Drug Development Research 24:343–353 (1991)

Subacute Toxicity of Aldicarb: Prevention and Treatment With Memantine and Atropine

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ABSTRACT

Gupta, R.C., and W.L. Kadel: Subacute toxicity of aldicarb: Prevention and treatment with memantine and atropine. Drug Dev. Res. **24**:343–353, 1991.

Daily administration (i.p.) of aldicarb in male Sprague-Dawley rats at various dosage levels for 21 days revealed 1) 0.1 mg/kg, nontoxic dose; 2) 0.2 mg/kg, moderately toxic dose; and 3) 0.4 mg/kg, severely toxic dose. Inhibition of acetylcholinesterase (AChE) in discrete brain regions and diaphragm muscle was dose dependent. Toxic signs were predominantly peripheral even though AChE inhibition was significantly higher in the brain (except striatum). Besides AChE inhibition, marked inactivation of carboxylesterases (false targets) was observed, suggesting a protective mechanism especially against low dosage by reducing free concentration of aldicarb. After 30 min following the 7th, 14th, or 21st dose of aldicarb, the degree of inhibition of esterase(s) remained the same, and consequently no tolerance developed to aldicarb. On day 21, administration of memantine HCl (18 mg/kg, i.p.) and atropine sulfate (16 mg/kg, i.p.) 30 min and 15 min, respectively, prior to aldicarb (0.4 mg/kg) injection provided complete protection. Therapeutic administration of these antidotes completely reversed the clinical manifestations of intoxication. The present findings indicated that memantine provided protection and reversal of AChE from inhibition in addition to reversible blockage of hyperneuromuscular activity.

Key words: anticholinesterase poisoning, antidotal treatment, acetylcholinesterase, carboxylesterase

Received final version September 3, 1991; accepted September 4, 1991.

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This work was presented in part at the Annual Meeting of Federation of American Societies for Experimental Biology, April 21–25, 1991, Atlanta, GA.

INTRODUCTION

During the last decade, the use of carbamate insecticides has increased tremendously over the use of organophosphate (OP) insecticides, because carbamates are considered comparatively safe. Although both classes of insecticides share the common mechanism of action, i.e., inhibition of acetylcholinesterase (AChE) at the synapses and neuromuscular junctions [Aldridge and Davison, 1952; Wilson et al., 1960; Cohen and Oosterban, 1963], the inhibition of AChE by carbamates (including aldicarb) is reversible [Casida, 1963]. To date, aldicarb has the highest mammalian toxicity of any pesticide registered for use by the U.S. Environmental Protection Agency [Dean et al., 1990]. In recent years, several outbreaks of aldicarb poisoning both in animals [Spierenburg et al., 1985; Dorman et al., 1990; Kerr et al., 1991] and in humans [Goes et al., 1980; Lee and Ransdell, 1984; Parks et al., 1987; Goldman et al., 1990] have been recorded which might draw national attention about continuation of its use.

In addition to malicious cases, contaminated food and water are reported to be the most common sources of aldicarb poisoning outbreaks [Zake et al., 1982; McWilliams, 1984; MMWR, 1986; Goldman et al., 1990]. Thus, chances of repeated exposure to aldicarb are greater than a single exposure.

To our knowledge, no systematic investigations on subacute toxicity of aldicarb have been conducted and no serious attempts have been made to establish a complete antidotal therapy against subacute aldicarb intoxication. Antidotal therapy with oximes against carbamates poisoning is of no advantage or in some cases it is contraindicated [Hayes, 1982; Murphy, 1985]. Therefore, the only choice of antidote rests with atropine sulfate. Atropine sulfate alone provides only partial protection, i.e., protection/reversal of muscarinic effects (hypersecretions), whereas the induced nicotinic effects such as muscle fasiculations, convulsions, and seizures remain unprotected. The mechanism of action of MEM, compared to ATS, in antagonizing the anticholinesterase poisoning seems more complex since MEM exerts multiple pharmacological actions. In recent studies, we demonstrated that a combined antidotal treatment with memantine (MEM) and atropine (ATS) afforded complete protection against acute toxicity of aldicarb and also reversed the toxicity when given therapeutically [Gupta and Kadel, 1991].

