Protective Effect of Ganglionic Blocking Agents on Traumatic Shock in the Rat.* (22211)

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The effectiveness of adrenergic blocking agents in reducing the mortality in rats subjected to traumatic shock has been described (1). Local anesthetics(2) and atropine (3,4), an anticholinergic agent, also have been reported to produce significant protection from mortality resulting from total body trauma in the rat. Since ganglionic blocking activity has been described as a property of both local anesthetics and anticholinergic agents(5,6,7), an appraisal of ganglionic blocking agents for the prevention of death due to trauma appeared justified. That ganglionic blocking agents of sufficient potency and duration of action significantly reduce the mortality associated with traumatic shock in the rat has been established in the present study.

Method. The method of inducing traumatic shock was that of tumbling in rotating drums, as described by Noble and Collip(8). The method was modified in that only one shelf was used per drum and the animals' feet were individually taped. White male Wistar strain rats weighing 300 to 500 g were used. The speed of the drums was set at 40 revolutions per minute and the total revolutions recorded on a mechanical counter activated by an electronic relay. Preliminary studies indicated that mortality was directly related to the total number of turns of the drums with a lethal trauma of 50% at 800 turns. Nine hundred turns was chosen as a standard trauma level in these experiments to assure a mortality of 50% or more. The average mortality of all untreated rats (192) reported here was 77.1%. Treated animals received drug injected intraperitoneally 15 or 30 minutes prior to drumming. The compounds were dissolved in 0.9% saline and the dosages administered as mg (base or cation)/kg. Following trauma the animals were observed continuously and times of death were recorded. Any animal dying during trauma or 15 minutes thereafter was considered an immediate death and a gross autopsy was performed. Any animal evidencing rupture of a major blood vessel or a viscus was discarded. All other animals dying in the ensuing 24-hour period were considered as delayed deaths. Animals alive at the end of 24 hours were considered as surviving indefinitely. One control rat was tested with each drug-treated rat. A total of 16 animals, constituting one experiment at one dose level, were subjected to the standard trauma on the same day. Although daily mortality in untreated groups of rats varied from 50 to 100%, the susceptibility to trauma was assumed to be comparable in each group of animals subjected to drumming in one experiment. The differences in mortality between treated and control animals in individual experiments were analyzed for significance by exact probabilities for a 2 x 2 contingency table obtained from 2 times the tabulated (½ P)'s from Mainland's table (9). The over-all analysis for significance of all dose levels of each compound causing a reduction in mortality and not showing evidence of drug toxicity was analyzed by the chi-square method corrected for continuity.

Results. Table I presents the results of treatment of rats prior to trauma with 4, 5, 6, 7-tetrachloro-2-(2-dimethylaminoethyl) -indolene bis-methochloride (chlorisondamine), 3-

* Statistical evaluation of results was performed by Joseph L. Ciminera, Department of Biometrics, Sharp & Dohme.

Chlorisondamine was kindly supplied by Dr. F. F. Yonkman, Ciba Pharmaceutical Products Inc., Summit, N. J. Pentolinium was obtained through the courtesy of Dr. J. Seifter, Wyeth Institute of Applied Biochemistry, Radnor, Pa. TEA was supplied through the courtesy of Dr. A. C. Bratton, Parke, Davis & Co., Detroit, Mich. Mecamylamine was made available through the kindness of Dr. K. Pfister, Chemical Division, Merck & Co. Inc., Rahway, N. J. Hexamethonium was prepared in the Department of Organic Chemistry, Sharp & Dohme.

TABLE I. Effects of Pretreatment with Ganglionic Blocking Agents on Traumatic Shock in the Rat.

