Acute Effect of 6 Methyl Prednisolone (Medrol®) on Impaired Water Excretion of Adrenal and Pituitary Insufficiency.* (24718)

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An impaired diuretic response to water is a characteristic abnormality of patient or animal with adrenal or pituitary insufficiency (1-6). This defect can only be corrected by administration of hydrocortisone-like steroids (3-6), probably by direct effect on kidney rather than by extra-renal mechanisms(4,7,9-12). Hydrocortisone increases glomerular filtration, renal blood flow and enhances tubular reabsorption of sodium in the adrenal and pituitary insufficient subject(7-12). However, our previous studies indicate that marked improvement in water diuresis caused by compound F cannot be explained solely by its effects on renal hemodynamics or solute excretion(7). It seemed therefore of interest to note the effect of Medrol® (6 methyl prednisolone) on impaired diuresis of adrenal and pituitary insufficiency. This potent adrenal cortical analogue does not enhance sodium reabsorption or alter renal hemodynamics in normal subjects(13).

Materials and methods. Six experiments were performed in 6 male patients: 4 with anterior pituitary insufficiency (secondary adrenal insufficiency) and 2 with primary adrenal insufficiency. Hydrocortisone replacement therapy was withdrawn from all patients for at least 1 week prior to experiments. Subjects with primary adrenal insufficiency were maintained on 100 μg of 9-alpha fluoro-hydrocortisone daily. Experiments were performed in the morning post-prandially, with subjects recumbent. An initial urine specimen was obtained for osmolality, after which an oral water load of 1000 cc was given; this positive water balance was maintained for duration of experiment by infusion of 2.5% glucose in water at a rate equal to urine flow. Collection periods were 20 to 30 minutes, and urine samples collected by spontaneous voiding or by indwelling catheters. When urine volume was below 2 cc/minute, air "wash outs" were also utilized. Samples of venous blood were obtained at midpoint of each period through an indwelling needle. Control collections were begun about 45 minutes after priming dose of inulin and para amino-hippurate and constant sustaining infusion had been started. After at least 3 control periods of maximally sustained urinary flow had been obtained (approximately 2½ hours after initiating the water load), 5-20 mg of Medrol® were administered into infusion tubing for 30 minutes. Urinary collections were continued for additional 3 to 5 hours. Experiments ranged from 5½ to 8 hours in duration. Analysis of serum and urine for sodium, potassium, chloride, inulin, PAH, creatinine, and freezing point depression (osmolality: milliosmols/kg of H_2O) were made utilizing methods previously reported(14,15). Characteristics of water diuresis were evaluated in each case by maximal urinary flow, minimal urinary osmolality and magnitude of free water clearance C_{H_2O}.† Since the experiments were too rigorous to permit *control* water loading studies *without drug administration* on each subject, urine volumes were measured in 3 other patients (2 pituitary and 1 adrenal insufficiency) maintained in sustained positive water balance for 5 hours; in these 3 control subjects, maximal urinary flows were attained in the first 2½ hours.

Results. The significant data from each study are presented in Table I and a representative experiment is outlined in Table II.

A. *Response to Water Loading*: Although

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† C_{H_2O} is equivalent to the volume of urine/minute virtually freed of solute during diluting process. It represents the difference between total urinary flow, V, and volume of fluid necessary to excrete all urinary solutes in an isosmotic solution, or osmolal clearance, Cosm : V − Cosm = C_{H_2O}.

TABLE I. Effect of Medrol® on Water Diuresis in Adrenal and Pituitary Insufficiency.

Subject	Period	Urine vol, ml/min.	Urine conc., mOsm/kg	UV sol,* μOsm/min.	C_{H_2O},† ml/min.	GFR,‡ ml/min.	RPF,§ ml/min.	$U_{Na}V$, μeq/min.	Serum osmolal., mOsm/kg
Adrenal insuff.	Control	2.8	298	834	− .4	68	275	144	264
	Medrol	10.0	100	1007	+6.4	70	277	257	274
Idem	Control	4.0	275	1100	− .1	60	240	560	267
	Medrol	10.3	62	638	+7.8	87		540	258
Ant. pit. insuff.	Control	1.2	432	518	− .7	80		128	285
	Medrol	9.8	109	1068	+5.5	100		281	257
Idem	Control	1.2	410	508	− .6	105	419	81	283
	Medrol	6.6	113	746	+4.0	105	414	112	277
"	Control	.9	787	716	− 1.5	95	350	162	294
	Medrol	10.0	98	984	+6.7	94	419	221	290
"	Control	2.1	410	853	− 1.3	84	341	250	254
	Medrol	7.0	120	840	+3.6	86	327	355	250

* Rate of solute excretion. † Free water clearance. ‡ Glomerular filtration rate.
§ Renal plasma flow.

maximal urinary flow was attained after time interval comparable to normal subjects, the magnitude of peak diuresis was distinctly subnormal (mean urinary flow 2 cc/min., range 0.9-2.8 cc/min.; mean urinary osmolality 435 mOsm/kg, range 275-787 mOsm/kg) and mean C_{H_2O} −0.9 cc/min., (range −0.4 to 1.5 cc/min.). Glomerular filtration rate (inulin clearance) and renal plasma flow (PAH clearance) were below normal in all subjects, when referred to surface area of 1.73m².