This investigation was undertaken with two objectives: 1) to study the profile of clinical and biochemical changes by subacute aldicarb toxicity; and 2) to evaluate the prophylactic and therapeutic potential of MEM and ATS as antidotes.

MATERIALS AND METHODS

Chemicals

Aldicarb (2-methyl-2-[methylthio] propionaldehyde]-0-[methylcarbamoyl] oxime, technical grade (98%), in a powder form was purchased from Chem Service Inc. (West Chester, PA). Atropine sulfate (ATS), acetylthiocholine iodide, tetraisopropyl-pyrophosphoramide (iso-OMPA), tributyrin (C4:0), and hydroxylamine HCl were purchased from Sigma Chemical Co. (St. Louis, MO). Memantine HCl, (1,3-dimethyl-5-aminoadamantane, MEM) was received as a gift from Merz & Co. (Frankfurt, FRG). All other chemicals of highest purity available were purchased from Fisher Scientific (Fair Lawn, NJ). For additional details see Gupta and Kadel [1991].

Animals

Male Sprague-Dawley rats weighing between 180 and 200 g were purchased from S.D. Sasco (St. Louis, MO) and were acclimatized to our standard laboratory conditions for 7–10 days before being used in these experiments. For other details see Gupta and Kadel [1991].

TABLE 1. Dosage Schedule of Antidotal Treatment (MEM and/or ATS) in Rats Subacutely Intoxicated for 21 Days With Aldicarb (0.4 mg/kg, i.p./day, for 21 days)*

Treatment	Group	Toxicant/Antidote(s)	Schedule of antidotal treatment
Control	I	DMSO	None
Intoxication	II	Aldicarb	None
Prophylactic treatment	III	MEM + Aldicarb	MEM 30 min before Aldicarb
	IV	ATS + Aldicarb	ATS 15 min before Aldicarb
	V	MEM + ATS + Aldicarb	MEM 30 min and ATS 15 min before Aldicarb
Therapeutic treatment	VI	Aldicarb + MEM	MEM 5–7 min after Aldicarb
	VII	Aldicarb + ATS	ATS 5–7 min after Aldicarb
	VIII	Aldicarb + MEM + ATS	MEM and ATS 5–7 min after Aldicarb

*Drugs and dosages: Memantine HCl (MEM, 18 mg/kg, i.p.); atropine sulfate (ATS, 16 mg/kg, i.p.) Rats were given the pre-treatment or post-treatment with MEM and/or ATS on day 21, the last day of aldicarb exposure. Sacrifice time: Rats were sacrificed on day 21, 30 min after aldicarb administration.

Experimental Protocol

This investigation was based on two sets of experiments.

Subacute toxicity of aldicarb. Rats, five in each group, were dosed daily with 0.1, 0.2, or 0.4 mg aldicarb/kg, i.p., for 7, 14, or 21 days. Rats were weighed daily and doses were adjusted accordingly. They were closely observed for obvious toxic signs following each dose. Control group rats received DMSO i.p. in an equal volume to the test group (100 μl/100 g rat wt). The selection of doses was made on the basis of preliminary findings (data not shown) and a detailed acute toxicity study [Gupta and Kadel, 1991]. In the acute study, following various doses of aldicarb, the maximal inhibition of AChE and CarbE was noted at 30 min, which was the time when peak severity was evident [Gupta and Kadel, 1991]. Based on these findings, in the subacute study, rats receiving daily doses of aldicarb were terminated 30 min after the 7th, 14th, or 21st dose to harvest tissue samples for biochemical assays.

Antidotal treatment. Details of the dosage schedule for antidotal treatment in rats subacutely intoxicated with aldicarb (0.4 mg/kg, i.p./day, for 21 days) are presented in Table 1. The rationale for the selection of MEM and ATS doses is discussed elsewhere [Patterson et al., 1988; Gupta and Kadel, 1989b, 1990b].

