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Effect of indomethacin and adrenocorticotrophic hormone on renal function in man: An experimental model of inappropriate antidiuresis

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Effect of indomethacin and adrenocorticotrophic hormone on renal function in man: An experimental model of inappropriate antidiuresis. The effect of prostaglandin synthesis inhibition on basal and ACTH-stimulated adrenal and renal function was investigated in normal volunteers. Data were collected during control and experimental study periods (13 days each). Adrenocorticotrophic hormone (Cosyntropin, 80 U/day) was administered i.v. on days 8 and 9 of each period. Indomethacin (150 mg/day) was given on days 5 through 13 of the experimental period. The subjects ate a constant diet containing 9 mEq of sodium, 100 mEq of potassium, and 2,500 ml of fluid daily. Indomethacin markedly inhibited urinary PGE excretion and plasma PGE concentration. The effect of ACTH alone as compared to the effect of ACTH and indomethacin showed: plasma sodium concentration, 139 ± 1 vs. 131 ± 3 mEg/liter ($P < 0.01$, mean ± SEM); plasma osmolality, 287 ± 3 vs. 270 ± 3 mOsm/liter ($P < 0.01$); free water clearance, 97 ± 66 vs. −1100 ± 380 ml/24hr ($P < 0.01$); urine volume, 2,000 ± 60 vs. 950 ± 200 ml/day ($P < 0.01$); and urine osmolality 282 ± 12 vs. 720 ± 144 mOsm/liter ($P < 0.01$). We conclude that the effects of ACTH and prostaglandin synthesis inhibition interact to result in inappropriate antidiuresis.

Effet de l'indométhacine et de l'hormone adrénocorticotrope sur la fonction rénale chez l'homme: Un modèle expérimental d'antidiurèse inappropriée. L'effet de l'inhibition de la synthèse de prostaglandine sur la fonction surrénalienne basale et stimulée par l'ACTH et sur la fonction rénale a été étudié chez des sujets normaux volontaires. Les résultats ont été obtenus au cours de périodes contrôles et expérimentales de 13 jours chacune. De l'hormone adrénocorticotrope (Cosyntropin) a été administrée par voie i.v. les 8ème et 9ème jours de chaque période à raison de 80 U par jour. L'indométhacine, 150 mg/jour, a été donnée du 8ème au 13ème jour de la période expérimentale. Les sujets ont été soumis à un régime constant contenant 9 mEq de sodium, 100 mEq de potassium, et 2,500 ml de liquide par jour. L'indométhacine a fortement inhibé l'excrétion urinaire de PGE et abaissé la concentration plasmatique de PGE. L'effet de l'ACTH seul comparé à l'effet de l'ACTH associé à l'indométhacine a montré: une concentration plasmatique de sodium de 139 ± 1 vs. 131 ± 3 mEq/litre ($P < 0,01$) moyenne et SEM); une osmolalité plasmatique de 287 ± 3 vs. 270 ± 3 mOsm/litre ($P < 0,01$); une clearance de l'eau libre de 97 ± 66 vs. − 1100 ± 380 ml/24 hr ($P < 0,01$); un débit urinaire de 2,000 ± 60 vs. 950 ± 200 ml/jour ($P < 0,01$); et une osmolalité urinaire de 282 ± 12 vs. 720 ± 144 mOsm/litre ($P < 0,01$). Nous considérons que les effets de l'ACTH et de l'inhibition de la synthèse de prostaglandine se combinent pour déterminer une antidiurése inappropriée.

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The maintenance of cellular, interstitial, and extracellular fluid isotonicity is dependent upon the integrated functions of the hypothalamus, pituitary, and kidney [1–6]. The molecular mechanism of action of vasopressin in the regulation of water permeability of epithelial membranes has been elucidated through numerous studies with the toad urinary bladder [7]. Vasopressin has been shown to activate adenylate cyclase, resulting in the accumulation of cyclic adenosine 3',5'-monophosphate (cyclic AMP) [8]. This increase in cellular cyclic AMP concentration results in an increase in the water permeability of the epithelial surface of the toad urinary bladder [9] and the mammalian renal collecting duct [10]. Exogenously administered cyclic AMP or theophylline, a cyclic nucleotide phosphodiesterase inhibitor, mimics the effects of antidiuretic hormone (ADH) in increasing the water permeability of the toad urinary bladder [9] and rabbit collecting duct in vitro [10].

