BAL and Testosterone Propionate in the Treatment of Mercuric Chloride Poisoning.* (17725)

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Acute toxic nephrosis still represents a therapeutic problem despite recent advances in therapy. BAL (2,3 dimercaptopropanol) has been shown to be a specific antidote for cases of this syndrome due to mercuric chloride. However, because of its own toxicity it will afford protection against only a certain lethal dose of the poison; experimental evidence indicates this is only a little less than twice the dose that is fatal for untreated animals(1). Previous studies have claimed that testosterone propionate by virtue of its renotrophic effect exerts a protective action when administered before(2) or shortly after (3) a given dose of mercuric chloride. It has also been claimed recently that testosterone may be effective in the treatment of the non-specific tubular damage of Asiatic cholera(4). In the investigation to be reported here the therapeutic effectiveness of testosterone in the acute toxic nephrosis of mercuric chloride poisoning was re-evaluated, and its use in conjunction with BAL was studied to determine if its renotrophic action had practical application in the treatment of tubular necrosis. The latter would be expected to be reflected by an increased survival rate of $HgCl_2$ poisoned animals treated with BAL and testosterone as compared to animals treated with BAL alone.

Methods. Mercuric chloride was dissolved in sterile distilled water to a concentration of 3 mg per cc. A selected dose was injected subcutaneously into the test animals. BAL and testosterone propionate† were obtained in the commercially available forms, being diluted when necessary to appropriate concentrations with corn oil. To avoid the error of using animals of different strains, rats of the "Sprague-Dawley" strain were employed. These animals were all males, weighing between 100 and 250 g. Water and food was always freely available to them. The kidneys of representative animals were studied histologically. Animals which were to be treated and the control animals were injected with mercuric chloride at the same time in each group of experiments. BAL and testosterone, or both, were given according to the schedule shown in Table I. Standard methods of statistical analysis were applied to the results and the conclusions drawn are based on these analyses. A preliminary survey indicated that 6 mg per kilo was approximately LD_{50} for untreated animals. This dose of mercuric chloride was used throughout the study so that any therapeutic effect of testosterone would be more easily detectable. The dose of BAL chosen was the maximal tolerated effective dose(1). Testosterone was given over a wide range corresponding respectively to the following: (1) the dose used by Henderson *et al.*(4) and reported of value in the renal failure of Asiatic cholera, (2) the dose which is equivalent to the maximum clinically applicable in man, (3) the dose used by Longley in rats and reported to be effective in mercury poisoning, (4) the maximal dose considered feasible in rats of the size used. Two groups of unpoisoned animals given the largest

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† BAL, 10% solution in sesame oil (H. W. and D.), testosterone propionate in oil 50 mg/cc (Perandren), courtesy of Ciba Pharmaceutical Products, Inc.

TABLE I.
Dose Schedule of Treatment.

Drug	Time and dose given, mg									
	½	6	24	48 hr	3	4	5	6	7	8 days
BAL, per K	30	15	15	15	7.5	7.5	7.5	7.5	7.5	7.5
Testosterone	50		25	25	25	25	25	25	25	25
"	10		10	10	10	10	10	10	10	10
"	1		1	1	1	1	1	1	1	1
"	.1		.1	.1	.1	.1	.1	.1	.1	.1

TABLE II.
Effect of Treatment with BAL and Testosterone in Animals Treated with 6 mg/K Mercuric Chloride.

Treatment	No. animals	No. dead	% mortality	χ^2	P
A. None	27	15	56		
B. BAL	16	3	19	5.59	.02
C. Testosterone					
(1) 0.1 mg/day	10	4	40	.71	.42
(2) 1 "	10	4	40	.71	.42
(3) 10 "	10	4	40	.71	.42
(4) 25 "	27	20	74	2.03*	.16
D. BAL + testosterone					
(1) 0.1 mg/day	10	1	10		
(2) 1 "	10	0	0		
(3) 10 "	10	1	10		
(4) 25 "	27	4	15		

* Fatality rate in this group is *higher* than controls, but not significantly so.

doses of testosterone and the corn oil diluent were not clinically affected and gained weight normally.