Tissue Collection and Preparation

On day 0, 7, 14, or 21, rats were terminated by guillotine, and tissues (brain, heart, liver, and hemidiaphragm) were excised quickly. Brains were further dissected into four discrete regions (cortex, stem, striatum, and hippocampus). Serum samples were harvested following centrifugation (3,000 rpm for 30 min) of clotted blood within 1 hr of sacrifice. All samples were stored at −70°C and were processed for biochemical analyses within 24 hr. For details regarding tissue preparation, see our recent report [Gupta and Kadel, 1991].

Assay of Acetylcholinesterase Activity (AChE, EC 3.1.1.7.)

AChE activity was assayed according to the method of Hestrin [1950] with some necessary modifications [Gupta and Dettbarn, 1987a; Gupta and Kadel, 1989a, 1991] (Table 3). The enzyme activity was calculated as μmole acetylthiocholine iodide hydrolyzed/g tissue/hr and expressed in terms of percentage remaining activity compared to controls (100%).

Assay of Carboxylesterase Activity (CarbE, Tributyrinase; EC 3.1.1.1.)

The CarbE activity was also assayed according to the method of Hestrin [1950] with some necessary modifications [Gupta et al., 1985; Gupta and Dettbarn, 1987a] (Table 3). The

TABLE 2. Antidotal Effectiveness of MEM (18 mg/kg, i.p.) and/or ATS (16 mg/kg, i.p.) in Rats Subacutely Intoxicated With Aldicarb (0.4 mg/kg, i.p./day, for 21 Days)*

		Clinical signs				
		Muscarinic		Nicotinic		
	Treatment	Salivation	Lacrimation	Tremors	Fasciculations	Convulsions
Control	DMSO	None	None	None	None	None
Intoxication	Aldicarb	Excessive	Excessive	Severe	Severe	Severe
Antidotal effects of MEM and/or ATS						
Prophylaxis	MEM + Aldicarb	+	+	+ + + +	+ + + +	+ + + +
	ATS + Aldicarb	+ + + +	+ + + +	+	−	−
	MEM + ATS + Aldicarb	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
Therapy	Aldicarb + MEM	+	+	+ + + +	+ + + +	+ + + +
	Aldicarb + ATS	+ + + +	+ + + +	+	−	−
	Aldicarb + MEM + ATS	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +

*Antidotal effectiveness ranked as: −, not effective, +, slightly effective; + +, moderately effective, + + +, very effective, + + + +, highly effective.

enzyme activity was calculated as μmole tributyrin hydrolyzed/g tissue/hr and expressed in terms of percentage remaining activity compared to controls (100%).

Statistical Analyses

Data were statistically evaluated using analysis of variance (ANOVA) coupled with Duncan's new multiple range test [Steel and Torrie, 1980].

RESULTS

Daily administration of aldicarb for 7, 14, or 21 days revealed 0.1 mg/kg, no obvious toxicity; 0.2 mg/kg, moderate toxicity; and 0.4 mg/kg, severe toxicity. Following each daily dose of aldicarb (0.2 mg/kg or 0.4 mg/kg), the onset of anticholinesterase signs appeared within 5–7 min and, with increasing propensity, the maximal severity was evident within 15–30 min. Therefore, animals receiving daily aldicarb treatment exhibited both toxicity (for 60–90 min) and complete recovery (within 2–3 hr) every day. In spite of daily exposure, at no time did animals show an increase in severity or tolerance development to the toxicity (data not shown). Animals exposed daily to DMSO (control) or to aldicarb at a low dose (0.1 mg/kg) did not show any adverse effects. The body weight gain in aldicarb-treated rats remained significantly indifferent ($P > .01$) compared to controls treated with DMSO (data not shown).

