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Nocturnal and morning asthma

Relationship to plasma corticosteroids and response to cortisol infusion

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Soutar, C. A., Costello, J., Ijaduola, O., and Turner-Warwick, M. (1975). *Thorax*, **30**, 436–440. **Nocturnal and morning asthma: its relationship to plasma corticosteroids and response to cortisol infusion.** Nocturnal and early morning breathlessness is a common and important symptom in asthmatic patients. Six patients in whom these symptoms were a major clinical problem have been studied by serial measurements of peak expiratory flow rate (PEFR) and plasma corticosteroids over two 24-hour periods. Although PEFR and plasma corticosteroids are lowest during the night or early morning, preventing the nocturnal fall in plasma corticosteroids by cortisol infusion did not prevent the fall in PEFR in five out of the six patients. The circadian rhythm of corticosteroid secretion does not appear to be the main cause of nocturnal and early morning asthma.

The predominance of nocturnal symptoms from bronchial asthma was recognized by Salter in 1882, but relatively few studies on its mechanism have been reported. Frequent measurement in asthmatics through 24 hours commonly reveals a regularly occurring increase in airway resistance in the early morning. These patients often complain of symptoms during the night or early morning, but evidence of airways obstruction may be absent throughout the rest of the day. A knowledge of the mechanism of nocturnal and early morning asthma (subsequently referred to as early morning asthma) may be particularly important in view of the numbers of unexpected deaths from asthma which have occurred during the early hours of the day.

It has been shown that the usual time of nocturnal breathlessness in a group of asthmatic patients was synchronous with the lowest four-hourly urinary excretion of 17-hydroxycorticosteroids during the 24 hours (Reinberg, Ghata, and Sidi, 1963). This observation suggests that the nocturnal or early morning asthma may be induced by the low plasma cortisol levels occurring during the early hours of the day as part of the normal circadian variation. Our work, by the infusion of cortisol to eliminate the circadian variation in plasma cortisol, was designed to show whether this relationship was causal.

PATIENTS

Asthmatic patients showing a regular nocturnal or early morning (between 11 pm and 9 am) fall in peak expiratory flow rate (PEFR) to values well below the lowest occurring during the rest of the day (an example is illustrated in Fig. 1), and who had not received corticosteroids for at least one year, were selected for study. They had all been admitted to hospital because of poor control of their asthma, and treatment with corticosteroids was being considered. The investigation was undertaken in an attempt to obtain better control

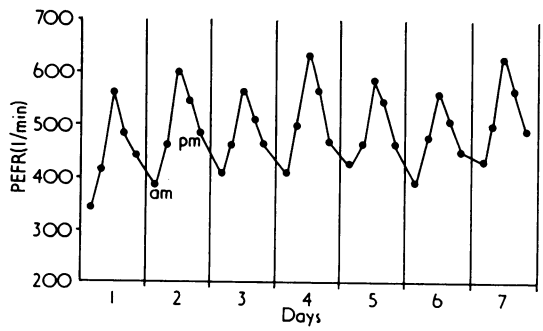

FIG. 1. *Circadian change of peak expiratory flow rate (PEFR) in an asthmatic patient (measurements made at* 0.600, 10.00, 14.00, 18.00, *and* 22.00 *hours).*

of the patient's asthmatic symptoms using minimal doses of steroids. The nature of and reasons for the investigation were explained to each of the six patients who consented to be studied. Patients were included when their lowest PEFRs between 11 pm and 9 am were at least 20% lower than at any other time of the day. Three were in their third decade, one in the fourth, and two in the fifth. Four had positive skin prick tests to common allergens and two had negative skin tests.

METHODS

The measurement was carried out over two 24-hour periods (days 1 and 2) separated by a rest day. On days 1 and 2 the patients' peak expiratory flow rate (best of three attempts) was measured at two-hourly intervals from 9 am for 24 hours. At the same times blood samples were taken for estimation of plasma fluorogenic corticosteroids through a small indwelling intravenous needle which was inserted an hour before the first blood sample was taken. In addition, on day 2 hydrocortisone sodium succinate in normal saline was infused through a second indwelling needle in the other arm, using an infusion pump.

