Nocturnal Events Related to “Morning Dipping” in Bronchial Asthma


The mechanism of early morning bronchospasm in asthma was investigated by analyzing circadian variations in the plasma levels of cortisol, ACTH, epinephrine, and norepinephrine, as well as in the serum neutrophil chemotactic activity and heart rate in asthmatic patients with (n = 6) and without (n = 7) “morning dipping” and normal subjects. Findings suggested that an exaggerated nocturnal nadir in plasma cortisol levels may precipitate “morning dipping” in some patients with asthma.

An increase in the severity of airway obstruction during the early morning hours is a common occurrence in bronchial asthma. Airway caliber exhibits a circadian rhythm with the trough occurring in the early morning hours, and the amplitude of variation being considerably greater in asthmatic than normal, individuals. It is probable that “morning dipping” in asthma is associated with this exaggerated circadian variation in pulmonary function, the precise cause of which remains, however, undefined.

The beneficial effects of epinephrine and cortisol in asthma lend credence to the postulate that “morning dipping” may be related to nocturnal troughs in the plasma levels of these hormones. A temporal association has been shown to exist between the diurnal nadirs in plasma cortisol, plasma epinephrine, and urinary catecholamine levels, and early morning bronchospasm in asthmatic patients. An unequivocal cause-effect relationship between these variables and airway function has not, however, been easy to confirm, and neither cortisol infusions nor therapeutic levels of salbutamol result in complete abolition of “morning dipping” in asthmatic patients.

Both antigen and exercise-induced bronchospasm are associated with increased serum neutrophil chemotactic activity. A similar phenomenon could be occurring in relation to “morning dipping” as a result of increased mast cell mediator release precipitated by the nocturnal nadirs in plasma catecholamine and corticosteroid levels. Documentation of this has not, however, been available.

There is a circadian variation in heart rate in normal subjects with the nadir occurring in the early morning. This may be related to a degree of sympathetic withdrawal, with a shift to dominant vagal tone. The possibility that “morning dipping” may be related to vagal mechanisms is suggested by the finding that it can be markedly attenuated by ipratropium bromide. Barnes has postulated that “morning dipping” may be due to the coincidence of a number of these variables in the early morning as a result of biologic rhythms originating in the hypothalamus. The object of the present study was to assess their relative importance by studying the diurnal changes in them in relation to fluctuations in airway caliber.

SUBJECTS AND METHODS

We studied 13 asthmatic patients and 11 normal subjects. Informed consent was obtained in each case, and the study was approved by the Ethics Committee of the University of the Witwatersrand. Each asthmatic patient was a nonsmoker with a long history of the disease, the diagnosis being confirmed by the finding of at least one of the following: (1) a FEV, level less than 70 percent of the predicted value with significant reversibility following inhalation of a bronchodilator; (2) a fall in peak expiratory flow rate (PEF) of at least 20 percent on exercise.

The asthmatic patients were divided into two subgroups, namely: “dippers” and “nondippers,” depending on whether or not they demonstrated significant morning dipping during the study. This was arbitrarily defined as a fall of 20 percent or greater in the PEF at 4:00 am compared with the basal value the previous afternoon, based on data suggesting that PEF may exhibit a circadian variation of up to almost 20 percent even in normal individuals (mean amplitude of variation 8.3 percent, standard deviation 5.2 percent).

Each patient was using a beta-adrenergic bronchodilator aerosol regularly. This was discontinued a week prior to the study. None was using another bronchodilator preparation. No patient had received systemic corticosteroid therapy for at least two years prior to the study. Ten patients were using beclomethasone dipropionate aerosol which was discontinued on the morning of the study. Full details of corticosteroid therapy in the asthmatic patients are given in Table 1.