Prostaglandins of the E series (PGE) are potent inhibitors of vasopressin-stimulated water permeability in the toad urinary bladder [11, 12] and rabbit collecting duct in vitro [13]. Furthermore, inhibitors of prostaglandin biosynthesis enhance the

water permeability response of these tissues [14]. These observations led Grantham and Orloff [13] to suggest that PGE was an in vivo modulator of ADH activity. Recent studies have revealed that vasopressin is a potent stimulant of PGE_2 biosynthesis in rabbit renomedullary interstitial cells in tissue culture [15, 16], in the rat [17, 18], and in the rabbit [19]. These studies suggested that the stimulation of PGE_2 biosynthesis by ADH in vivo might inhibit vasopressin-stimulated water permeability. Zusman, Keiser, and Handler demonstrated that in the toad urinary bladder in vitro arginine vasopressin is a potent stimulant of PGE biosynthesis [20]. Vasopressin-stimulated PGE biosynthesis by the urinary bladder inhibits vasopressin-stimulated water permeability. Mepacrine, a phospholipase inhibitor; the nonsteroidal antiinflammatory agents, such as indomethacin, naproxen, ibuprofen, and meclofenamate; and the sulfonylureas, such as chlorpropamide, tolbutamide, and glyburide inhibit vasopressin-stimulated PGE biosynthesis and, as a consequence, enhance vasopressin-stimulated water permeability [20, 21].

Adrenal steroid hormones also enhance vasopressin-stimulated water flow in the toad urinary bladder [22]. This effect was thought to be caused by the steroids' inhibition of cyclic nucleotide phosphodiesterase, with a resultant increase in cyclic AMP accumulation [23]. Zusman, Keiser, and Handler [24] have shown that adrenal steroid hormones are potent inhibitors of PGE biosynthesis in the toad urinary bladder. Thus, the enhancement of vasopressin-stimulated water flow by adrenal steroid hormones in the toad bladder is caused by the inhibition of cyclic nucleotide phosphodiesterase as well as the inhibition of PGE biosynthesis.

The purpose of this investigation was to determine the effects of prostaglandin synthesis inhibition and the administration of adrenocorticotrophic hormone (ACTH) on adrenal and renal function.

Methods

Study protocol. Fourteen normal volunteers (2 men and 12 women), aged 19 to 23 years old (mean age, 21 years), were studied as inpatients of the National Heart, Lung, and Blood Institute. Each volunteer underwent complete physical examination, chest radiograph, electrocardiogram, and laboratory screening tests prior to the study. None of the subjects took any medications in the 2 weeks before the beginning of the protocol nor did they take any medications other than those associated with the investigation during the study. The protocol for the study was approved by the NIH Clinical Research Committee, and all subjects gave informed consent in writing.

Data were collected during the control and experimental periods. The duration of each period was 13 days; the periods were separated by 14 days. During each study period, the subjects adhered to a constant diet containing 9 mEq of sodium and 100 mEq of potassium per day. Each subject drank 2,500 ml of fluid daily, with the exception of the days on which ACTH was administered, when 1,500 ml was given orally and 1,000 ml was given i.v. On days 8 and 9 of each period, Cosyntropin, 80 U/day (noon to noon), was given i.v. in a total volume of 1,000 ml of 5% dextrose in water. During the experimental period, indomethacin (50 mg per os, three times per day, with meals) was given on days 5 through 13.

Daily (noon to noon) urine samples were collected. Venous blood samples were obtained for measurement of sodium, potassium, osmolality, and creatinine. Plasma cortisol levels were determined before and during the ACTH infusion at 4 P.M. and 9 A.M. Venous blood samples for determining PGE and plasma renin activity were obtained before and during the ACTH infusion between 8 A.M. and 9 A.M. with the subject in the supine position, and between 11 A.M. and noon after 3 hours in the upright position. Urinary and plasma sodium, potassium, osmolality, and creatinine were measured by the National Institutes of Health Clinical Laboratories. Plasma cortisol, and urinary 17-hydroxy and 17-keto-steroids were measured by Bio-Science Laboratories. Plasma renin activity, and the concentrations of plasma renin, plasma renin substrate, and urinary aldosterone were measured by Hazelton Laboratories (Rockville, Maryland) under a special contract with the National Heart, Lung, and Blood Institute. Plasma PGE was measured by radioimmunoassay [25, 26]. Urinary PGE excretion was measured by radioimmunoassay, as previously described [27].

Statistical analysis. The control value for all measurements was the mean of the three observations on days 5, 6, and 7 of the control period. During the control period, values for days 8 through 13 were compared with control values to assess the effect of ACTH administration by Student's t test for paired observations [28]. During the experimental period, statistical comparison was made with the corresponding day of the control period to assess the effect of prostaglandin synthesis inhibition by Student's t test for paired observations [28].

Results

Effect of indomethacin on plasma PGE concentration and urinary PGE excretion (Fig. 1, Table 1). The plasma PGE concentration was 149 ± 10 pg/ml (mean ± SEM) with subjects in the supine position and was unaffected by the upright position or by ACTH administration. Control urinary PGE excretion was 35.2 ± 4.1 ng/hr, and was unaffected by ACTH administration.

During indomethacin administration, the plasma PGE concentration fell to 22 ± 3 pg/ml in the supine position and was unaffected by the upright position or by ACTH administration. Plasma PGE levels were significantly lower in the experimental than they were in the control periods ($P < 0.001$). During indomethacin administration, urinary PGE excretion fell to 74.2 ± 10.5% of control value ($P < 0.05$) on day 5; for days 6 through 13, urinary PGE excretion was 48.3 ± 2.0% of control PGE excretion ($P < 0.001$).