Different doses of hydrocortisone were infused in the six patients in an attempt to eliminate the circadian variation and at the same time produce a range of plasma corticosteroid levels. Initially, doses were calculated by extrapolation from the half-life of hydrocortisone given in single much larger doses (Collins *et al.*, 1970) and were subsequently modified in the light of experience. The patients were encouraged to sleep in similar postures on the two days. Other therapy, including oral and inhaled sympathomimetic agents and disodium cromoglycate, if required, was given at exactly equal intervals throughout the 24 hours on both days.

Blood samples were placed in heparinized tubes, the plasma was immediately separated, and 1 ml aliquots were stored at −20°C. They were later analysed for plasma corticosteroids by one of us (OI) using the fluorogenic method of Mattingly (1962) as recommended by the Medical Research Council Working Party (1971). All measurements were done in duplicate.

RESULTS

Plasma corticosteroids of all six patients on day 1 are shown in Figure 2. In spite of the disturbance caused by waking every two hours, normal circadian variations were recorded and the values fell within the normal range (Cope, 1972).

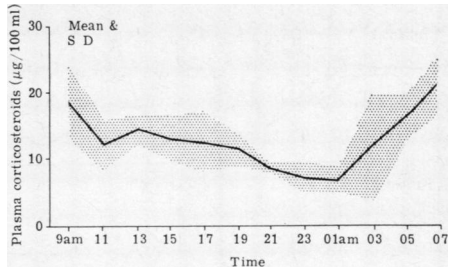

FIG. 2. *Mean plasma corticosteroids of six asthmatic patients on day 1 (line) and standard deviation (stippled area).*

Cortisol infusions on day 2 raised the nocturnal plasma corticosteroids by a series of increments, the nocturnal values achieved ranging from 9·5 to 36 μg/100 ml. The doses of cortisol infused and the increment in the minimum blood levels achieved are illustrated in Table I and Figure 3. The plasma corticosteroid values for each patient throughout the two days are plotted in Figure 4.

TABLE I

LOWEST NOCTURNAL PLASMA CORTICOSTEROIDS ON DAYS 1 AND 2, CORTISOL INFUSION RATES, AND THE INDUCED INCREMENT IN PLASMA CORTICOSTEROIDS

Patient	Lowest Plasma Corticosteroids		Cortisol Infusion Rate (μg/kg/hr)	Increment in Lowest Plasma Corticosteroids (μg)
	Day 1	Day 2		
1	4·3	11·0	30	6·7
2	5·5	14·1	40	8·6
3	6·0	10·0	30	4·0
4	8·7	25·8	80	17·1
5	5·2	34·0	45	28·8
6	5·1	11·9	60	6·8

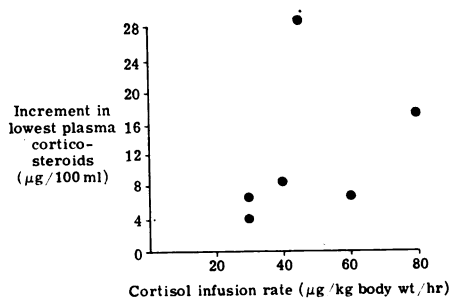

FIG. 3. *Increments in lowest plasma corticosteroids induced by various hydrocortisone infusion rates.*