The normal subjects were nonsmokers with no history of bronchial asthma or any atopic condition. Each had normal pulmonary function...
Table 1—Details of Corticosteroid Therapy in Asthmatic Patients Ranked in Ascending Order of Midnight Plasma Cortisol Levels

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Midnight Cortisol Level (ng/ml)</th>
<th>Fall in PEF During Use of Beclomethasone* (%)</th>
<th>Use of Systemic Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dippers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>55</td>
<td>Regular short-term (500 μg)</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>20</td>
<td>Regular long-term (400 μg)</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>27</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>25</td>
<td>Regular long-term (300 μg)</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>20</td>
<td>Regular long-term (300 μg)</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>21</td>
<td>Nil</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>13</td>
<td>Regular long-term (300 μg)</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>11</td>
<td>Irregular short-term</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>7</td>
<td>Nil</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>7</td>
<td>Regular long-term (400 μg)</td>
</tr>
<tr>
<td>Nondippers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>28</td>
<td>5</td>
<td>Irregular short-term</td>
</tr>
<tr>
<td>12</td>
<td>108</td>
<td>10</td>
<td>Irregular short-term</td>
</tr>
<tr>
<td>13</td>
<td>138</td>
<td>15</td>
<td>Irregular short-term</td>
</tr>
</tbody>
</table>

*Short-term is less than one month; long-term, more than 2 years; doses given in parentheses are maximum daily doses.

and none had a significant fall in PEF on exercise.

The subjects were studied individually in the recumbent position in a quiet room. A 19-gauge or larger cannula was inserted into an arm vein at midday and kept patent with a saline infusion. Subsequently, each subject was attached to a 24-hour ambulatory electrocardiograph (ECG) recorder. A standardized light meal was given at 6:00 PM. Water was the only beverage permitted. Blood was sampled through the cannula at 4:00 PM, 4:30 PM, midnight, 4:00 AM, and 8:00 AM. Aliquots of the blood taken at each time were kept for measurement of the plasma levels of epinephrine, norepinephrine, cortisol, and adrenocorticotropic hormone (ACTH), and for assessment of the serum neutrophil chemotactic activity. However, as the number of investigations was limited by cost, measurements of plasma catecholamines and studies of serum neutrophil chemotactic activity were omitted at midnight, and plasma ACTH levels measured only in the midnight and 8:00 AM specimens.

For plasma specimens, aliquots of blood were placed into iced tubes, immediately centrifuged, and the separated plasma then stored at −20°C until assayed. For serum specimens, blood was allowed to clot at room temperature for 20 to 30 minutes and then centrifuged, and the separated serum stored at −20°C until analysis.

Measurements of PEF were made subsequent to the sampling of blood at 4:00 PM, 4:30 PM, 4:00 AM, and 8:00 AM using a Wright’s peak flow meter. The best of three readings was recorded at each time. The basal PEF was the arithmetic mean of the values obtained at 4:00 PM and 4:30 PM.

### Analytical Methods

**Hormones.** Plasma cortisol and ACTH levels were measured using radioimmunoassay kits (lower limits of sensitivity 4 ng/ml for cortisol; 10 pg/ml for ACTH).

Plasma epinephrine and norepinephrine levels were measured by a radioenzymatic method (lower limits of sensitivity 2 to 5 pg/ml).

The intraassay coefficient of variation for each of these assays was less than 5 percent. Each sample was assayed in duplicate, the mean of the two radioactivity counts being used to calculate the final value.

For basal hormone levels, equal aliquots of the 4:00 PM and 4:30 PM specimens were mixed and integrated basal levels obtained.

**Serum Neutrophil Chemotactic Activity.** Polymorphonuclear leukocytes (PMNLs) were prepared from heparinized venous blood obtained from adult human donors.¹

(1) PMNL migration assay: The leukotactic potential of the

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Table 2—Demographic and Pulmonary Function Data

<table>
<thead>
<tr>
<th></th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>FEV₁ (% Predicted)</th>
<th>Airway Resistance (cmH₂O/L/s)</th>
<th>Fall in PEF on Exercise (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects (n = 11)</td>
<td>21.2 (3.2)</td>
<td>6M,5F</td>
<td>107.2 (11.2)</td>
<td>1.5 (0.5)</td>
<td>1.7 (2.8)</td>
</tr>
<tr>
<td>Dippers (n = 6)</td>
<td>20.3 (2.9)</td>
<td>3M,3F</td>
<td>67.0 (22.5)*</td>
<td>6.9 (4.9)*</td>
<td>32.5 (14.3)</td>
</tr>
<tr>
<td>Nondippers (n = 7)</td>
<td>21.1 (5.5)</td>
<td>4M,3F</td>
<td>88.6 (16.9)*</td>
<td>3.2 (1.9)*</td>
<td>31.1 (8.7)</td>
</tr>
</tbody>
</table>

