Effect of Adrenocorticotrophic Hormone on Tissue Distribution and Acute Toxicity of Beryllium. (19705)

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Many human cases of chronic pulmonary granulomatosis produced by inhalation of beryllium compounds have shown clinical improvement after treatment with adrenocorticotrophic hormone (ACTH)(1,2). These findings prompted the following study of the effects of ACTH on (a) the tissue distribution of injected radioberyllium, Be^7, and on (b) the survival of mice acutely poisoned with beryllium.

Methods. Beryllium was administered intravenously and ACTH intraperitoneally into young adult female CF #1 mice, weighing 21 to 27 g. In the tissue distribution studies, Be^7 was injected as the chloride either in tracer amounts (<0.001 μg/kg) or with sufficient carrier $BeSO_4$ to give each mouse approximately 0.3 mg Be/kg. This is a sublethal dose, the 14-day LD_{50} being 0.5 mg Be/kg. In the survival studies, mice in groups of 10 each received an LD_{95} of $BeSO_4$ in water, 0.7 mg Be/kg. Beginning immediately after the administration of beryllium, freshly prepared ACTH* in aqueous solution was given twice daily, in 1.25 mg amounts (equivalent to 2.5 mg of the standard ACTH), a dose schedule which will maintain a sustained eosinopenia and leucopenia in mice(3). In the survival studies, ACTH was given to the experimental group until death of the animals (2.5 days). In the distribution study, it was administered for 10 consecutive days and the mice were sacrificed on the 11th day when various tissues were removed for radioactivity analyses. Methods of assay were the same as described earlier(4).

Results. The data in Table I indicate that after 10 days of treatment ACTH had no significant effect on the distribution of radioberyllium in the presence of sublethal amounts of carrier $BeSO_4$. At the tracer level, however, there is a suggestion that ACTH leads to slightly increased elimination of Be^7, the probability values for the differences between femurs, residual carcasses, and total animals being 0.047, 0.036, and 0.06, respectively. These results extend those obtained in preliminary work(5) in which no change in tracer Be^7 tissue distribution was found at 3 days after a single intraperitoneal injection of 0.25 mg ACTH given either immediately or 42 hours after the administration of Be^7. The presence of carrier in sublethal amounts led to significantly greater retention of radioberyllium by the mouse than occurred with carrier-free Be^7, a result consistent with the findings in rats and rabbits(6).

Survival of mice given an LD_{95} of $BeSO_4$ was not affected by the ACTH treatment. The mortality curves for the treated and the untreated groups were almost identical, and the time to 50% death was 2.0 days for the former and 2.2 for the latter.

Discussion. To the extent that extrapolation from the mouse data is valid, these results indicate that ACTH probably is not responsible for any gross redistribution or excretion of Be in human cases of chronic berylliosis. It appears from available clinical data that there is no change in Be excretion during ACTH therapy of cases of chronic pulmonary granulomatosis produced by Be (1,7).

The fact that ACTH had no effect on acute experimental Be poisoning in mice, in which liver necrosis is the predominant pathological feature, while human cases of chronic pulmonary berylliosis are frequently benefited by this drug, reflects the differences between these conditions. These differences include route of administration or manner of exposure, the physical-chemical nature and the amounts of the beryllium compounds, and the lengths of time the tissues are exposed to beryllium. In the human cases ACTH is thought to be of benefit by producing a resolution of the granu-

* ACTH, Lot 212-103, 2 U.S.P. Units per mg, kindly furnished by the Armour Laboratories, Chicago, Ill.

TABLE I. Effect of ACTH on Distribution of Radioberyllium 11 Days after Injection of Be^7. % injected dose of Be^7.*

Tissue	Carrier-free Be^7		Be^7 + carrier	
	Be only	Be + ACTH	Be only	Be + ACTH
Liver	13.7 ± 1.7	10.4 ± 1.3	19.5 ± .3	17.8 ± .9
Femurs	2 ± .1	1.6 ± .1	1.9 ± .2	2 ± .04
Kidneys	.15 ± .02	.17 ± .03	.51 ± .06	.49 ± .02
Spleen	.58 ± .03	.47 ± .04	3 ± .2	2.8 ± .5
Lungs	.07 ± .004	.08 ± .004	.22 ± .02	.22 ± .03
Carcass	27.9 ± 1	24.3 ± .6	32.4 ± 1.4	31.7 ± 1.3
Total	44.4 ± 2.7	37.1 ± .8	57.5 ± 2	55 ± .7

* Each value is a mean based on 3 mice, except in the Be^7 + carrier control group, which consisted of 2 mice. Deviation is expressed as the standard error of the mean.

lomatous infiltration and possibly of the fibrosis(1,8) with resultant reduction of the alveolar-arterial difference in oxygen partial pressure(9).

The lack of effect of ACTH both on the survival of mice acutely poisoned with Be and on Be distribution suggests that there is no direct reaction between beryllium and either ACTH or any substance produced by ACTH activity. On the other hand, successful antidotal action against acute experimental beryllium poisoning in mice in the case of aurintricarboxylic acid is associated with the known ability of this substance to react chemically with Be under physiological conditions even though it produces no redistribution or increased excretion of Be(10,11).

Summary. Adrenocorticotrophic hormone (ACTH) had no appreciable effect on the distribution or retention of radioberyllium, injected into mice with and without carrier beryllium sulfate. The survival of mice acutely poisoned with beryllium sulfate was not influenced by ACTH.

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Protective Effect of Serotonin and of Para-Aminopropiophenone Against Lethal Doses of X-Radiation. (19706)

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In a previous publication(1) it was demonstrated in rats that pretreatment with pitressin or epinephrine afforded pronounced protection against total body x-irradiation. The protective effect was assumed to result from the production of a temporary tissue anoxia