Effect of ACTH and prostaglandin synthesis inhibition on sodium, potassium, and water metabolism (Figs. 2-5, Table 1). Plasma sodium concentration was 139 ± 1 mEq/liter throughout the control period. During the experimental period, plasma sodium concentration was 140 ± 1 mEq/liter before ACTH administration, but fell to 131 ± 3 mEq/liter after 48 hours of ACTH ($P < 0.01$). Plasma sodium concentration rose to 138 ± 1 mEq/liter 96 hours after the ACTH infusion was completed.

Urinary sodium excretion was 3.9 ± 1.1 mEq/liter prior to ACTH administration during the control and experimental periods. Sodium excretion fell to 1.1 ± 0.4 and 0.3 ± 0.2 mEq/24 hr on the first and second days of ACTH administration ($P < 0.01$), respectively, during the control and experimental periods.

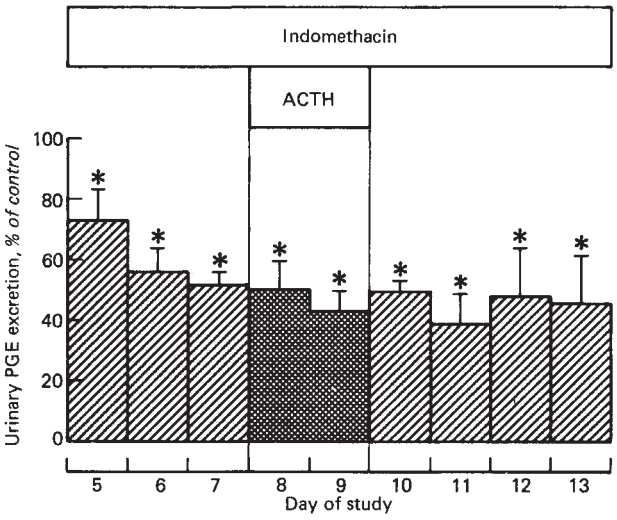


Fig. 1. *Effect of indomethacin on urinary prostaglandin E (PGE) excretion during the experimental period.* An *asterisk* (*) indicates statistical significance ($P < 0.05$) compared to the equivalent study day of the control period.

Plasma potassium concentration 4.0 ± 0.1 mEq/liter, was unaffected by ACTH, indomethacin, or a combination of the two. Basal urinary potassium excretion was 88.3 ± 3.6 mEq/24 hr during the control study period. During the first day of ACTH infusion, urinary potassium excretion rose to 131 ± 9.4 mEq/24 hr ($P < 0.001$) but subsequently fell to

Table 1. The effect of prostaglandin synthesis inhibition and adrenocorticotrophic hormone (ACTH) on renal function in normal man

	Control period[a]		Experimental period[a]	
	Basal	ACTH	Basal	ACTH
Plasma sodium, *mEq/liter*	139 ± 1	139 ± 1	140 ± 1	131 ± 3[c]
Plasma osmolality, *mOsm/liter*	287 ± 3	287 ± 3	283 ± 2	270 ± 3[c]
Urine volume, *ml/24 hr*	2220 ± 60	1999 ± 78	1740 ± 65[c]	950 ± 200[c]
Urine osmolality, *mOsm/liter*	250 ± 16	282 ± 12	259 ± 17	720 ± 144[c]
Free water clearance, *ml/24 hr*	333 ± 110	97 ± 66[b]	201 ± 90	−1090 ± 380[c]
Aldosterone excretion rate, *μg/24 hr*	62.5 ± 7.4	192.4 ± 26.3[b]	49.4 ± 1.9[c]	118.3 ± 7.7[c]
PRA (supine), *ng/ml/hr*	3.3 ± 0.5	5.0 ± 0.7[b]	3.2 ± 0.5	4.8 ± 2.8
PRA (upright), *ng/ml/hr*	9.0 ± 1.0	14.2 ± 1.3[b]	6.9 ± 1.2[c]	4.5 ± 1.5[c]
PRS (supine), *μg/ml*	0.91 ± 0.06	1.44 ± 0.07[b]	0.95 ± 0.07	1.25 ± 0.14
PRS (upright), *μg/ml*	0.82 ± 0.09	1.41 ± 0.14[b]	1.02 ± 0.13	1.50 ± 0.17
PRC (supine), *μU/ml*	167 ± 37	205 ± 59	121 ± 30	125 ± 106
PRC (upright), *μU/ml*	485 ± 119	691 ± 157	156 ± 45[c]	65 ± 21[c]

[a] In the control and experimental periods, the "basal" value represents the mean of observations on days 5, 6, and 7 of each period. The "ACTH" value represents the observation after 48 hours of ACTH infusion, with the exception of the aldosterone excretion rate, which is the value observed after 24 hours of ACTH infusion.

[b] $P < 0.05$ compared to "basal".