*Dippers vs nondippers significantly different (p < 0.025).
specimens was measured using modified Boyden chambers with 5 μm pore-size millipore filters. The sera were diluted to a final concentration of 20 percent. The filters were processed after incubation for 60 minutes at 37°C and the results expressed as PMNL per microscopic high-powered field. Corresponding control specimens for random migration in the absence of serum were included and subtracted from each test.

(2) Activation of PMNL membrane-associated oxidative metabolism: The effects of the serum specimens on PMNL membrane-associated oxidative metabolism were measured by a myelo-peroxidase-mediated iodination assay as an alternative method of detection of serum-associated leukoattractants. Sera were tested at a final concentration of 20 percent and the results expressed in fmol using Spearman’s rank correlation coefficient.

Each individual specimen was coded prior to storage, the code only being broken once the results were available.

The basal value in the tests of neutrophil chemotactic activity was the arithmetic mean of the 4:00 AM and 4:30 PM values.

ECG Analysis. For ECG analysis, strips of 20 beats taken five, ten, and 15 minutes prior to each sampling of blood were studied. From these 60 beats, the maximum, minimum, and mean heart rates and the magnitude of respiratory sinus arrhythmia (RSA) were obtained for each time in the study.

The basal value for each ECG variable was the arithmetic mean of the values obtained at 4:00 AM and 4:30 PM values.

Statistical Analysis. For each variable, comparisons were made between the following: (1) asthmatic dippers and asthmatic nondippers; (2) dippers and normal subjects; and (3) nondippers and normal subjects. Pairwise comparisons were made using the two-tailed Mann-Whitney U test conducted at a simultaneous 5 percent Bonferroni level. The degree of variation in each variable during the study was assessed within each group using Friedman’s two-way analysis of variance. Correlations between variables were done using Spearman’s rank correlation coefficient.

RESULTS

On the basis of the fluctuations in PEF during the study, the asthmatic patients were subdivided into six dippers and seven nondippers.

Demographic and pulmonary function data are shown in Table 2. The FEV1 was lower and the airway resistance higher in the dippers than in the nondippers (p<0.025). There was no difference between these subgroups, however, in the PEF response to exercise.

Fluctuations in PEF during the study are shown in Table 3. The mean fall in PEF from the basal value to that at 4:00 AM was 28.0 ± 14.0 percent in the dippers and 9.8 ± 3.7 percent in the nondippers (p<0.001). The PEF exhibited a significant degree of variation in both dippers and nondippers (p<0.01), but not normal subjects (p = >0.1).

Hormones

Plasma cortisol levels are shown in Table 4. The plasma cortisol exhibited a significant degree of variation in each group of subjects during the study (dippers and nondippers, p<0.0001; normal subjects, p<0.001). Midnight plasma cortisol levels were significantly lower in the asthmatic dippers than in either the nondippers (p<0.005) or the normal subjects (p<0.001). There was no difference, however, between nondippers and normal subjects in the midnight plasma cortisol level (p>0.38). The dippers exhibited greater fluctuations in the plasma cortisol level during the study, the ratio between the basal and midnight levels being higher than in nondippers (p<0.025) or normal subjects (p<0.001). There was no difference, however, between nondippers and normal subjects in this ratio (p>0.16).

Plasma ACTH levels are shown in Table 5. The mean values in each group were consistent with the normal diurnal levels for our laboratory. There was no significant difference between the groups at either time.

