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EFFECT OF BECLOMETHASONE DIPROPIONATE ON THE DIURNAL VARIATIONS IN PLASMA CORTISOL LEVEL

By

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It is now well established that the plasma cortisol level of the normal subject varies in a predictable manner during the course of the 24-hour day-night cycle. This was first reported by Bliss et al., (1953) and confirmed by other workers (Gemzell, 1954; Engel et al., 1955). The highest levels are reached at about 0700 hours and the lowest levels at about midnight. More recently, using a frequent sampling technique, it has been shown that the secretory activity of the adrenal cortex, and hence the plasma cortisol level, does not vary smoothly during the 24 hours as was originally assumed, but in an episodic series of "bursts" followed by quiescent periods when no cortisol is secreted (Weitzmann et al., 1966; Takahashi et al., 1968; Orth & Island, 1969). There is evidence that peak secretory activity is associated with rapid eye movement (REM) sleep periods (Helman et al., 1970). In the normal subject there are a mean of nine secretory episodes per 24 hours, as indicated by a rise in the level of plasma cortisol of $2 \mu\text{g}/100 \text{ ml}$ or more. The mean difference between the lowest level and the highest level (the "tidal height") is $18.5 \mu\text{g}/100 \text{ ml}$ and the mean highest level reached is $19.1 \mu\text{g}/100 \text{ ml}$, and this occurs within one hour of 0700 hours (Weitzmann et al., 1971). There are more secretory episodes between 0200 and 0900 than during the remainder of the 24-hour period,

and between these hours the episodes occur at fairly regular intervals, the mean interval being 1 episode every 1.7 hours. In view of these findings it was thought to be of interest to investigate the effects of the recent therapeutic innovation beclomethasone dipropionate aerosol on this cyclical, episodic activity. Beclomethasone dipropionate is a chlorinated corticosteroid which is used in the form of an aerosol in the treatment of chronic asthma. It is administered by inhalation of the pressurised aerosol in metered doses, of the order of 100 μg four times daily, or less. Clinical trials (Morrow-Brown et al., 1972; Clark, 1972) have shown it to be highly effective in reversing airways obstruction in asthma, particularly in those patients previously dependent on corticotrophin injections, or oral steroids. Many of these patients have been successfully transferred to treatment with beclomethasone dipropionate.

Using the short ACTH stimulation test (Wood et al., 1965) and the response of the plasma cortisol level to insulin-induced hypoglycaemic stress (Landon, et al., 1963) no suppression of these responses has been observed in patients undergoing therapy with beclomethasone dipropionate aerosol (Morrow-Brown et al., 1972; Clark, 1972) in contrast with the marked suppression produced by the administration of oral steroids and, to a lesser extent, corticotrophin.

MATERIALS AND METHODS

Seven patients were examined, all of whom had chronic asthma but none had received steroid or corticotrophin therapy at any time. All received inhalations of beclomethasone dipropionate aerosol in a dosage of 100 μg four times daily for a month or more. All achieved a satisfactory therapeutic response measured subjectively and objectively using a Wright Peak Flow Meter. The treatment continued during the study. A sterile catheter was introduced into a suitable forearm vein and taped into position. A three way tap was attached to the distal end of the catheter to enable blood to be withdrawn without disturbing either the patient or the catheter. A solution of 3.8 per cent sodium citrate was used to prevent coagulation occurring within the lumen of the catheter. Blood samples were withdrawn at intervals of 30 minutes throughout the subsequent 24 hours, approximately 6 ml blood being removed each time, and after centrifugation, a 2 ml aliquot of plasma was deep frozen to await estimation of 11-hydroxycorticosteroids, which for the purposes of the present study will be taken as being

TABLE I
Data of Age, Sex and Plasma Cortisol Variations in Seven Patients Treated With Beclomethasone Dipropionate Aerosol.

Patient	Age	Sex	Plasma cortisol $\mu\text{g}/100\text{ ml}$ Range of variations day/night	Max rise above basal level	No of peaks 1 $\mu\text{g}\%$	Hour of highest peak
1	26	F	2-18	16	9	0700
2	24	M	7-24	17	12	0730
3	12	F	2-15	13	5	0700
4	49	F	3-18	15	8	0700
5	17	F	5-34	29	10	0700
6	48	F	6-27	21	11	0600
7	52	M	5-20	15	8	0700