[c] $P < 0.05$ compared to "control" period.

levels below control for 72 hours before returning to control levels. During the experimental period, basal potassium excretion, 75 ± 3.1 mEq/24 hr, was lower than that of the control period ($P < 0.02$). During the first day of ACTH administration, potassium excretion increased to 110.8 ± 10.1 mEq/24 hr, which was greater than the basal potassium excretion for the experimental period ($P < 0.01$), but

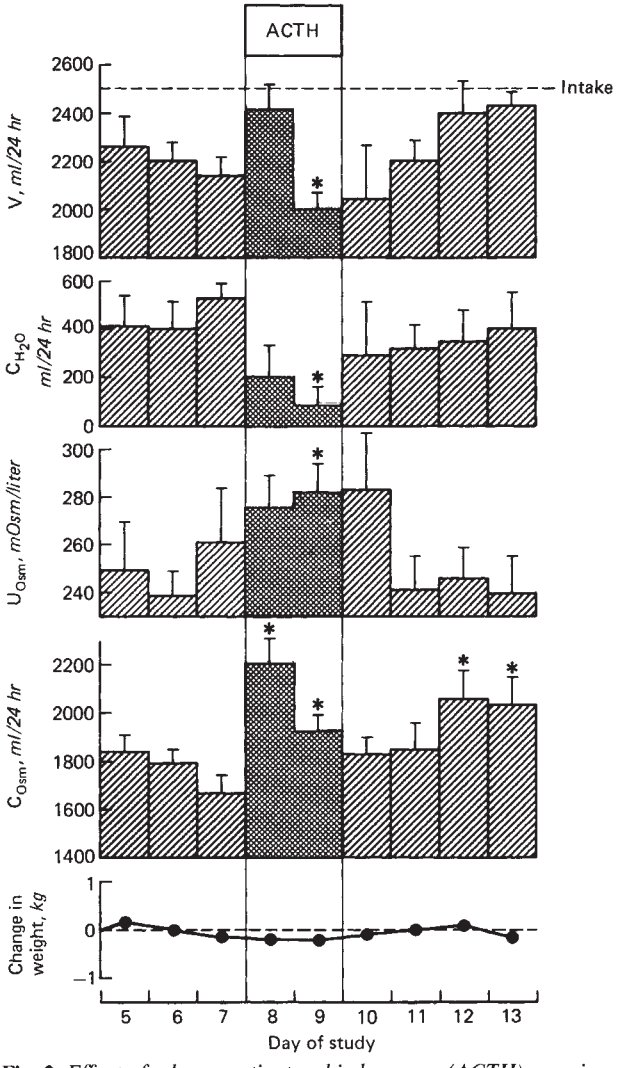


Fig. 2. *Effect of adrenocorticotrophic hormone (ACTH) on urine volume (V), free water clearance (C_{H_2O}), urine osmolality (U_{Osm}), osmolar clearance (C_{Osm}), and weight.* An *asterisk* (*) indicates statistical significance ($P < 0.05$) compared to the mean of the values on days 5, 6, and 7.