Plasma catecholamine levels are shown in Table 6. The plasma norepinephrine level exhibited a significant degree of variation in the normal subjects during the study (p<0.02). There was no significant variation in norepinephrine levels, however, in either the asthmatic dippers or the nondippers. Although plasma

| Table 3—Peak Expiratory Flow Rates* |
|-------------------------------|----------|----------|----------|
|                               | Basal    | 4:00 AM  | 8:00 AM  |
| Normal subjects               | 490 (73) | 477 (69) | 490 (72) |
| (n = 11)                      |          |          |          |
| Dippers                       | 323 (94) | 238 (102)| 284 (111)|
| (n = 6)                       |          |          |          |
| Nondippers                    | 443 (107)| 402 (106)| 416 (112)|
| (n = 7)                       |          |          |          |

*Values are mean (SD) liters/minute. (Percent fall in PEF at 4:00 AM compared with basal value—dippers = 28.0 ± 14.0%; nondippers = 9.8 ± 3.7%—p = <0.0001.)

| Table 4—Plasma Cortisol Levels* |
|-------------------------------|----------|----------|----------|----------|
|                               | Basal    | Midnight | 4:00 AM  | 8:00 AM  | Ratio     |
|                               |          |          |          |          | Basal:Midnight |
| Normal subjects               | 74.6 (26.1)| 50.5 (32.3) | 97.5 (48.8)| 151.8 (32.5)| 1.8 (0.7)  |
| (n = 11)                      |          |          |          |          |            |
| Dippers                       | 57.3 (16.9)| 13.8 (3.7) | 63.8 (29.2)| 119.2 (35.8)| 4.3 (1.7)  |
| (n = 6)                       |          |          |          |          |            |
| Nondippers                    | 87.1 (50.3)| 50.4 (48.5) | 81.3 (44.1)| 173.7 (48.6)| 2.5 (1.1)  |
| (n = 7)                       |          |          |          |          |            |

*Values are mean (SD) ng/ml; conversion to nmol/L × 2.76.

†Normal subjects vs dippers significantly different (p = <0.001).
‡Nondippers vs dippers significantly different (p = <0.005).
§Nondippers vs dippers (p = <0.025).
epinephrine levels appeared to exhibit minor degrees of variation, this was not statistically significant in any group. There was no significant difference between the groups in either the epinephrine or norepinephrine levels at any time.

Serum Neutrophil Chemotactic Activity

The results of measurements of the serum neutrophil chemotactic activity are shown in Table 7. Serum neutrophil chemotactic activity did not vary significantly in any group during the study. There was no significant difference between the groups at any time.

ECG Analysis

The ECG data are shown in Table 8. There was no significant variation in the heart rates or the RSA in either normal subjects or nondippers during the study. In the dippers, on the other hand, all heart rates and the RSA varied significantly during the study (maximal heart rate p<0.005, minimum heart rate p<0.05, mean heart rate p<0.05, RSA p<0.005). The maximum heart rate tended to diminish to a greater degree in the dippers than in either the nondippers or the normal subjects at midnight and 4:00 AM, with corresponding decreases in the RSA at these times. There was no significant difference, however, between the groups in any of the ECG variables at any time.

Correlations

When the data from the two subgroups of asthmatic patients (dippers plus nondippers n = 13) were combined, there was a strong inverse correlation between the midnight plasma cortisol levels and the magnitude of the fall in PEF from the basal value to that at 4:00 AM (r = -0.79, p<0.0002) (Table 1). There was no correlation between the 4:00 AM plasma cortisol level and the fall in PEF (r = -0.15, p<0.6). No correlation could be demonstrated between either the 4:00 AM plasma epinephrine or norepinephrine levels and the magnitude of respiratory sinus arrhythmia.

Table 5—Plasma ACTH Levels*

<table>
<thead>
<tr>
<th></th>
<th>Midnight</th>
<th>8:00 AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects (n = 11)</td>
<td>76.9 (24.6)</td>
<td>100.8 (40.9)</td>
</tr>
<tr>
<td>Dippers (n = 6)</td>
<td>71.3 (8.8)</td>
<td>110.0 (24.6)</td>
</tr>
<tr>
<td>Nondippers (n = 7)</td>
<td>98.0 (34.6)</td>
<td>113.6 (21.7)</td>
</tr>
</tbody>
</table>

*Values are mean (SD) pg/ml; conversion to pmol/L X 0.0055 for epinephrine, X 0.0059 for norepinephrine.