Results. The effects of treatment with BAL and testosterone are shown in Table II. It is evident that BAL in the dose level used significantly reduced the mortality rate but was not completely protective. Testosterone, on the other hand, was totally ineffective in improving the survival rate.

In the second series of experiments (Table II) the effect of combined treatment with testosterone and BAL was compared to BAL alone to determine whether any synergistic action might be present. It is clear by inspection that the results were not appreciably improved. P values for each experiment were determined and were found not to be significant.

Histologic sections of kidneys from representative animals were studied by Dr. Simon Koletsky‡ whose report follows:

"Microscopic study was made of kidneys from rats sacrificed 3, 6 and 9 days after injection of an LD_{50} dose of mercuric chloride. Some animals received either BAL or testosterone, or both, while others were not treated and served as controls.

"Untreated animals and those treated with testosterone could not be separated by examining the sections, both showing the tubular necrosis typical of mercuric chloride poisoning. The sections showed that BAL did not prevent tubular necrosis; moreover, it was not possible to make an objective distinction in the amount of necrosis between BAL treated and untreated rats. No significant difference was noted in the rapidity and intensity of repair in recovery animals, whether treated or untreated. The beneficial effect of BAL may be chemical or physiological or explained on the basis of a quantitative alteration in the necrotic effect of mercury not detectable microscopically in these particular experiments."

Discussion. That testosterone stimulates renal tubular epithelium is well established, but the therapeutic significance of this fact

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remains unsettled. It would seem reasonable that a stimulating action upon the renal tubules could offer protection if the hormone were given before the renal insult, and Selye's work(2) supports this hypothesis. But whether such a stimulus is effective after tubular injury has already occurred is problematical. Although Longley's study appeared to favor such a possibility, the animals he used were not of uniform age and strain(5).

Henderson *et. al.* have suggested that testosterone was of benefit in the uremia of Asiatic cholera, stating: "We realize full well that in such a limited number of cases mortality statistics are not strictly applicable; nevertheless it is our firm belief that testosterone propionate is beneficial in this form of uremia." The evidence presented does not entirely support such a point of view. In their paper these authors do not present data on comparable controls, there was concomitant therapy with parenteral fluids and a sulfonamide, and in the majority of cases there are no blood chemical findings listed. Furthermore, cholera has a different mortality in different epidemics(6). With parenteral fluid therapy alone a mortality as low as 8% may be anticipated(7), results equal to those obtained by Henderson *et al.* with testosterone therapy. Regarding the renal pathology in this disease it has been stated that "in many instances there is little or no pathologic change, suggesting that kidney failure is largely extrarenal in origin"(8).

BAL, on the other hand, is definitely protective, as indicated by a significant reduction in mortality rate. It was rather surprising not to be able to determine the nature of this beneficial effect on microscopic study of the kidneys of the poisoned animals. Significant tubular necrosis was found in the BAL treated animals who would be expected to go on to recovery. One can only postulate that either the necrosis was quantitatively less severe than in the control animals, although this was not satisfactorily demonstrated in sections, or that the BAL protected enzyme systems in a way not reflected in tissue sections. The former possibility would be susceptible to proof by studying the kidneys of an adequate number of animals sacrificed shortly after poisoning and treatment.

Summary. 1. Male albino rats weighing between 100 and 250 g were poisoned with mercuric chloride and treated with BAL, testosterone propionate or a combination of both.

2. It was demonstrated that in rats as in other species BAL effectively combats the toxicity of mercuric chloride.

3. Testosterone propionate over a wide range of doses administered after mercuric chloride had no apparent effect upon the toxicity, either alone or in combination with BAL.

4. Histologic study of the kidneys failed to demonstrate any stimulating effect of testosterone on the damaged tubules. The definite protection afforded by BAL could not be correlated with any detectable microscopic changes in the tubules.

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