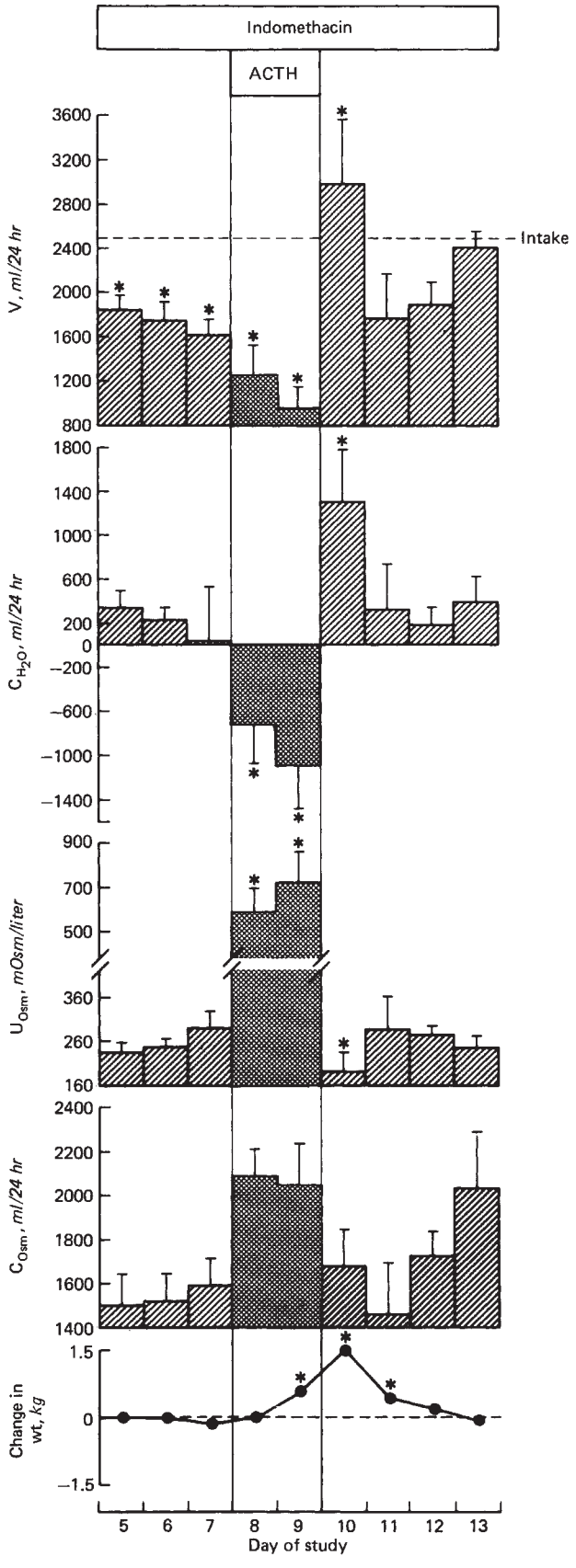
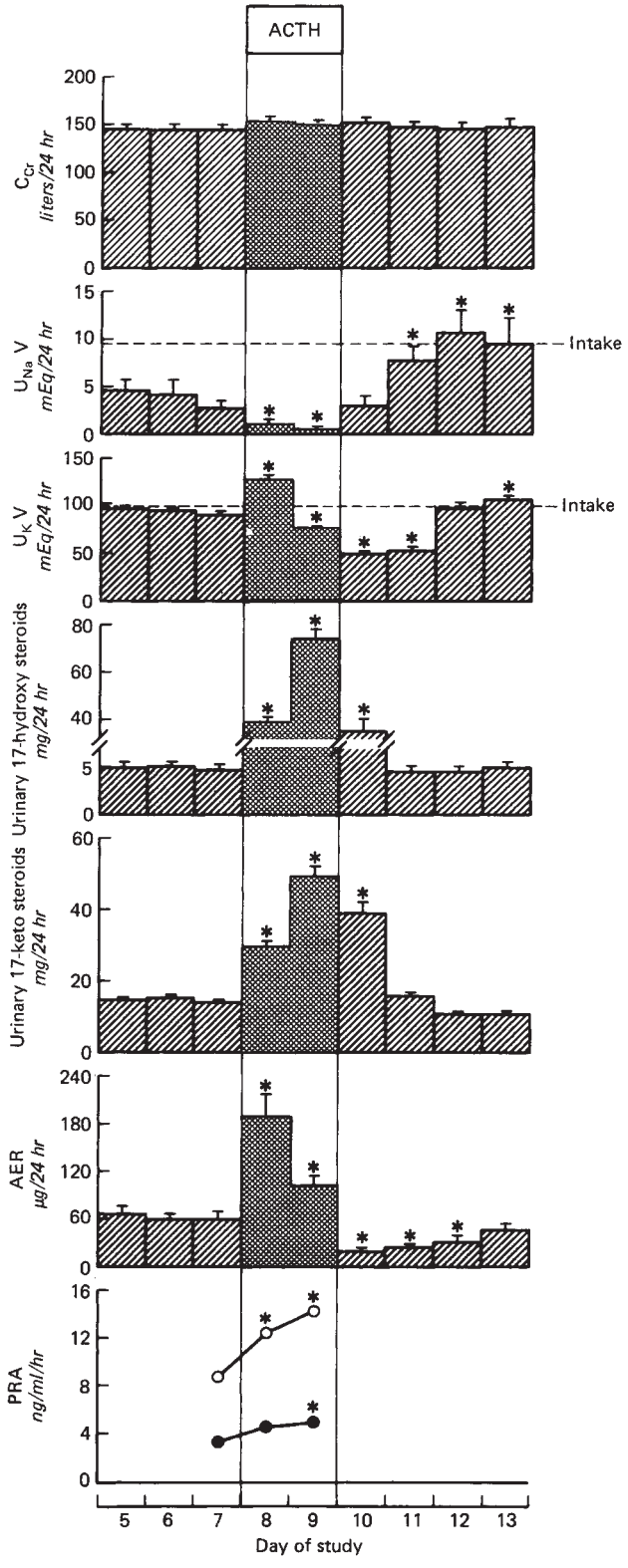


Fig. 3. *Effect of adrenocorticotrophic hormone (ACTH) and prostaglandin synthesis inhibition with indomethacin, 150 mg/day, on urine volume (V), free water clearance (C_{H_2O}), urine osmolality (U_{Osm}), osmolar clearance (C_{Osm}), and weight.* An *asterisk* (*) indicates statistical significance ($P < 0.05$) compared to the equivalent study day of the control period (shown in Fig. 2).

less than urinary potassium after ACTH administration during the control period ($P < 0.01$).



Plasma creatinine, 0.94 ± 0.02 mg/100 ml, and creatinine clearance, 145 ± 2.0 liter/24 hr, were unaffected by ACTH, indomethacin, or a combination of the two.

Plasma osmolality was constant, 287 ± 3 mOsm/liter, during the control period and was unaffected by the administration of indomethacin or ACTH. After 48 hours of ACTH administration during the experimental period, plasma osmolality fell to 270 ± 3 mOsm/liter ($P < 0.01$).

