

ADRENOCORTICAL FUNCTION IN HOSPITALISED PATIENTS WITH PULMONARY TUBERCULOSIS RECEIVING A RIFAMPICIN-BASED REGIMEN

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INTRODUCTION

Tuberculosis (TB) is a major cause of morbidity and mortality in sub-Saharan Africa.¹ The disease has a relatively high mortality rate in the first few days after diagnosis despite initiation of treatment with anti-tuberculous drugs.² Standard therapy of TB includes the antibiotic rifampicin, which is a potent hepatic enzyme inducer that might contribute to adrenal insufficiency by accelerating the catabolism of cortisol.³

AIM OF THE STUDY

To compare adrenocortical function in patients diagnosed with acute pulmonary TB during the first five days of therapy with either rifampicin or ciprofloxacin.

PATIENTS

Twenty hospitalised patients who had sputum-positive TB were randomised into two groups of 10 (5 men and 5 women in each group).

Therapy

- Rifampicin group - 300mg/day if weight was < 50kg or 450mg/day if weight was > 50kg.
- Ciprofloxacin group - 500mg/day irrespective of weight.

METHODS

- Clinical measurements** Respiratory rate, pulse rate and supine blood pressure (BP) were recorded prior to the start of therapy.
- Biochemical indices, electrolytes and osmolality** On days 1, 3 and 5, fasting blood samples were analysed for glucose, sodium, potassium, chloride, total CO₂, urea and creatinine. Serum osmolality was calculated.
- Pituitary-adrenocortical hormones** From day 1 to day 5, fasting blood samples were analysed for adrenocorticotropin hormone (ACTH), cortisol, dehydroepiandrosterone-sulphate (DHEA-S) and aldosterone.
- Intravenous ACTH (250µg) stimulation tests** On days 1 and 5, stimulation tests were performed. Fasting blood samples were taken for basal measurements and thereafter 250µg synacthen (Novartis Pharma AG, Basle, Switzerland) was administered as an intravenous bolus. Additional blood samples were taken at 30 min and 60 min for measurement of cortisol, and a normal response was defined as an increment of >200 nmol/l at 60 min.⁴
- Statistical analysis** Results were analysed using the Student's t-test for parametric data, and the Wilcoxon Rank Sum Test or Signed Rank Test when distribution of the data was non-parametric. The effect of ACTH stimulation was analysed by comparison of the incremental rises in cortisol, which were calculated by subtracting the basal level from the peak level attained at 30 min and 60 min (Δ change). Results are expressed as mean \pm SEM and a value of $P < 0.05$ was considered significant.

RESULTS

- Clinical measurements of the two groups were similar, except for BP which was significantly lower in the ciprofloxacin group (Table 1).
- There were no significant differences between the two groups before or during therapy for any of the biochemical indices, electrolytes or calculated osmolality (Table 2).
- There were no significant differences between the two groups before or during therapy for any of the pituitary-adrenocortical hormones (Table 3). Basal cortisol concentrations were consistently below normal and DHEA-S levels were consistently above normal, resulting in a high cortisol to DHEA-S ratio.
- Cortisol concentrations at baseline and after ACTH stimulation did not differ significantly at any time point on day 1 or day 5 between the rifampicin and ciprofloxacin groups (Figure 1). Cortisol responses to ACTH stimulation within the rifampicin group decreased at each time point on day 5 compared with day 1 ($P = 0.001$). However, a significantly higher mean incremental rise from the basal cortisol concentration was measured on day 5 at 60 min ($P = 0.04$).

Table 1 Clinical measurements of two groups of patients on admission to hospital

	Rifampicin (N=10)	Ciprofloxacin (N=10)
Age (years)	28 \pm 3	35 \pm 3
Weight (kg)	51.5 \pm 8.7	51.0 \pm 4.1
Respiratory rate/min	21 \pm 1	20 \pm 1
Pulse rate/min	101 \pm 3	99 \pm 3
Systolic BP (mmHg)	114 \pm 7	96 \pm 4*
Diastolic BP (mmHg)	76 \pm 4	63 \pm 3**

Results are mean \pm SEM. * Significantly lower than Rifampicin group, $p = 0.03$. ** Significantly lower than Rifampicin group, $p = 0.01$.

