

# Recovery of plasma corticotrophin and cortisol levels after a three-week course of prednisolone

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**ABSTRACT** Patients with chronic airflow obstruction were given a three-week course of prednisolone 40 mg per day. The basal plasma cortisol level and response to tetracosactrin were depressed after such a course. Basal plasma cortisol and corticotrophin (ACTH) levels were measured on five consecutive days after three weeks of treatment with prednisolone and were found to rise simultaneously to control levels within three days. Pituitary and adrenal functions were depressed for four days after short high dose courses of corticosteroids and patients may be at risk if they encounter stress during this time

Short high dose courses of corticosteroids are commonly given to patients with chronic airflow obstruction. After such a course, the corticosteroids are either tailed off or stopped abruptly since adrenal function is often assumed to be normal. A recent report has demonstrated depression of adrenal function in cancer patients receiving chemotherapy and short high dose courses of corticosteroids.<sup>1</sup> We have studied the time course of response to a short high dose course of prednisolone in patients with chronic airflow obstruction.<sup>2</sup> This provided us with an opportunity to study hypothalamic-pituitary-adrenal (HPA) function in these patients.

## Methods

All the patients studied had chronic airflow obstruction. None had received corticosteroids within three months of the study and none had ever been on long-term treatment with corticosteroids. In the first part of the study a short tetracosactrin test<sup>3</sup> was used to assess adrenal function in eight patients before and after a three-week course of prednisolone 20 mg twice daily. In the short tetracosactrin test a basal plasma cortisol level is measured and followed immediately by an intramuscular injection of 250 µg of synthetic corticotrophin (tetracosactrin). Thirty minutes after the injection of tetracosactrin a blood sample is taken for measurement of plasma cortisol. The

first tetracosactrin test was performed on the day before starting prednisolone and the second test performed on the first day after the three-week course of prednisolone 20 mg twice daily.

The results of the first experiment confirmed that both the basal cortisol and the response to tetracosactrin were suppressed, and we went on to investigate the time course of the recovery of the basal cortisol and ACTH levels after a three-week course of prednisolone 40 mg daily (20 mg bd) in a further seven patients. In this second experiment basal cortisol and ACTH levels were measured on two occasions during the week before treatment and again on days 1, 2, 3, 4, and 5 after treatment with prednisolone. Each blood sample was taken between 0800 and 1000. In four of these seven patients a short tetracosactrin test was repeated on day 5 after treatment with prednisolone.

The plasma cortisol concentration was measured by an automated modification<sup>4</sup> of the acid-fluorescence method of Mattingley.<sup>5</sup> The normal range of basal cortisol levels between 0800 and 1000 is 150-700 nmol/l. The normal response 30 minutes after 250 µg of tetracosactrin is an increase of not less than 190 nmol/l reaching a minimum of 550 nmol/l. The plasma ACTH concentration was measured by the cytochemical section bioassay method.<sup>6</sup> Normal values for this method are not so well established as with the more commonly used but less sensitive radioimmunoassay but probably lie within the range 10-80 ng/l.

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## Results

Figure 1 shows the results of the short tetracosactrin test before and on day 1 after prednisolone. The mean basal cortisol before prednisolone was 381 nmol/l and 76 nmol/l afterwards ( $p < 0.01$ ). The mean cortisol level in response to tetracosactrin before prednisolone was 881 nmol/l and afterwards 207 nmol/l ( $p < 0.001$ ).

The results of the second experiment are shown in the table and fig 2. Patient 7 had prednisolone for two weeks only because her airflow obstruction was abolished during the second week of treatment and it was felt unnecessary to continue treatment. The cortisol samples after treatment on patient 4 were mislaid. The mean basal cortisol and ACTH levels were suppressed and both rose simultaneously to normal levels within three days. Cortisol and ACTH levels in one patient failed to return to normal levels until the fourth day after treatment. The four short tetracosactrin tests on the fifth post-treatment day were all normal.

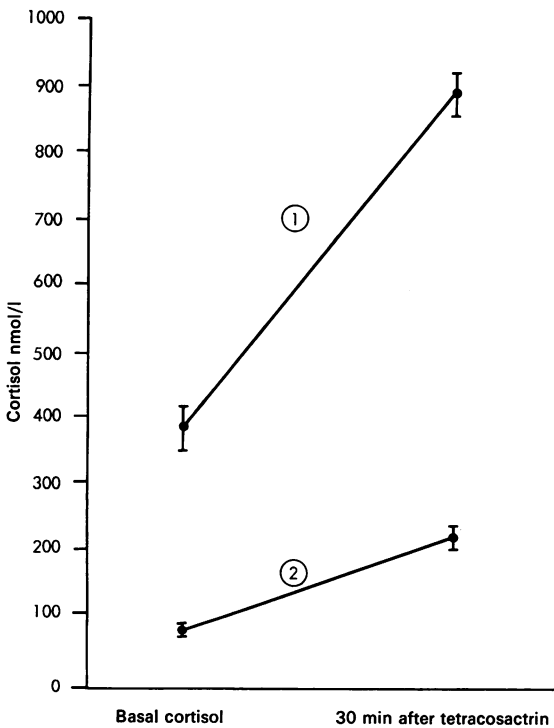


Fig 1 Cortisol responses to tetracosactrin before and after three-week course of prednisolone. (1) Short synacthen test before prednisolone (2) short synacthen test after prednisolone. Results are mean  $\pm$  1 SE.