Basal osmolar clearance was 1,780 ± 50 ml/24 hr during the control period. Osmolar clearance rose to 2,210 ± 100 ml/24 hr ($P < 0.001$) and 1,910 ± 70 ml/24 hr ($P < 0.05$) on the first and second days of ACTH administration, respectively. Basal osmolar clearance and the increase in osmolar clearance after ACTH administration were unaffected by indomethacin.

Urine volume was 2,220 ± 60 ml/24 hr throughout the control period; basal urine volume during the experimental period was 1,740 ± 65 ml/24 hr and was statistically lower ($P < 0.01$) than the basal urine volume was during the control period. On the first and second days of ACTH infusion, urine volume fell to 1,250 ± 250 ml/24 hr ($P < 0.02$) and 950 ± 200 ml/24 hr ($P < 0.01$), respectively. A weight gain of 1.5 ± 0.3 kg/subject ($P < 0.001$) was associated with the marked fall in urine volume during ACTH infusion.

During the control period, basal urine osmolality was 250 ± 16 mOsm/liter. During the ACTH infusion, urine osmolality rose slightly to 282 ± 12 mOsm/liter ($P < 0.01$). Basal urine osmolality during the experimental period was 259 ± 17 mOsm/liter. In the experimental study period, urine osmolality rose to 579 ± 118 and 720 ± 144 mOsm/liter ($P < 0.01$) during the first and second days of ACTH infusion, respectively. On the first day after the termination of ACTH infusion, a diuresis was observed during the experimental period. The urine volume was 2,980 ± 580 ml/24 hr ($P < 0.02$) and the urine osmolality was 190 ± 47 mOsm/liter ($P < 0.01$).

Free water clearance during the control period was 333 ± 110 ml/24 hr, and fell to 97 ± 66 ml/24 hr ($P < 0.02$) on the second day of the ACTH infusion.

Fig. 4. *Effect of adrenocorticotrophic hormone (ACTH) on creatinine clearance (C_{Cr}), urinary sodium excretion ($U_{Na}V$), urinary potassium excretion (U_KV), urinary 17-hydroxy-, and 17-keto-steroids, aldosterone excretion rate (AER), and plasma renin activity (PRA).* An *asterisk* (*) indicates statistical significance ($P < 0.05$) compared to the mean of values on days 5, 6, and 7.

Basal free water clearance during the experimental period was 201 ± 90 ml/24 hr. During the ACTH infusion in the experimental study period, the free water clearance fell to −725 ± 365 and −1,090 ± 380 ml/24 hr ($P < 0.01$) during the first and second days, respectively. On the day immediately following termination of the ACTH infusion, free water clearance rose to 1,310 ± 480 ml/24 hr ($P < 0.02$) during the experimental period.

Effect of prostaglandin synthesis inhibition on basal and ACTH-stimulated adrenal steroidogenesis (Figs. 4 and 5, Table 1). Plasma cortisol concentrations during the control period were 7.1 ± 0.6 and 12.4 ± 0.4 ng/100 ml at 4 P.M. and 9 A.M., respectively. During ACTH infusion, the plasma cortisol levels rose to 45.2 ± 3.5 and 47.7 ± 4.0 ng/100 ml at 4 P.M. and 9 A.M., respectively. Basal urinary 17-hydroxy-steroid excretion was 5.0 ± 0.4 mg/24 hr. Urinary 17-hydroxy-steroid excretion increased to 36.7 ± 4.2 and 72.4 ± 5.6 mg/24 hr ($P < 0.01$) by the first and second days of ACTH infusion, respectively. Basal urinary 17-keto-steroid excretion, 14.5 ± 0.9 mg/24 hr, increased to 28.6 ± 2.8 and 48.8 ± 4.8 mg/24 hr ($P < 0.001$) during the first and second days of ACTH infusion, respectively. Basal and ACTH-stimulated plasma cortisol levels and urinary 17-hydroxy and 17-keto-steroid excretion were unaffected by indomethacin.

Basal urinary aldosterone excretion was 62.5 ± 7.4 μg/24 hr. During ACTH infusion, aldosterone excretion increased to 192.4 ± 26.3 and 100.3 ± 11.8 μg/24 hr ($P < 0.001$) on the first and second days of ACTH infusion, respectively. Basal aldosterone excretion during the experimental period was 49.4 ± 1.9 μg/24 hr; this value was significantly lower ($P < 0.02$) than was the value obtained during the control period. Aldosterone excretion on the first and second days of the ACTH infusion in the experimental period was 118.3 ± 7.7 and 51.6 ± 8.1 μg/24 hr, respectively. Aldosterone excretion was significantly lower ($P < 0.01$) during the ACTH infusion in the experimental period than it was in the control period.