The degree of AChE inhibition in brain regions and in muscles was dose-dependent, although not linear, and remained of the same order throughout the exposure period (Table 4). With lower dosage of aldicarb (0.1 mg/kg), among brain regions, only the cortex and stem indicated significant ($P < .01$) inhibition of AChE. AChE activity was maximally inhibited in cortex and least inhibited in striatum following either dosage of aldicarb (Table 4).

The pattern of CarbE inhibition by the aldicarb was similar to that of AChE Tables 4 and 5 in that the degree of inhibition was the same every day throughout the exposure period. A complete inhibition of CarbE activity in the serum, 80% in liver, and >50% in other tissues suggested a substantial nonspecific binding of aldicarb.

Pretreatment with MEM (18 mg/kg) in combination with ATS (16 mg/kg) provided complete protection against subacute aldicarb (0.4 mg/kg, i.p./day for 21 days) intoxication and also reversed the aldicarb-induced clinical signs when given therapeutically (Table 2). Pretreatment with MEM alone provided full protection against aldicarb-induced nicotinic

TABLE 3. Normal Values of Acetylcholinesterase (AChE) and Carboxylesterase (CarbE) Activities in Tissues of Rats*

Tissues	AChE activity (μmole acetylthiocholine/g/hr)	CarbE activity (μmole tributyrin/g/hr)
Brain regions		
Cortex	266 ± 8.8	68 ± 2.6
Stem	504 ± 10.7	68 ± 2.3
Striatum	1,596 ± 30.6	71 ± 1.5
Hippocampus	357 ± 11.0	72 ± 3.1
Muscles		
Diaphragm	99 ± 2.0	67 ± 2.0
Heart	42 ± 2.7	92 ± 2.9
Liver	N.A.	3,014 ± 6.0
Serum	N.A.	30 ± 2.0

*N.A. = not analyzed. Each value is the mean ± SE (n = 5).

TABLE 4. Time Course of Acetylcholinesterase Activity in Tissues of Rats Following Subacute Exposure to Aldicarb (0.1, 0.2, or 0.4 mg/kg, i.p./day, for 7, 14, and 21 Days)†

Tissues	Duration of exposure (days)	Acetylcholinesterase (percent remaining) activity (means ± SE; n = 5) 0.1 mg/kg/day	0.2 mg/kg/day	0.4 mg/kg/day
Brain cortex	7	71.1 ± 3.2	43.3 ± 1.8	18.9 ± 1.7
	14	64.0 ± 3.3	45.9 ± 3.9	18.9 ± 2.2
	21	71.2 ± 4.1	48.6 ± 1.7	19.8 ± 1.8
Stem	7	70.9 ± 2.2	55.2 ± 2.3	32.4 ± 1.8
	14	68.1 ± 1.4	57.6 ± 1.8	30.0 ± 2.3
	21	71.4 ± 1.3	55.2 ± 1.7	37.1 ± 1.6
Striatum	7	92.9 ± 1.9*	84.7 ± 1.3*	71.3 ± 1.4
	14	89.6 ± 1.1*	86.8 ± 2.1*	70.4 ± 1.5
	21	93.2 ± 1.3*	83.3 ± 1.9*	80.8 ± 2.2
Hippocampus	7	85.9 ± 2.7*	57.7 ± 2.5	36.2 ± 1.6
	14	83.9 ± 3.3*	51.0 ± 3.1	36.9 ± 1.5
	21	91.3 ± 1.6*	53.0 ± 2.2	39.6 ± 3.2
Diaphragm	7	64.6 ± 2.9	25.0 ± 3.0	12.9 ± 3.0
	14	59.7 ± 2.0	27.4 ± 3.0	15.3 ± 3.0
	21	58.1 ± 5.9	26.6 ± 3.5	15.3 ± 4.8
Heart	7	60.3 ± 4.8	32.1 ± 3.5	26.4 ± 5.3
	14	62.3 ± 2.3	34.9 ± 2.8	25.5 ± 7.6
	21	58.5 ± 4.6	34.0 ± 3.8	32.1 ± 3.5