Compound	Dose, mg/kg	Controls D/T	Controls %	Treated D/T	Treated %	% survival above controls	Significance (P) Individual	Significance (P) Over-all
Chlorisondamine*	1.0	6/8	75.0	3/8	37.5	37.5	N.S.	<.001
	2.5	8/8	100.	2/8	25.0	75.0	.007	
	5.0	"	100.	3/8	37.5	62.5	.0256	
	10.0	5/8	62.5	5/8	62.5	0	—	
Mecamylamine*	1.0	7/8	87.5	7/8	87.5	0	—	"
	2.5	4/8	50.0	3/8	37.5	12.5	N.S.	
	5.0	7/8	87.5	0/8	0	87.5	.0014	
	5.0	6/8	75.0	1/8	12.5	62.5	.0406	
	10.0	5/8	62.5	3/8	37.5	25.0	N.S.	
Pentolinium*	.5	5/8	62.5	1/8	12.5	50.0	N.S.	"
	1.0	6/8	75.0	"	12.5	62.5	.0406	
	2.5	8/8	100.	4/8	50.0	50.0	N.S.	
	5.0	5/8	62.5	0/8	0	62.5	.0128	
	5.0	7/8	87.5	3/8	37.5	50.0	N.S.	
	10.0	6/8	75.0	4/8	50.0	25.0	"	
Hexamethonium†	5.0	4/8	50.0	1/8	12.5	37.5	N.S.	<.01
	10.0	6/8	75.0	3/8	37.5	37.5	"	
	20.0	"	75.0	2/8	25.0	50.0	"	
	30.0	5/8	62.5	7/8	87.5	−25.0	—	
Tetraethylammonium†	5.0	6/8	75.0	7/8	87.5	−12.5	—	
	10.0	"	75.0	6/8	75.0	0	—	
	20.0	"	75.0	"	75.0	0	—	
	35.0	8/8	100.	8/8	100.	0	—	
	50.0	"	100.	"	100.	0	—	

* Injected 30 min. prior to trauma. † Injected 15 min. prior to trauma.
D/T = No. deaths/No. tested.

methylaminoisocamphane hydrochloride (mecamylamine), pentamethylene-1:5-bis-(1-methylpyrrolidinium bitartrate) (pentolinium), 1,6-bis-(tri-methylammonium)-hexane diiodide (hexamethonium), and tetraethylammonium chloride (TEA). The specificity of these agents for producing ganglionic blockade has been established(10-14).

Significant protection from mortality induced by trauma was observed with one or more dose levels in at least two experiments with chlorisondamine, mecamylamine and pentolinium. Hexamethonium and TEA failed to provide significant protection in any one experiment. In an over-all analysis of significance for all dose levels providing protection with no evidence of toxicity, significant protection also was apparent with hexamethonium. TEA failed to provide any protection, possibly because of its known evanescent effect(15,16).

The influence of pretreatment with ganglionic blocking agents on total, immediate, and delayed deaths from drum shock is presented in Table II. These represent the pooled experimental results from the individual experiments in which statistically significant protection was produced by chlorisondamine, mecamylamine and pentolinium. While by far the greatest protection from death was apparent in those animals dying in the delayed death group, 50% reduction in mortal-

TABLE II. Reduction in Immediate and Delayed Deaths by Protective Doses of Ganglionic Blocking Agents.

Procedure	No. of rats	Mortality: Total No.	Total %	Immediate deaths No.	Immediate deaths %	Delayed deaths No.	Delayed deaths %
Control	48	40	83.3	13	27.1	27	56.2
Treated	48	7	14.5	4	8.3	3	6.2
Reduction in mortality—%			68.8		18.8		50.0

TABLE III. Increased Mortality in the Immediate Death Group from Pretreatment with Toxic Doses of Ganglionic Blocking Agents.

Procedure	No. of rats	Mortality: Total No.	Total %	Immediate deaths No.	Immediate deaths %	Delayed deaths No.	Delayed deaths %
Control	56	44	78.6	10	17.8	34	60.8
Treated	56	43	76.7	31	55.3	12	21.4
± % change in mortality			−1.9		+37.5		−39.4

ity, a surprisingly significant ($P = <0.05$) reduction in mortality of 18.8% in the immediate death group also was observed.