Effect of prostaglandin synthesis inhibition and ACTH on plasma renin activity (Figs. 4 and 5 and Table 1). Plasma renin activity (PRA) during the

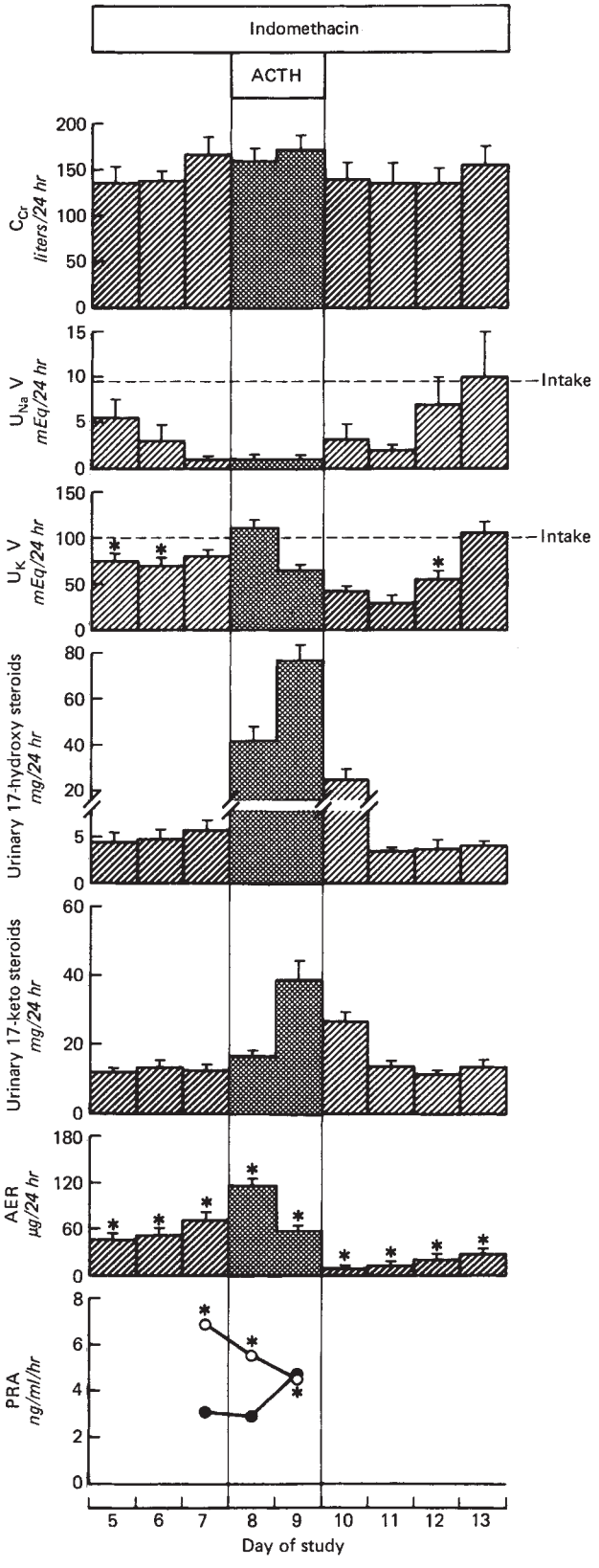


Fig. 5. *Effect of adrenocorticotrophic hormone (ACTH) and prostaglandin synthesis inhibition with indomethacin, 150 mg/day, on creatinine clearance (C_{Cr}), urinary sodium excretion ($U_{Na}V$), urinary potassium excretion (U_KV), urinary 17-hydroxy- and 17-keto-steroids, aldosterone excretion rate (AER), and plasma renin activity (PRA).* An *asterisk* (*) indicates statistical significance ($P < 0.05$) compared to the equivalent study day of the control period (shown in Fig. 4).

control period was 3.3 ± 0.5 and 9.0 ± 1.0 ng/ml/hr with subjects in the supine and upright positions, respectively. After 48 hours of ACTH infusion, PRA increased to 5.0 ± 0.7 ($P < 0.02$) and 14.2 ± 1.3 ng/ml/hr ($P < 0.001$) in the supine and upright positions, respectively. During the experimental period, PRA was 3.2 ± 0.5 and 6.0 ± 1.2 ng/ml/hr in the supine and upright positions, respectively. The basal "upright" PRA was lower ($P < 0.01$) during the experimental than it was in the control period. After ACTH infusion, PRA was 4.8 ± 2.8 and 4.5 ± 1.5 ng/ml/hr in the supine and upright positions, respectively; the "upright" PRA was lower ($P < 0.005$) during the experimental than it was during the control period.

The increase in PRA during ACTH infusion was secondary to an increase in the plasma renin substrate concentration. Basal plasma renin substrate (PRS) concentration was 0.91 ± 0.06 and 0.82 ± 0.09 μg/ml in the supine and upright positions, respectively. During ACTH administration, PRS concentration increased to 1.44 ± 0.07, and 1.41 ± 0.14 μg/ml ($P < 0.001$) in the supine and upright positions, respectively. Plasma renin substrate concentration was unaffected by prostaglandin synthesis inhibition during the basal or ACTH-infusion periods.