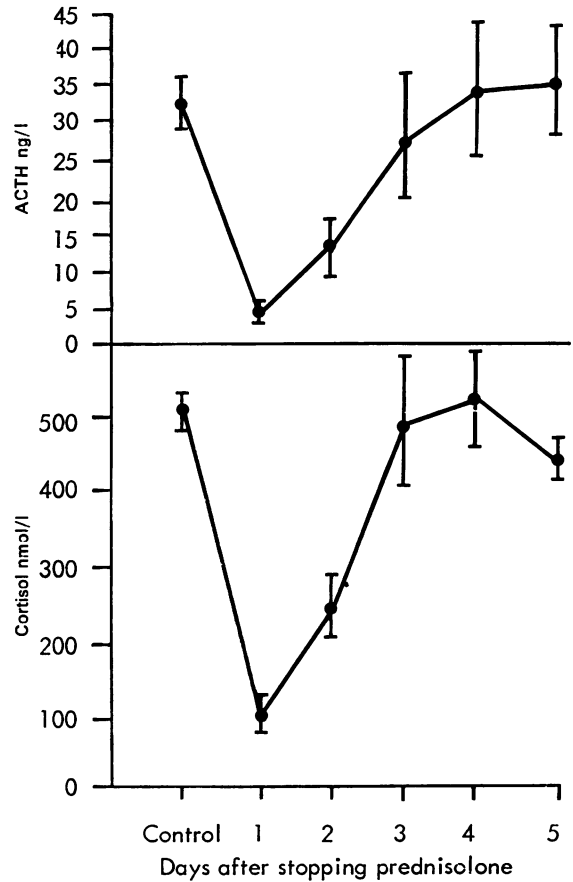


Fig 2 Recovery of ACTH and cortisol levels after finishing course of prednisolone. Results are mean  $\pm$  1 SE.

## Discussion

Biochemical suppression of adrenal function and adrenal atrophy has previously been shown to occur within five days of a dose of approximately 20 mg prednisolone per day.<sup>7,8</sup> Our results confirm suppression of both the basal cortisol and response to tetracosactrin after a short high dose course of prednisolone. We have also demonstrated that the basal ACTH level is suppressed, a finding which has been assumed but has not been possible to verify accurately previously because of the relative insensitivity of the radioimmunoassay method of measuring ACTH levels.

Recovery of HPA function after long-term treatment with corticosteroids is poorly correlated with duration of therapy.<sup>9,10</sup> Graber *et al*<sup>11</sup> showed in patients on high doses of corticosteroids for more than one year that the basal cortisol levels

Table Response of cortisol and corticotrophin after stopping corticosteroids

Patient		Control	Control	Days after corticosteroid therapy					
				1	2	3	4	5	
1	ACTH ng/l	35	22.5	3.8	11.0	18.5	6.5	17.0	Tetracosactrin → 870
	Cortisol nm/l	480	575	100	225	610	585	410	
2	ACTH ng/l	43	40	6.5	24.5	23.5	36.5	35	Tetracosactrin → 820
	Cortisol nm/l	595	690	100	290	545	550	460	
3	ACTH ng/l	36	20	2.1	4.0	18.0	16.0	—	
	Cortisol nm/l	504	540	100	405	800	840	—	
4	ACTH ng/l	17	20	3.0	2.7	22.5	17.0	15.0	
	Cortisol nm/l	485	525	—	—	—	—	—	
5	ACTH ng/l	31.0	31.5	1.5	2.4	4.5	47.0	41.0	
	Cortisol nm/l	465	435	75	60	55	280	375	
6	ACTH ng/l	60	46	10.5	28.0	37.0	75.0	63	Tetracosactrin → 710
	Cortisol nm/l	425	635	100	235	325	400	400	
7	ACTH ng/l	34.5	23	2.4	18.0	70.0	40.0	39.0	Tetracosactrin → 990
	Cortisol nm/l	300	520	105	270	645	480	560	

lagged behind the basal ACTH levels in returning to normal values, and that the ACTH levels rose above normal values before the basal cortisol levels became normal. The simultaneous rise of cortisol and ACTH levels to normal values in our patients do not suggest any delay in recovery of the adrenal gland with respect to the anterior pituitary gland and similar conclusions have been drawn by Donald and Espiner.<sup>12</sup> The tetracosactrin tests suggest that the ability of the adrenal gland to respond to stress is normal within five days and probably earlier in many patients. The negative feedback response of the pituitary, as judged by the basal ACTH levels, returned to normal within four days in all the patients. We did not assess the pituitary response to stress and it is not possible to predict when this would have returned to normal because there is conflicting evidence concerning the relative speed of recovery of the negative feedback response and the response to stress.<sup>9 10</sup>

In conclusion our findings confirm an earlier report that adrenal suppression does occur after a short high dose course of corticosteroids and in addition show ACTH levels to be suppressed. We have also shown that both adrenal and pituitary glands recover simultaneously. Our findings suggest that patients may be theoretically at risk if they encounter stress within a few days of a short high dose course of corticosteroids.

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