with the cholinergic receptors of the respiratory tract (7, 8) besides inhibiting cholinesterase as reported in the case of other organophosphorus compounds (9, 10). Bronchoconstriction and respiratory depression or failure precede death in organophosphate intoxication (11, 12). However, unlike other organophosphorus compounds sarin when administered subcutaneously failed to cause bronchoconstriction in

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<th>Table I: Effect of pyridostigmine or physostigmine pretreatment on pulmonary dynamic mechanics in rats exposed to sarin aerosol. Each value represents mean ± S.E. of five animals.</th>
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<td><strong>Groups</strong></td>
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The units of air flow, transthoracic pressure (Press.), Tidal volume (T.V.), Compliance, Air way-resistance, Minute volume (Min Vol) and Respiratory rate (Resp. rate) are expressed as ml/sec, cm of water, ml, ml/cm of water, cm of water/ml/sec, ml/min and respiration/min respectively.

a = P<0.05 as compared to control group; b = P<0.02 as compared to control group; c = P<0.01 as compared to control group; d = P<0.05 as compared to sarin treated group; e = P<0.023 as compared to sarin treated group.
mice (13). In the present study sarin exposure to rats failed to increase the air way-resistance (Table I) which is in agreement with the earlier finding (13). The significant increase in transthoracic pressure may be due to central involvement, because sarin inhalation already depressed the respiratory rate and decreased the air flow (Table I), and these changes should have caused a fall in blood pH and thereby stimulation of chemoreceptors, and reflex stimulation of respiration (14). On the contrary, in our study the respiratory rate has significantly decreased. Nevertheless, the involvement of CNS can not be ignored as the tidal volume has increased (Table I) which suggests that the system tried to compensate the decrease in respiratory rate by elevating transthoracic pressure to increase the depth of respiration. It seems reasonable to state that the elasticity and recoiling properties of the lungs remained unaffected as the dynamic compliance did not show any change. The changes induced by sarin in dynamic pulmonary mechanics which may be by its direct interaction with the cholinergic receptors or as a consequence of ChE inhibition. However, our previous studies have shown that pulmonary ChE inhibition and survival time were not well correlated in rats pretreated with carbamates and exposed to sarin aerosol (15). However, interaction of carbamates with acetylcholine receptor ionic channel complex has been suggested by Albuquerque et al (16). It is concluded that the protection offered by carbamates pretreatment may be more attributed to central effects rather than to the local effects.

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REFERENCES