The fall in PRA during indomethacin administration was secondary to a fall in plasma renin concentration [20]. Basal plasma renin concentration (PRC) was 167 ± 37 and 485 ± 119 μU/ml ($P < 0.01$) in the supine and upright positions, respectively. During the experimental study period, PRC was 121 ± 30 and 156 ± 45 μU/ml in the supine and upright positions, respectively. The PRC in the upright position was significantly lower than that in the control period ($P < 0.01$). The PRC was unaffected by the ACTH infusion during the control or experimental study periods. Indomethacin's effect on plasma renin concentration but not on plasma renin substrate is consistent with prior observations of the role of prostaglandins in the regulation of plasma renin activity [30–35].

Discussion

Although previous studies [36–42] have suggested that PGE might mediate the stimulation of adrenal steroidogenesis by ACTH, this study does not support the role of prostaglandins in basal or ACTH-stimulated adrenal function. Although significant inhibition of plasma and urinary PGE levels was achieved, no change occurred in basal or ACTH-stimulated plasma cortisol, or in urinary 17-hydroxy- or 17-keto-steroid levels. The basal and ACTH-stimulated urinary aldosterone excretion rate fell during the indomethacin-treatment period. Although this might reflect a selective role for the prostaglandins in the regulation of aldosterone biosynthesis, the decrease in plasma renin activity that was observed during the indomethacin administration is a more likely explanation for the fall in aldosterone excretion.

In contrast to the findings of other workers, we found that prostaglandin synthesis inhibition had no effect on plasma creatinine or creatinine excretion. Previous studies had shown that prostaglandin synthesis inhibition in patients with Bartter's syndrome [27], rheumatoid arthritis [43], and systemic lupus erythematosus [44] resulted in a fall in renal creatinine clearance. In each of these diseases, excretion of urinary PGE-like material is abnormally high; thus, renal blood flow may be dependent upon a sustained elevation of renal prostaglandin biosynthesis. Inhibition of prostaglandin biosynthesis has not consistently altered renal function. Friedman et al [45] and Donker et al [46] found that prostaglandin synthesis inhibitors decreased creatinine clearance, whereas Burry and Dieppe [47] found that salicylates had no effect on creatinine clearance. Despite a 50% reduction in urinary PGE excretion, no change in creatinine clearance was observed in this study.

In our study, indomethacin did not affect sodium excretion in subjects on a diet of 9 mEq of sodium per day. Indomethacin reduced potassium excretion during the basal and ACTH periods as compared with the control period. This decrease in potassium excretion is consistent with observations made in other studies [27].

The striking changes in water balance during ACTH and indomethacin administration have not been previously recorded. During simultaneous ACTH and indomethacin administration, we observed a marked fall in urinary volume and free water clearance. Decreased plasma sodium concentration and plasma osmolality, increased urine osmolality, and weight gain were all associated with the fall in free water clearance. Prostaglandin E inhibits vasopressin-stimulated water flow by inhibiting vasopressin-stimulated accumulation of cyclic 3′,5′-adenosine monophosphate [48]. Prostaglandin synthesis inhibition is known to enhance vasopressin-stimulated water flow in rat [49], dog [50], man [51], and toad urinary bladder in vitro [14, 20, 21, 24]. In this study, inappropriate antidiuresis was observed during the simultaneous administration of

ACTH and indomethacin. The inappropriate antidiuretic phase was dependent on both the ACTH and the indomethacin; as soon as the ACTH infusion was discontinued, a prompt diuresis occurred. Antidiuresis was observed in previous studies of the effect of ACTH on adrenal and renal function [52]. In those studies, a crude pituitary preparation of ACTH was used; these pituitary preparations were no doubt contaminated by ADH, thus accounting for the antidiuretic activity observed. We used Cosyntropin, a synthetic ACTH polypeptide. This synthetic peptide has no homologous structure to ADH, and it has not been previously reported to possess antidiuretic activity.

We conclude that prostaglandin synthesis inhibition and the administration of ACTH result in inappropriate antidiuresis. The mechanism for the stimulation of water reabsorption despite plasma hypoosmolality and hyponatremia is not known, although a number of possibilities should be considered. Robertson, Shelton, and Athar [3] have shown that plasma vasopressin concentrations fall to low but detectable levels in normal subjects despite hypoosmolality. Prostaglandin synthesis inhibition is known to enhance renal vasopressin action in man [51]. Furthermore, adrenal steroid hormones are known to enhance vasopressin-stimulated water flow in the toad urinary bladder [22–24]. The effect of steroid hormones on vasopressin-stimulated water flow in the toad urinary bladder is due in part to the inhibition of PGE biosynthesis [24] but is also due to a decrease in phosphodiesterase activity [23]. During the experimental period, adrenal steroidogenesis was markedly increased, and PGE biosynthesis was decreased. These two factors could potentially enhance the effectiveness of even low concentrations of circulating vasopressin and, therefore, result in inappropriate antidiuresis. Or, inappropriate antidiuresis may occur because ACTH and prostaglandin synthesis inhibition interact to: *(1)* induce persistent release of antidiuretic hormone from the pituitary, similar to the persistent release of vasopressin observed in patients with malignancies, *(2)* result in a failure in osmoreceptor function, or *(3)* result in the release or activation of a substance, other than arginine vasopressin, with antidiuretic hormone-like activity.

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