Drug toxicity usually was evident in individual experiments from an increased mortality above the control group in those animals dying immediately, or by a decreased percentage of the treated animals surviving when the dosage range was increased, or both. Table III presents the pooled results from all individual experiments where drug toxicity was evident. A significant increase in the percentage of treated animals dying in the immediate period during or following trauma was apparent, although the difference in total mortality between treated and control rats was not significant. The decreased mortality in the delayed death group was not significant in that it represented a shift in deaths, or numbers of animals, to the immediate group.

Discussion. That pretreatment with ganglionic blocking agents produced significant protection from the mortality of drum trauma provides additional support for the observation that blockade of the sympathetic nervous system during physical assault prevents the sequence of pathologic events ultimately resulting in death(1). The role of the parasympathetic division is more difficult to assess, since the well characterized cholinergic blocking agents produce some degree of autonomic ganglionic blockade(6,7,15,17). The lack of a protective effect of atropine at lower dose ranges that effectively block the peripheral parasympathetic system indicates that postganglionic discharge of this division plays a less important part in the processes initiated by trauma. That atropine reduces mortality only when given in relatively large doses of 20 to 50 mg/kg(2,4) suggests that ganglionic blockade(6,7) was responsible for the observed protection. The protection observed from local anesthetics(2) may well, likewise, be the result of ganglionic blockade(5).

A critical dose range of the effective compounds was required to produce a significant degree of protection. Doses below the critical level provided insignificant or erratic protection. The higher dose levels tested caused a decreased protective effect due to addition of drug toxicity to the stress inflicted, even though such doses, in the absence of trauma, were below the lethal level. These observations have also been made with adrenergic blocking agents(1).

The finding that a significant reduction in mortality of those animals usually dying during trauma, or shortly thereafter, was achieved by pretreatment with ganglionic blocking agents indicates that common mechanisms may be involved in both early and delayed deaths due to trauma, or that the early deaths merely represent the more susceptible individuals in the test population. In contrast to this observation, an increase in the relative incidence of immediate deaths was noted with doses of adrenergic blocking agents that provided significant protection against drum shock(1).

The differences observed pertaining to the effects of drug treatment on early mortality between these and previous data(1) possibly are explainable on differences of duration of trauma. The duration of drumming in the studies presented was 23 minutes, as compared to 15 minutes of drum rotation (with two shelves per drum) as reported by Levy *et al.*(1).

Summary. 1. Significant protection from death due to drum shock in the rat has been demonstrated by intraperitoneal pretreatment

with the ganglionic blocking agents, chlorisondamine, mecamylamine, pentolinium and hexamethonium. 2. TEA failed to provide protection from mortality due to trauma. 3. Significant protective effects were demonstrable only at certain critical dose ranges. 4. The results provide added support to the observations that blockade of the sympathetic nervous system affords protection from the lethal effects of physical trauma.

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Renal Interstitial Pressure in Normal and in Anuric Man: Based on Wedged Renal Vein Pressure.* (22212)

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Knowledge of the interstitial pressure of kidneys would be of special interest in patients with acute anuria, as suggested by Peters(1) and Oliver, MacDowell and Tracy (2), that anuria is due to raised interstitial pressure caused by interstitial edema. However, this suggestion has never been substantiated by measurements in man. In dogs suffering from a renal lesion induced by clamping the renal artery for 3 to 4½ hours, the pressure recorded in a needle inserted in the renal tissue was within the normal range(3).

The method of assessing interstitial, or capillary, pressure in human tissues by wedging a cardiac catheter into small venules of an organ has been applied to lungs and liver, but never to kidneys. Such a technic is presented in this report. From the finding of a normal wedged renal vein pressure (WRVP) in acute anuria following shock it is concluded that the anuria in such cases is not caused by raised interstitial pressure.

Methods and material. With patients in the supine position a cardiac catheter No. 7-9 (in a boy of 7 yrs. No. 4) was passed under fluoroscopic guidance into a renal vein, most often the right. After entering the renal vein the catheter was advanced as far as possible into the kidney veins. When the catheter was properly wedged, pressure measurements were performed with a condenser manometer (4) connected with a cathode ray oscillograph and a photographic recorder. At beginning of

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