B. *Response to Medrol®.* A noticeable increase in urinary flow and fall in urinary osmolality occurred within 2½ hours after administration of the steroid, while peak response was observed in 4 to 5 hours (Table II). The difference from control periods was striking. Urinary flow increased to a mean of 9 cc/min. (range 6.6-10.3 cc/min.), C_{H_2O} to a mean of +4.2 cc/min. while urinary osmolality fell to 100 mOsm/kg (range 62-120 mOsm/kg). Sodium and total solute excretion increased moderately in 5 of the 6 subjects. Although inulin clearance increased significantly in 2 subjects, there was no correlation between magnitude of improvement of water diuresis and increment in glomerular filtration rate.

Discussion. These studies clearly indicate that acute administration of 5 to 20 mg of Medrol® (6 methyl prednisolone) can markedly improve all parameters of the impaired water diuresis associated with adrenal and pituitary insufficiency. This effect is comparable in all respects to that observed follow-

TABLE II. Effect of Medrol® on Impaired Water Diuresis of Patient.

Time	Urine vol, ml/min.	Urine conc., mOsm/kg	UV sol,* μOsm/min.	C_{H_2O},† ml/min.	GFR, ml/min.	RPF, ml/min.	$U_{Na}V$, μeq/min.	Serum osmolal., mOsm/kg
60	.8	922	738	− 1.6	107		154	307
90	.8	867	711	− 1.6	87	375	143	293
120	.9	789	686	− 1.6	95	350	139	
150	.9	787	716	− 1.5	103	350	162	294
‡180	.8	818	638	− 1.4	91		147	
210	.7	820	607	− 1.3	96		139	295
240	.8	820	672	− 1.3	196		145	
270	1.0	790	797	− 1.8	120	403	167	285
300	1.4	686	960	− 1.9	115	455	221	
330	2.6	380	969	− .8	99	420	176	289
360	5.4	176	956	+2.1	93	421	195	
390	8.5	116	988	+5.1	92	397	222	290
420	10.0	98	984	+6.7	94	419	221	

* Rate of solute excretion. † Free water clearance. ‡ 20 mg of Medrol® given intrav. at start of this period.

ing administration of 100-200 mg of hydrocortisone to similar patients‡(7). It is readily apparent that this response was not dependent on increased glomerular filtration rate or renal plasma flow (Table I, II), although it seems reasonable that any improvement in renal hemodynamics would enhance the diuretic response(16).

Medrol® caused a net decrease in tubular reabsorption of sodium and a slight increase in solute excretion in these subjects (Table I). These alterations could not have appreciably enhanced urinary dilution or flow.

If, as available data suggests, compound F like steroids does not alter metabolism of antidiuretic hormone(4,7,9-13), the present studies lend further support to the concept that these steroids improve water diuresis by inhibiting the back diffusion of water in diluting segments of the nephron; a permissive action.

Summary. Acute administration of 6 methyl prednisolone (Medrol®) can markedly improve impaired water diuresis of adrenal and pituitary insufficiency. This effect is not dependent on altered renal hemodynamics or sodium reabsorption, and it suggests a specific action on the diluting segment of the nephron.

‡ In adrenal and pituitary insufficient patients as little as 3 mg of Medrol®, administered intravenously 1 hour prior to oral injection of 1500 cc of water, can completely correct impaired response to this load(14).

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Glucocorticoids and Maintenance of Blood Pressure and Plasma Volume of Adrenalectomized Dogs Subjected to Stress.* (24719)

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Mild stress is rapidly fatal to adrenalectomized (adx) dogs adequately maintained on desoxycorticosterone or high salt therapy, whereas animals with intact cortices are extremely hardy and withstand severe stress. Moreover, the adx dog primed with cortical extract(1), with cortisone or hydrocortisone, becomes refractory to traumatic or other deleterious stimuli(2). Intravenous infusions of those steroids with an oxygen function at Carbon 11 and 17, or their more potent analogs,

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