Table 2 Fasting serum biochemical indices, electrolytes and osmolality in two groups of patients before and during therapy

	Rifampicin group (N=10)			Ciprofloxacin group (N=10)		
	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5
Glucose (mmol/l)	5.3 \pm 0.4	5.4 \pm 0.4	4.6 \pm 0.3*	5.1 \pm 0.5	5.0 \pm 0.5	5.1 \pm 0.4
Sodium (mmol/l)	129 \pm 1	133 \pm 1	133 \pm 1	133 \pm 2	133 \pm 1	135 \pm 1
Potassium (mmol/l)	3.7 \pm 0.1	3.7 \pm 0.1	3.9 \pm 0.1	3.9 \pm 0.1	3.7 \pm 0.1	3.8 \pm 0.1
Chloride (mmol/l)	99 \pm 2	102 \pm 1	102 \pm 1	99 \pm 2	102 \pm 2	105 \pm 2
Total CO ₂ (mmol/l)	20 \pm 1	20 \pm 1	20 \pm 1	22 \pm 1	21 \pm 1	20 \pm 1
Urea (mmol/l)	4.5 \pm 1.0	4.2 \pm 0.7	3.1 \pm 0.4*	3.2 \pm 0.6	3.3 \pm 0.3	2.7 \pm 0.3
Creatinine (µmol/l)	84 \pm 6	80 \pm 6	73 \pm 7*	75 \pm 6	74 \pm 3	68 \pm 2*
Calculated osmolality (mOsm/kg)	277 \pm 2	283 \pm 2	282 \pm 2	283 \pm 3	282 \pm 2	287 \pm 3

Results are mean \pm SEM.
Glucose * $p = 0.03$ day 1, 3 vs. day 5
Urea * $p = 0.001$ day 1, 3 vs. day 5
Creatinine * $p = 0.001$ day 1, 3 vs. day 5

Normal ranges: Glucose 3.0-6.0 mmol/l; sodium 135-147 mmol/l; potassium 3.5-5.3 mmol/l; chloride 99-113 mmol/l; total CO₂ 18-29 mmol/l; urea 2.6-7.0 mmol/l; creatinine 60-120 µmol/l (men) and 60-100 µmol/l (women); osmolality 30-1200 mOsm/kg.

Table 3 Fasting serum concentrations of pituitary-adrenocortical hormones in two groups of patients before and during therapy

	Rifampicin group (N=10)				
	Day 1	Day 2	Day 3	Day 4	Day 5
ACTH (ng/l)	26 \pm 5*	46 \pm 20	30 \pm 7	68 \pm 26	34 \pm 6
Cortisol (nmol/l)	1258 \pm 180	1232 \pm 130	1144 \pm 88	1098 \pm 127	918 \pm 97*
DHEA-S (µmol/l)	2.7 \pm 1.0	2.3 \pm 0.8	1.8 \pm 0.6	1.0 \pm 0.2	1.0 \pm 0.1*
Aldosterone (pmol/l)	372 \pm 108	297 \pm 86	393 \pm 101	328 \pm 117	135 \pm 34*

	Ciprofloxacin group (N=10)				
	Day 1	Day 2	Day 3	Day 4	Day 5
ACTH (ng/l)	26 \pm 4	62 \pm 25	37 \pm 9	66 \pm 22	32 \pm 8
Cortisol (nmol/l)	989 \pm 124	1090 \pm 104	864 \pm 113	953 \pm 129	793 \pm 102
DHEA-S (µmol/l)	1.4 \pm 0.3	1.5 \pm 0.3	1.4 \pm 0.4	1.5 \pm 0.3	1.2 \pm 0.2
Aldosterone (pmol/l)	144 \pm 56	256 \pm 112	212 \pm 75	265 \pm 183	138 \pm 52

Results are mean \pm SEM.

ACTH * $p = 0.001$ day 1 vs. day 2, 3, 4, 5
Cortisol * $p = 0.003$ day 1 vs. day 5
DHEA-S * $p = 0.007$ day 1 vs. day 2, 3, 4, 5
Aldosterone * $p = 0.001$ day 1 vs. day 5

Normal ranges: ACTH <46 ng/l; cortisol 190-660 nmol/l; DHEA-S 4.0-13.3 µmol/l (men) and 0.9-8.7 µmol/l (women) for age range 20-40 years; aldosterone <440 pmol/l (supine).

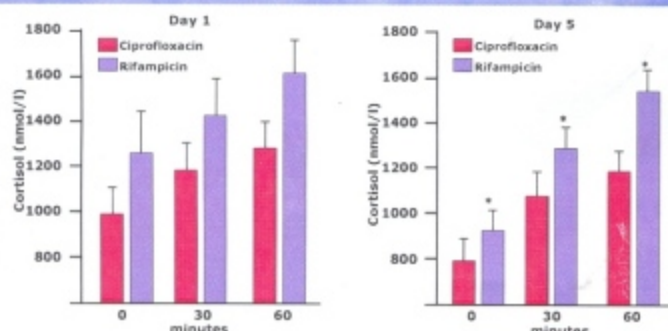


Figure 1.

Serum cortisol responses following intravenous ACTH administration (250µg) in two groups of patients with pulmonary TB treated with rifampicin (n=10) and ciprofloxacin (n=10). Results are expressed as mean \pm SEM.

*P=0.001 for each of the time points.

CONCLUSION

Rifampicin did not impair adrenocortical function during the initial phase of therapy.

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