Interaction of Spironolactone and Indomethacin at the Renal Level (36775)

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(Introduced by Donald L. Cook)

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Drug interaction studies involving spironolactone (Aldactone) and nondiuretic agents have been limited. The co-administration of aspirin has been reported to reduce the antialdosterone response of spironolactone in man (1) and laboratory animals (2). Recently, it has been shown that pretreatment with spironolactone and then simultaneous administration of indomethacin (Indocin) resulted in only a limited depression of the indomethacin anti-inflammatory activity in the rat, adjuvant arthritis model (3). The present study was undertaken to assess at the renal level the possible effect of indomethacin on the mineralocorticoid blocking properties of spironolactone.

Materials and Methods. Intact male albino rats (178–224 g) were orally loaded with 25 ml/kg of 0.86% NaCl containing a standard dose (20 mg/kg) of spironolactone (S). Additional animals were given indomethacin (I) in dosages of 1, 5 and 10 mg/kg in the oral load, alone or with S. One or 2 drops of Tween 80 were added/100 ml to suspend drugs. To simulate a hypermineralocorticoid state deoxycorticosterone acetate (DCA) was simultaneously injected sc in all treatment groups at a standard dose of 50 μg in 0.1 ml corn oil. Groups of 4 animals were placed in metabolism cages and following bladder-palpation a pooled urine sample was collected 5 hr later for total urine volume and Na and K (mEq) determinations.

In other experiments 24 hr after bilateral adrenalectomy groups of 4 rats (160–180 g) were dosed orally with 1 or 3 mg S alone or together with 0.3 mg I. Multiplying milligram doses by 5.8 will give approximate milligram per kilogram dosages. All drug treatments were administered in 0.5 ml corn oil in addition to a sc injection of 12 μg DCA in 0.1 ml corn oil and 2.5 ml isotonic saline. A pooled 4 hr urine sample was obtained and diluted to 50 ml with distilled water for NA and K (mEq/liter) measurements. Electrolyte concentrations were transformed into logs for homogeneous variances.

In all experiments reported the degree of DCA blockade was determined from increases in the previously depressed urinary log (NA $\times$ 10/K)[1] ratio rather than enhanced sodium excretion (4–6). No toxicity was noted in any of the assays. Significant differences in treatment versus control or treatment combinations were assessed using nonpaired Student's t tests. Fiducial limits (95% CL) were calculated as mean $\pm$ t $\times$ SE.

Results. In the intact rat injected DCA, as expected, significantly decreased urine volume (—19%) and Na output (—45%) while enhancing (+35%) K excretion and consequently exerted a strong 2.8-fold reduction in the urinary Na/K ratio (Table I). A standard 20 mg/kg dose of spironolactone effectively, but not completely reversed all of the renal effects induced by DCA. Indomethacin at dosages of 1, 5 and 10 mg/kg was inactive; failing to exert in a dose related manner any pro- or anti-DCA responses. No significant or probable interaction was observed with these drugs at 20:10 through 20:1 dosage ratios of S:I. These drug combinations effectively blocked the renal effects of DCA at levels indistinguishable from the responses of S, alone.

[1] Multiplication of Na concentrations by 10 eliminated negative log Na/K values.

TABLE I. Interaction of Spironolactone (S) and Indomethacin (I) in the DCA-Treated Rat.[a]

Treatment	Dose (mg/kg)	Urine (ml/5 hr)	Na (mEq/5 hr)	K (mEq/5 hr)	Log (Na × 10/K)
Saline	—	8.0[b]	2.08[b]	0.51[b]	1.61[b]
DCA (50 μg)	—	6.5	1.14	0.78	1.16
S[c]	20	7.4	1.36[b]	0.63[b]	1.41[b]
I	1	5.3[b]	1.06	0.70	1.16
I	5	5.5	1.30	0.82	1.19
I	10	6.0	1.33[b]	0.82	1.21
S + I	20/1	6.2	1.43[b]	0.61[b]	1.36[b]
S + I	20/5	6.2	1.69[b]	0.66[b]	1.41[b]
S + I	20/10	6.1	1.50[b]	0.70	1.33[b]

[a] Av wt = 200 g/rat. 8 groups (4 rats/group) for DCA controls: 95% fiducial limits = ±1.0, ±0.18, ±0.11 and ±0.06 for urine, Na, K and log (Na × 10/K) ratio. 7 groups for saline control and S. 6 groups for all other treatments which included sc DCA. A change of 0.3 unit in the log (Na × 10/K) ratio represents a 2-fold change in arithmetic ratio.

[b] $p < .05$ vs DCA control.

[c] No significant interaction of S + I vs S.