†Rats were sacrificed 30 min after the last dosage of aldicarb. Values of acetylcholinesterase activity, determined as μmole acetylthiocholine iodide hydrolyzed/g tissue/hr, are presented as percent activity of controls (100%). Control values are shown in Table 3.
*Not statistically significantly different from controls ($P > .01$).

effects, while ATS alone provided full protection against muscarinic effects. Therapeutic administration of MEM or ATS alone antagonized the nicotinic and muscarinic effects correspondingly (Table 2). Neither MEM nor ATS produced any observable side effects. MEM

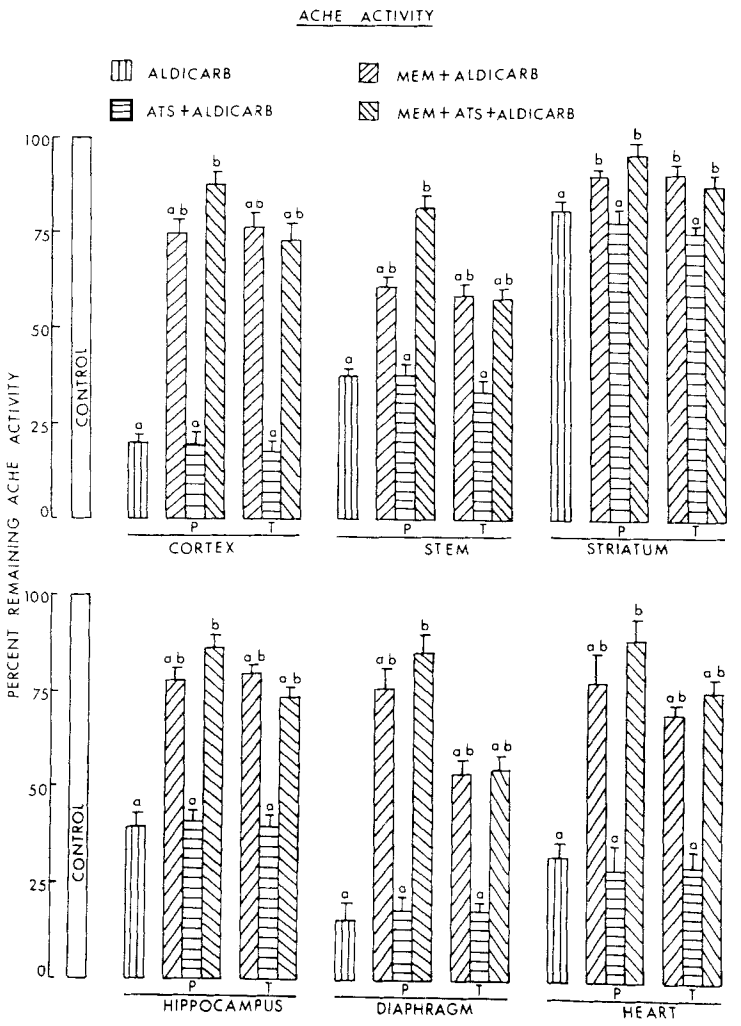

Fig. 1. Effects of MEM (18 mg/kg, i.p.) and/or ATS (16 mg/kg, i.p.), given prophylactically (P) or therapeutically (T), on AChE activity in the brain regions, diaphragm, and heart of the rats subacutely intoxicated with aldicarb (0.4 mg/kg, i.p./day for 21 days). Rats were sacrificed 30 min after aldicarb administration. Values are means ± SE presented as percent activity of controls (100%). For details see Materials and Methods. a = significant difference between controls and treated rats ($P < .01$). b = significant difference between aldicarb and aldicarb + antidote (MEM and/or ATS)-treated rats ($P < .01$).

alone or in combination with ATS had no effect on AChE or CarbE, but significantly attenuated the inhibitory effect of aldicarb (Figs. 1, 2).

DISCUSSION

The purpose of this investigation was to study the profile of subacute aldicarb intoxication and also to evaluate the prophylactic and therapeutic efficacy of MEM and ATS.