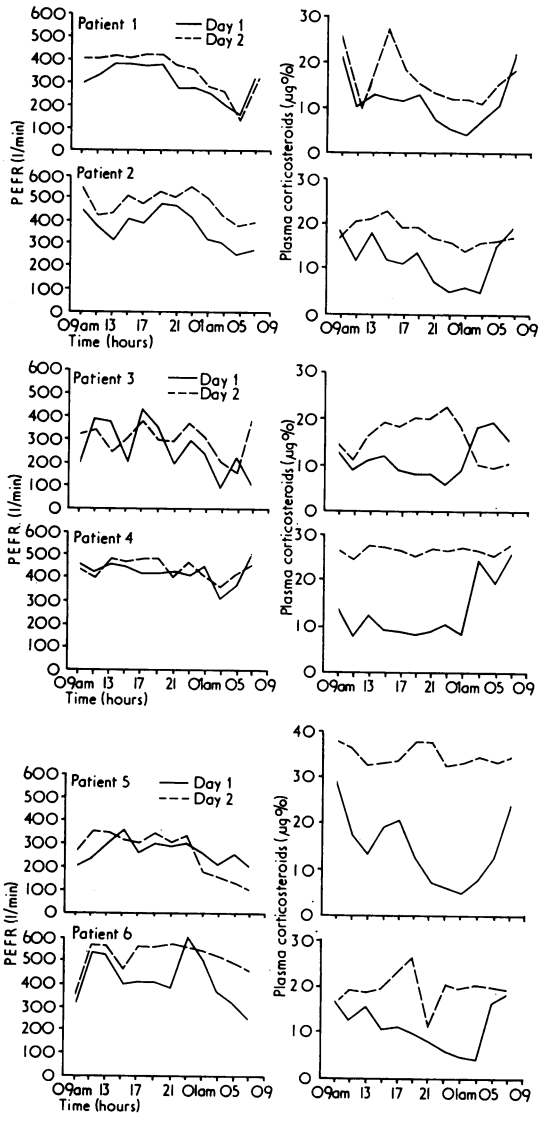

FIG. 4. *Peak expiratory flow rates and plasma corticosteroids.*

PEAK EXPIRATORY FLOW RATE During day 1 the lowest peak expiratory flow rate (PEFR) in each patient at night (11 pm–9 am) was worse than the lowest reading during the rest of the day by amounts varying from 60 to 130 l/min (19–60%) (see Table II). During cortisol infusion on day 2 a nocturnal fall in PEFR still occurred in five out of the six patients (Fig. 4, patients 1–5; Table II).

TABLE II

NOCTURNAL FALL IN PEFR ON DAYS 1 AND 2

Patient	Nocturnal Fall in PEFR (l/min)		Improvement (see text)
	Day 1	Day 2	
1	120	240	−100%
2	60	40	+ 33%
3	120	90	+ 25%
4	100	50	+ 50%
5	125	100	+ 20%
6	130	10	+ 92%

In one patient, however, the nocturnal asthma was much improved (fall in PEFR only 10 l/min), although the configuration of the peak flow chart suggested that the nocturnal fall was still occurring, though in a much modified form (Fig. 4, patient 6). This patient, a 24-year-old male engineer without apparent relevant occupational exposure, had positive skin prick tests to multiple antigens and highly labile asthma.

For the purposes of comparison the index

$$\frac{\text{fall in PEFR, day 1} - \text{fall in PEFR, day 2}}{\text{fall in PEFR, day 1}} \times 100$$

was used to express the improvement in nocturnal asthma during cortisol infusion (such that 0%= no improvement, 100%=complete cure). Comparison of this index of improvement with the elevation of lowest nocturnal plasma corticosteroid achieved by cortisol infusion failed to reveal any clear relationship between the increment in plasma corticosteroids and the improvement in nocturnal asthma (Fig. 5).

It was not possible in every patient to eradicate a circadian variation of some sort since the normal variation was, in three patients, apparently superimposed upon the elevation in plasma corticosteroids produced by the infusion. In spite of this, the plasma corticosteroids on day 2 were maintained above 9 μg/100 ml in all patients, and some values were considerably higher than this.

In three patients the plasma corticosteroids remained at virtually the same level for the whole of day 2 (patients 4, 5, and 6) so that there was no circadian variation in plasma cortisol whatever. In spite of this, the early morning asthma still occurred in two of these patients (2 and 5). In the third patient (6) the asthma was substantially modified.

DISCUSSION

While unpredictable variation of asthma throughout the 24 hours is very common, a regular circadian rhythm in asthmatic symptoms is frequently seen. Asthmatic patients who complain of

dyspnoea or wheezing during the night or on getting up in the morning are frequently seen in hospital practice and so are the patients who complain of asthma when they get up but have no measurable airways obstruction when seen in outpatients an hour or two later. This rhythmic fluctuation can also be detected by simple measurements in many asthmatic patients who are not aware that their asthma is worse at night. Study of the mechanism of this variation may throw some light on the mechanism of sudden death in asthmatics, for the majority of unexpected deaths from asthma in one hospital series (Cochrane and Clark, 1975) occurred during the early hours of the morning.