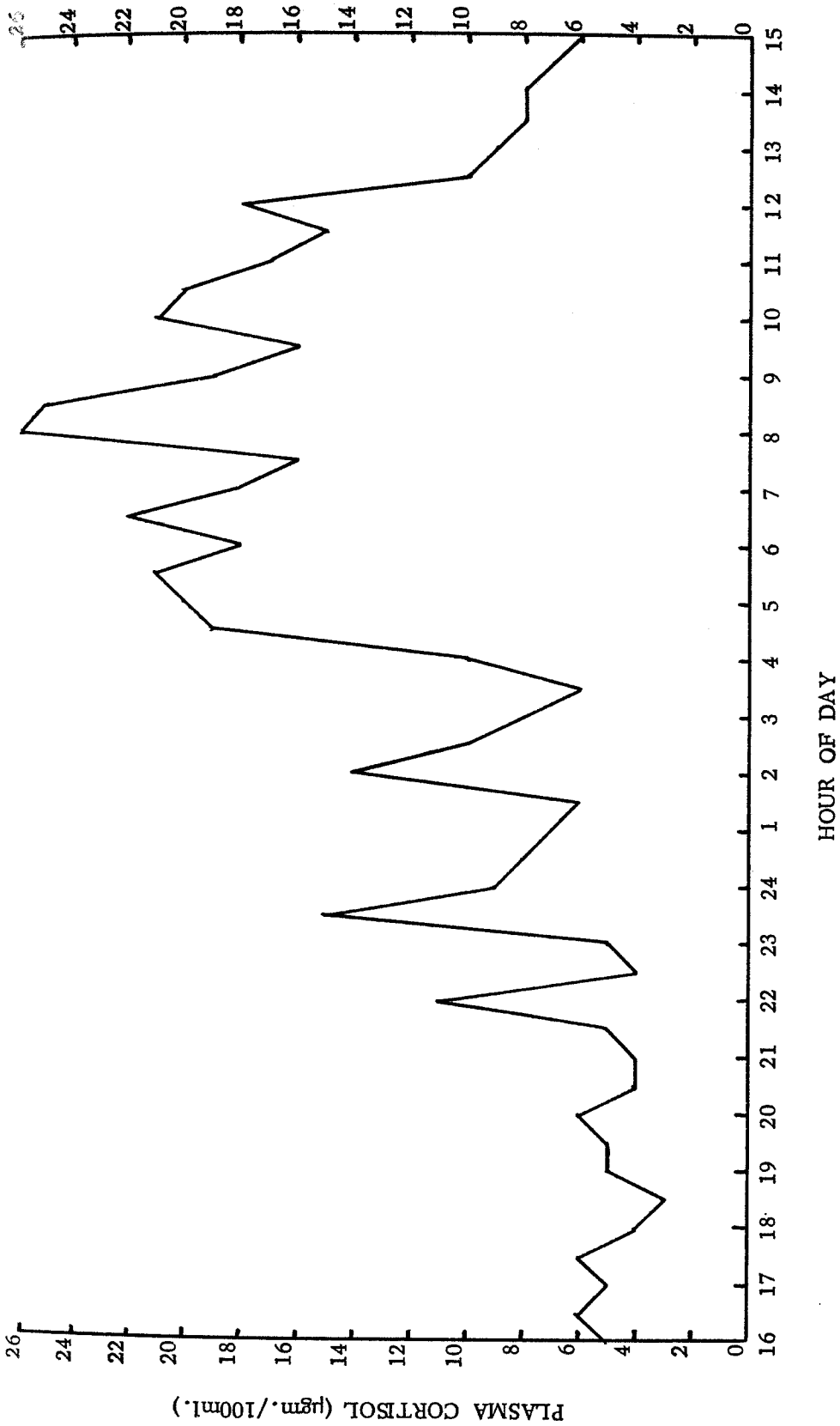


Fig. 1.

Pattern of plasma cortisol levels during 24 hours in a patient treated with beclomethasone dipropionate aerosol (patient 1).

approximately equal to plasma cortisol level. Each patient was ambulant during the day, and slept normally throughout the night. The estimations were performed using an automated fluorimetric technique (Townsend & James, 1968).

RESULTS

The data for each patient is summarised in Table 1 and the graph of the variations in plasma cortisol for patient 1 is shown in Fig. 1. From the data given in Table 1 it can be seen that the diurnal patterns of plasma cortisol levels are comparable with each other, and with those seen in the normal subject (Weitzmann et al., 1966; Takahashi et al., 1968; Orth & Island, 1969; Helman et al., 1970). All seven show a wide range of variations in plasma cortisol level, the "tidal height" varying from a minimum of $13 \mu\text{g}/100 \text{ ml}$ to a maximum of $29 \mu\text{g}/100 \text{ ml}$ (mean 17.8); all show episodic activity with an average of 9 secretory episodes per 24 hours, the highest level being achieved at 0700 hours ± 1 hour.

CONCLUSIONS

At a therapeutic dosage of $400 \mu\text{g}$ per 24 hours, the inhalation of beclomethasone dipropionate aerosol does not suppress the episodic diurnal rhythm of plasma cortisol variations, and using this criterion it is concluded that it does not appear to disturb the normal function of the hypothalamic-pituitary adrenal system.

SUMMARY

The effect of beclomethasone dipropionate aerosol upon the cyclical, episodic secretory activity of the adrenal cortex was assessed by estimating the plasma 11-hydroxycorticosteroid level of blood samples taken at 30 minute intervals throughout a 24-hour period, in patients undergoing therapy with this drug. It was found that no alterations from the normal diurnal patterns occurred.

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