Despite daily administration of aldicarb for up to 21 days, animals showed toxic signs

TABLE 5. Time Course of Carboxylesterase Activity in Tissues and Serum of Rats Following Subacute Exposure to Aldicarb (0.1, 0.2, or 0.4 mg/kg i.p./day, for 7, 14, and 21 Days)†

	Duration of exposure (days)	Carboxylesterase (percent remaining) activity (means ± SEM, n = 5)		
		0.1 mg/kg /day	0.2 mg/kg /day	0.4 mg/kg /day
Brain cortex	7	78.4 ± 6.1	62.6 ± 3.4	43.0 ± 3.5
	14	73.7 ± 5.3	56.7 ± 3.3	37.2 ± 3.5
	21	74.4 ± 2.8	61.4 ± 3.0	40.7 ± 2.8
Stem	7	81.4 ± 3.2	67.4 ± 1.4	34.9 ± 3.7
	14	77.9 ± 3.5	66.3 ± 1.4	32.6 ± 3.5
	21	76.7 ± 2.8	59.8 ± 1.4	30.2 ± 2.8
Striatum	7	67.4 ± 3.1	39.3 ± 3.1	31.5 ± 3.3
	14	69.7 ± 3.8	44.3 ± 2.5	28.1 ± 3.8
	21	71.9 ± 2.7	42.0 ± 4.1	28.1 ± 3.1
Hippocampus	7	77.8 ± 3.1	45.6 ± 6.7	37.8 ± 3.8
	14	80.0 ± 5.4	44.2 ± 4.5	31.6 ± 1.8
	21	81.1 ± 5.4	43.1 ± 4.6	35.6 ± 4.5
Diaphragm	7	76.2 ± 5.4	50.2 ± 3.5	34.5 ± 4.4
	14	77.4 ± 5.0	51.2 ± 5.2	34.5 ± 2.9
	21	78.6 ± 5.5	48.6 ± 3.2	33.3 ± 3.6
Heart	7	86.2 ± 2.7*	60.7 ± 4.2	56.9 ± 3.2
	14	85.3 ± 2.1*	59.7 ± 2.1	49.1 ± 5.6
	21	87.1 ± 2.1*	58.9 ± 2.5	51.7 ± 5.3
Liver	7	53.8 ± 1.5	41.7 ± 1.5	20.4 ± 1.2
	14	52.6 ± 2.2	38.8 ± 3.8	18.5 ± 1.8
	21	56.7 ± 1.6	37.9 ± 2.4	22.0 ± 2.0
Serum	7	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	14	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	21	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

†Rats were sacrificed 30 min after the last dosage of aldicarb. Values of carboxylesterase activity, determined as μmole tributyrin hydrolyzed/g tissue or serum/hr, are presented as percent activity of controls (100%). Control values are shown in Table 3.
*Not statistically significantly different from controls ($P > .01$).

to the same degree after each dosage, and at no time was there any evidence of cumulative toxicity or development of tolerance to the aldicarb. Daily, animals exhibited complete recovery after a convalescence of 60–90 min following each dose (data not shown). The complete recovery of animals from intoxication, each day, was probably due to complete recovery of AChE from its reversible inhibition [Casida, 1963; Gupta and Kadel, 1991]. Throughout the exposure period, the degree of inhibition of AChE and CarbE at the time of peak severity, following each dosage, was found to be the same (Tables 4, 5). Therefore, the subacute exposure to aldicarb, at all dose levels tested, exhibited the same profile of clinical and biochemical changes as reported for its acute exposure [Gupta and Kadel, 1991]. In contrast, daily administration of diisopropylphosphorofluoridate (DFP), an irreversible AChE inhibitor, showed the development of tolerance to its toxicity by inducing de novo synthesis of AChE and CarbE, in addition to several other underlying mechanisms [Overstreet and Yamamura, 1978; Gupta and Dettbarn, 1986, 1987b; Thomsen and Wilson, 1988; Van Dongen and Wolthuis, 1989]. Repeated administration of DFP and other organophosphate compounds in equitoxic doses, i.e., doses similar to doses of aldicarb producing sublethal signs, produced death following the second or third dose indicating cummulative toxicity [Gupta et