The vital capacities of normal individuals and most asthmatics tend to be reduced slightly by lying down, although in some asthmatics this manoeuvre actually increases the vital capacity (Michelson and Lowell, 1958). Changes in vital capacity, pulmonary blood flow, and distribution of gas in the lungs induced by lying down (Bryan *et al.*, 1964) would also be expected to be rapidly reversed by sitting up, or partially prevented by sleeping propped up on many pillows. We have encouraged a few of our patients to sit up as far as possible at night without noticeable change in their nocturnal or morning asthma. Accumulation of bronchial secretions during the night may be a contributory factor, but early morning asthma is also seen in some patients who do not produce sputum.

The supine posture appears to increase the sensitivity of asthmatics to inhaled histamine (Bouhuys, 1963) and therefore possibly to inhaled allergens, but this change is too small to be an important cause of nocturnal asthma. Asthmatics have also been shown to be more sensitive to inhaled histamine by night than by day (de Vries *et al.*, 1962). This does not necessarily imply an intrinsic change in the patient, for increased inhalation of allergens at night could cause increased histamine sensitivity. Certainly the highly allergenic house dust mite is found in high concentration in bedding and may be the cause of nocturnal asthma in some patients. However, this is unlikely to be the cause in all cases, as the phenomenon is common in skin test negative patients as well as atopic asthmatics. In some cases of asthma caused by industrial exposure to inhaled agents, such as piperazine (McCullagh, 1968; Pepys, Pickering, and Loudon, 1972) and Red Cedar wood dust (Gandevia and Milne, 1970), asthmatic symptoms are often worse at night. This may partly be the result of the late asthmatic

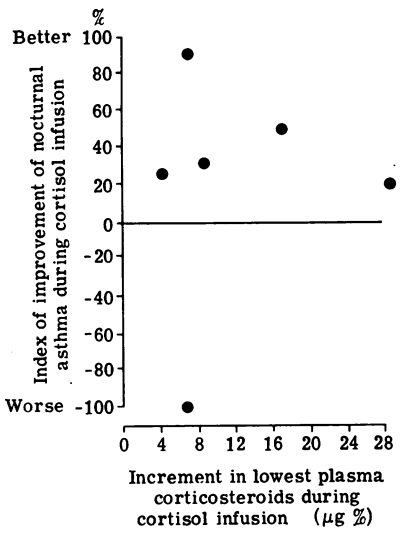

FIG. 5. *Comparison of improvement of nocturnal asthma with increment in lowest plasma corticosteroids during hydrocortisone infusion.*

reaction which has been shown to occur in these patients, but the recurrence of the nocturnal asthma for several days after the exposure ceased in a patient suffering from asthma due to Red Cedar dust (Gandevia and Milne, 1970) suggests that the nocturnal and morning worsening of asthma was the result of some additional factor having a circadian fluctuation.

The demonstration by Reinberg *et al.* (1963) that the early morning asthmatic attacks in a group of patients was synchronous with the lowest four-hourly urinary excretion of 17-hydrocycorticosteroids during the 24 hours raised the obvious question whether there was a causal relationship. This seemed a reasonable suggestion although it had been our clinical impression that early morning asthma often persisted in spite of conventional therapeutic doses of corticosteroids.

The investigation of six cases of asthma reported in this paper showed that in all but one, early morning asthma persisted in spite of preventing the plasma corticosteroids from falling below levels which might be regarded as high in the physiological range. Serial eosinophil counts were not performed but might have been useful in confirming that the physiological effects of the circadian change in plasma cortisol had been modified. We conclude, however, that the circadian variation in cortisol secretion is not the main cause of the circadian variation in airways obstruction in most asthmatic patients.

It was most interesting that the plasma corticosteroids on the control day were remarkably normal in spite of our awakening the patients every two hours and in spite of quite uncomfortable dyspnoea in the case of two patients, suggesting that the early morning asthma observed by us was not sufficient stress to cause increased secretion of cortisol.

Chronobiological investigations have demonstrated that many other metabolic processes exhibit circadian rhythm. The relationship between these and early morning asthma should now be explored.

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