11415 P

Zinc Salts and Oil in Prolongation of Therapeutic Effect of Pitressin in Experimental Diabetes Insipidus.

D. J. STEPHENS. (Introduced by W. S. McCann.)

From the Department of Medicine, University of Rochester School of Medicine, and the Medical Clinic, Strong Memorial and Rochester Municipal Hospitals, Rochester, N. Y.

It has been shown by previous investigators that the addition of zinc salts increases the activity of hypophyseal gonadotropic extracts[1,2] and prolongs the hypoglycemic effect of insulin.[3] Boyd and Clark[4] have reported that the addition of zinc salts to posterior pituitary extracts prolongs the retention of water taken up by frogs. Keeney, Pierce and Gay[5] have shown that the effect of epinephrine is greatly prolonged when it is given suspended in oil. The present communication is a preliminary report of an investigation of the effect of zinc salts and of oil on the action of pitressin in experimental diabetes insipidus.

A dog with experimental diabetes insipidus[6] was loaned to the author for this study by Dr. Roland Bellows of the Department of of Neurosurgery. The animal was fed once daily at 9 A.M.; liberal amounts of drinking water were available at all times. The urine was collected in fractional samples every 4 hours, with the exception of the period between 1 A.M. and 9 A.M., when a single 8-hour specimen was collected. The urine volume and specific gravity were accurately measured.

Test substances were injected in a single dose at 9 A.M. The results of the subcutaneous injection of 1 cc of 0.2% zinc acetate solution, of 1 cc of pitressin* and of a mixture of 1 cc of pitressin and 1 cc of 0.2% zinc acetate solution are shown in Table I. The subcutaneous administration of zinc acetate alone had no effect. The administration of a single dose of 20 units of pitressin resulted in a moderate reduction of the urine volume. The pitressin effect was

1 Fevold, H. L., Hisaw, F. L., and Greep, R., *Am. J. Physiol.*, 1936, **117**, 68.

2 Saunders, F. J., and Cole, H. H., PROC. SOC. EXP. BIOL. AND MED., 1936, **33**, 505.

3 Scott, D. A., and Fisher, A. M., *J. Pharm. and Exp. Therap.*, 1935, **55**, 206.

4 Boyd, E. M., and Clark, K. J., *Am. J. Med. Sci.*, 1939, **198**, 171.

5 Keeney, E. L., Pierce, J. A., and Gay, L. N., *Arch. Int. Med.*, 1939, **63**, 119.

6 Bellows, R. T., and VanWagenen, W. P., *J. Nerv. and Mental Dis.*, 1938, **88**, 417.

* The pitressin and the pitressin-in-oil used in this study were generously supplied by Dr. E. A. Sharp of the Parke-Davis Co.

TABLE I.

Treatment	No. of Exp.	Avg urine volume in cc 9-1	1-5	5-9	9-1	1-9	24 hr Total
Control	15	980	1410	950	660	975	4975
1 cc 0.2% ZnAc	4	1110	1230	870	650	1120	4980
1 " pitressin	7	290	380	500	540	980	2690
1 " 0.2% ZnAc 1 " pitressin	8	260	150	190	140	690	1430
Pitressin-in-oil	3						
Control day		970	1250	970	640	1100	4930
First "*		445	320	50	120	200	1135
Second "		0	320	220	80	490	1110
Third "		200	770	870	290	780	2910
Fourth "		860	1030	510	350	1000	3750
Fifth "		700	1550	1160	460	980	4850

*Pitressin-in-oil, 1.3 cc (20 units), injected intramuscularly at 9 A.M., on the first day only.

most striking during the first 4 hours, with some reduction in urine volume for as long as 12 hours after injection. The administration of a mixture of 1.0 cc of pitressin and 1.0 cc of 0.2% zinc acetate solution resulted in prolongation and intensification of the pitressin effect during the period from 4 to 16 hours after injection. The effect of both the aqueous pitressin and the zinc-pitressin mixture was dissipated within 24 hours.

The effect of the administration of a preparation of pitressin suspended in peanut oil was more striking. The results of 3 experiments are summarized in Table I. A single intramuscular injection of 1.3 cc (20 units) of pitressin-in-oil resulted in a maximal pitressin effect of fully 48 hours' duration, as contrasted with a 4- to 8-hour maximum effect in the case of a similar dose in aqueous solution and a 16-hour maximum effect when given in an aqueous solution of a mixture of pitressin and zinc acetate. With the oil preparations there was some effect evident for as long as 72 hours.

These observations suggest that when pitressin is given alone, in watery solutions, it is rapidly absorbed and its full effect lost through destruction or excretion of the active principle. The data presented in this communication are compatible with the view that absorption of the pitressin is delayed when given in the presence of zinc acetate, or in oil.

Summary. The presence of 0.1% zinc acetate prolonged and intensified the effect of aqueous solutions of pitressin in reducing the water exchange in experimental diabetes insipidus. The use of a preparation of pitressin suspended in oil resulted in a much more marked prolongation and intensification of the pitressin effect.