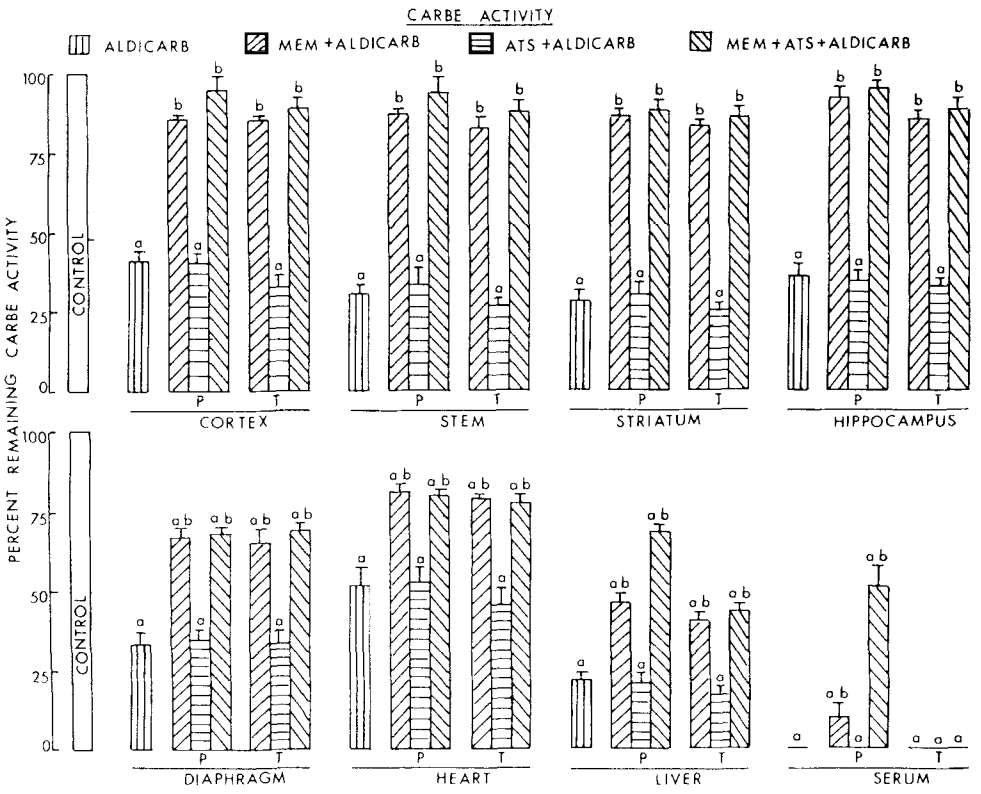

Fig. 2. Effects of MEM (18 mg/kg, i.p.) and/or ATS (16 mg/kg, i.p.), given prophylactically (P) or therapeutically (T), on CarbE activity in brain regions, diaphragm, heart, liver, and serum of the rats subacutely intoxicated with aldicarb (0.4 mg/kg, i.p./day for 21 days). Rats were sacrificed 30 min after aldicarb administration. Values are means ± SE presented as percent activity of controls (100%). For details see Figure 1 and Materials and Methods. a = significant difference between controls and treated rats ($P < .01$). b = significant difference between aldicarb and aldicarb + antidote (MEM and/or ATS)-treated rats ($P < .01$).

al., 1985, 1987]. The lack of tolerance development following repeated exposure to aldicarb might also be attributed to its strong immunosuppressive effects (Thomas et al., 1990; Dean et al., 1990).