In the adrenalectomized rat exogenous DCA reduced urinary Na excretion by more than 50% relative to untreated controls along with insignificant increase in urine volume and K excretion (Table II). As seen previously, DCA induced nearly a 3-fold reduction in the urinary Na/K ratio. Spironolactone at both the 1 and 3 mg/rat dosages effectively, but not completely blocked the renal effects of DCA with up to a 2-fold increase in the urinary Na/K ratio. At the highest dose S significantly antagonized the Na retaining and kaliuretic responses of injected DCA. Indomethacin at a dosage of 0.3 mg/rat (ca. 1.7 mg/kg) uniformly decreased urine flow and electrolyte excretion by about 50% with no observed alteration in the urinary Na/K ratio as compared to DCA controls. The simultaneous administration of I (0.3 mg) and S (1 mg) resulted in a severe reduction in urine flow (—72%) and Na (—58%) and K (—68%) excretion below the already depressed DCA control levels. At the other I (0.3 mg) and S (3 mg) combination these urinary parameters were somewhat elevated and yet remained significantly below that of S, alone. The urinary Na/K ratios observed for these drug combinations were equivalent to that of S, alone, primarily as a result of the I-induced uniform depression in both Na and K excretion.

Discussion. Available data indicate that in the intact rat indomethacin is devoid of diuretic effects at dosages (1 to 10 mg/kg) equal to or exceeding that required for an anti-inflammatory response (3). The prominent anti-DCA effects of spironolactone (5, 7), *i.e.*, reversal of Na retention and kaliuresis were observed in the present study. The combined administration with a fixed dosage of spironolactone at ratios up to 20:1 exhibited anti-mineralocorticoid responses equivalent to that observed with this diuretic, alone. Changes in urine volume, Na and K excretion and the urinary Na/K ratio were unaltered following addition of indomethacin to the treatment regimen.

To extend the profile of their interaction, spironolactone and indomethacin were administered in combinations up to 10:1 to DCA-treated adrenalectomized rats. When administered to adrenalectomized rats indomethacin no longer remained devoid of activity at the renal level. Even at a lower dose (ca. 1.7 mg/kg) urine volume and electrolyte excretion levels were uniformly reduced to one half of DCA controls. Unreported studies indicated that a reduction in glomerular filtration rate (inulin clearance) could explain the antidiuretic response of indomethacin in the adrenalectomized rat. The urinary Na/K ratio (index of anti-DCA activity) remained

TABLE II. Interaction of Spironolactone (S) and Indomethacin (I) in the DCA-Treated Adrenalectomized Rat.

Treatment (dose/rat)				Mean urinary response/4 hr[a]			
Compound	mg	DCA (μg)	N[e]	Vol (ml)	Na (mEq/liter)	K (mEq/liter)	Log (Na × 10/K)
—	—	—	8	5.3	6.66[b]	5.88	1.05[b]
—	—	12	10	5.8	2.98	6.78	0.60
S	1	12	9	5.2	3.87	6.50	0.74[b]
S	3	12	9	4.9	4.13[b]	5.25[b]	0.87[b]
I	0.3	12	8	2.5[b]	1.62[b]	3.19[b]	0.66
I + S	0.3/1	12	7	1.6[bc]	1.26[bc]	2.16[bcd]	0.68
I + S	0.3/3	12	7	2.1[bc]	1.94[bc]	2.65[bc]	0.86[bd]

[a] All measured urine samples diluted to 50 ml with distilled water. Na and K concentrations (mEq/liter) were transformed into logs for calculation of log (Na × 10/K) ratios.

[b] $p \leq 0.05$ relative to DCA treatment alone; least significant change = ±1.56, 1.03, 1.01 and 0.13 for urine volume, Na, K and log (Na × 10/K), respectively.

[c] $p \leq .05$ relative to same dose of S.

[d] $p \leq .05$ relative to I.

[e] N = number of measurements (4 animals/group). Av wt = 172 g/rat. SE were 5 to 10% of means.

unaltered following indomethacin versus DCA control. Elevated Na/K ratios were equivalent for combined treatment versus individual responses of spironolactone. However, the drug combination elicited a relative oliguria with a uniformly low concentration of Na and K.

As indicated by Aspinall (3) spironolactone may be beneficial as an adjunct in reducing the ulcerogenic response of indomethacin while maintaining the indomethacin anti-inflammatory activity. The present study suggested that when spironolactone is prescribed clinically for its antimineralocorticoid activity (functioning adrenal present) a significant interaction with indomethacin is not anticipated.

Summary. The effect of indomethacin in altering the anti-mineralocorticoid activity of spironolactone was assessed in the DCA-treated intact and adrenalectomized rat. In the intact rat, simulating a hypermineralocorticoid state, indomethacin was devoid of activity at the renal level in dosages up to 10 mg/kg and also failed to alter the anti-DCA response of spironolactone when combined at dosage ratios as high as 20:1. Indomethacin (ca. 1.7 mg/kg) induced a uniform 50% reduction in urine volume and Na and K excretion in the adrenalectomized rat. In the latter study the anti-DCA response of spironolactone (elevation in urinary Na/K ratio) was unaltered following combined indomethacin treatment. However, a relative oliguria and uniformly low concentration of Na and K was observed with the drug combination.

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