Aldicarb showed remarkable brain regional selectivity for inhibition of AChE activity, i.e., striatal AChE was least affected (Table 4). Although the striatum had the lowest inhibition of AChE on a percentage basis, it normally had 3 to 5 times higher AChE activity and thus, in absolute terms might have the equal or greater inhibition of AChE activity. Brain regions with much lower AChE activity showed the highest percentage inhibition mainly because they contained lower numbers of binding sites. To our knowledge, this finding is in accordance only with VX, an OP nerve agent [Gupta et al., 1991], while in contrast to most carbamate and OP compounds [Gupta et al., 1986, 1987; Gupta and Kadel, 1989a, 1990a, 1991]. Whether there are regional differences in affinity for aldicarb in the AChE molecular forms remains to be seen.

The significant inactivation of CarbE activity with the lower dosage of aldicarb (0.1 mg/kg/day) suggests substantive nonspecific binding to non-AChE serine-containing enzymes. Nonspecific binding of aldicarb might have reduced its free concentration to a level insufficient

to produce the critical level (>70%) of AChE inactivation which is associated with apparent toxicity [Gupta et al., 1985; Gupta and Kadel, 1989a]. Therefore, CarbEs inhibition may provide the protective mechanism, especially when exposure is at low levels. The reasons for variations seen in the degree of CarbE inhibition in different tissues by aldicarb and other carbamate insecticides have been discussed in detail elsewhere [Gupta and Kadel, 1989a, 1990a, 1991]. It should be noted that aldicarb and related carbamates and organophosphate insecticides bind to nonspecific sites, and, therefore, their simultaneous exposure must be limited in order to avoid toxic synergism [Sterri, 1981; Dettbarn and Gupta, 1989; Gupta and Kadel, 1989a, 1990a].

Pretreatment or treatment with MEM and ATS was found equally effective against subacute aldicarb toxicity as reported recently for acute aldicarb or carbofuran toxicity [Gupta and Kadel, 1989b, 1991]. Therefore, it seems plausible that MEM might have antagonized the induced muscle fasciculations in subacute aldicarb toxicity by the same multiple mechanisms as discussed against acute aldicarb intoxication [Gupta and Kadel, 1991]. Briefly, MEM in combination with ATS may prevent or antagonize the aldicarb subacute toxicity by 1) protecting AChE or rapid reactivation from inhibition (Fig. 1), 2) direct effects to prevent neural hyperexcitability [McLean, 1987], 3) reversible neuromuscular transmission blockade [Masuo et al., 1986], and/or 4) muscarinic cholinolytic action of ATS.

It appears that MEM either prevents the aldicarb interaction with the AChE or reactivates the AChE, thereby not allowing accumulation of ACh. But unlike nicotinic effects, MEM did not protect muscarinic effects (Table 2), which suggests that a sufficient amount of accumulated ACh still remained unhydrolyzed to which muscarinic receptors showed comparatively greater sensitivity. Perhaps MEM lacks a direct effect on muscarinic receptors. Similar observations have also been reported with MEM against acute intoxication by carbofuran, methyl parathion, and aldicarb [Gupta and Kadel, 1989b, 1990b, 1991], and with 2-PAM against malathion [Gupta, 1984]. The blockage of nicotinic effects by MEM in subacute aldicarb intoxication might be attributed to blocking of nicotinic receptors through interaction with ACh receptor-ion channel complex [Masuo et al., 1986], and central muscle relaxation [Grossman and Jurna, 1977], thereby producing reversible neuromuscular blockade. In addition to protection of AChE, MEM also provided protection of CarbE (Fig. 2), which might have facilitated the bioelimination of aldicarb similar to that reported in acute intoxication by carbofuran, methyl parathion, or aldicarb [Gupta and Kadel, 1989b, 1990b, 1991].

Based on the results reported here and elsewhere, it is concluded that MEM in combination with ATS can prevent or antagonize the acute as well as subacute anticholinesterase poisoning due to carbamate or organophosphate insecticide(s).

ACKNOWLEDGMENTS

The authors thank Mr. Clay H. King for the preparation of this manuscript and Ms. Judy Craft for making the photographs.

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