Table 6—Plasma Catecholamine Levels*

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>4:00 AM</th>
<th>8:00 AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects (n = 11)</td>
<td>37.1 (17.4)</td>
<td>27.1 (12.6)</td>
<td>39.1 (17.4)</td>
</tr>
<tr>
<td>Dippers (n = 6)</td>
<td>23.5 (12.1)</td>
<td>19.2 (1.5)</td>
<td>30.2 (7.5)</td>
</tr>
<tr>
<td>Nondippers (n = 7)</td>
<td>33.9 (18.4)</td>
<td>25.6 (11.6)</td>
<td>29.4 (11.0)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects (n = 11)</td>
<td>223.5 (103.5)</td>
<td>153.9 (43.0)</td>
<td>135.5 (65.4)</td>
</tr>
<tr>
<td>Dippers (n = 6)</td>
<td>137.0 (34.5)</td>
<td>106.2 (39.3)</td>
<td>242.5 (230.7)</td>
</tr>
<tr>
<td>Nondippers</td>
<td>218.4 (169.6)</td>
<td>144.9 (51.2)</td>
<td>137.8 (57.4)</td>
</tr>
</tbody>
</table>

*Values are mean (SD) pg/ml; conversion to pmol/L X 0.22.

Table 7—Serum Neutrophil Chemotactic Activity

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>4:00 AM</th>
<th>8:00 AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphonuclear leukocyte migration assay*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects (n = 11)</td>
<td>53 (28)</td>
<td>53 (29)</td>
<td>53 (24)</td>
</tr>
<tr>
<td>Dippers (n = 6)</td>
<td>54 (25)</td>
<td>63 (25)</td>
<td>58 (23)</td>
</tr>
<tr>
<td>Nondippers (n = 7)</td>
<td>57 (30)</td>
<td>58 (19)</td>
<td>60 (25)</td>
</tr>
<tr>
<td>Polymorphonuclear leukocyte membrane-associated oxidative metabolism†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>6160 (4115)</td>
<td>5890 (3977)</td>
<td>5856 (4028)</td>
</tr>
<tr>
<td>Dippers (n = 6)</td>
<td>6211 (3718)</td>
<td>6132 (3879)</td>
<td>5725 (4011)</td>
</tr>
<tr>
<td>Nondippers (n = 7)</td>
<td>4980 (1322)</td>
<td>5119 (1605)</td>
<td>4395 (1290)</td>
</tr>
</tbody>
</table>

*Values are mean (SD) polymorphonuclear leukocytes/high-powered field.
†Values are mean (SD) fmoles pmol.

Table 8—ECG Data*

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Midnight</th>
<th>4:00 AM</th>
<th>8:00 AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects (n = 11)</td>
<td>54 (8)</td>
<td>51 (9)</td>
<td>50 (8)</td>
<td>57 (11)</td>
</tr>
<tr>
<td>Dippers (n = 6)</td>
<td>52 (7)</td>
<td>50 (10)</td>
<td>48 (7)</td>
<td>56 (10)</td>
</tr>
<tr>
<td>Nondippers (n = 7)</td>
<td>56 (12)</td>
<td>55 (8)</td>
<td>55 (7)</td>
<td>59 (12)</td>
</tr>
<tr>
<td>Maximum heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects (n = 11)</td>
<td>72 (9)</td>
<td>67 (10)</td>
<td>70 (12)</td>
<td>76 (13)</td>
</tr>
<tr>
<td>Dippers (n = 6)</td>
<td>72 (9)</td>
<td>64 (11)</td>
<td>64 (11)</td>
<td>80 (11)</td>
</tr>
<tr>
<td>Nondippers (n = 7)</td>
<td>79 (9)</td>
<td>74 (5)</td>
<td>75 (4)</td>
<td>82 (9)</td>
</tr>
<tr>
<td>Mean heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects (n = 11)</td>
<td>62 (9)</td>
<td>59 (8)</td>
<td>59 (10)</td>
<td>65 (11)</td>
</tr>
<tr>
<td>Dippers (n = 6)</td>
<td>60 (9)</td>
<td>56 (11)</td>
<td>56 (11)</td>
<td>66 (11)</td>
</tr>
<tr>
<td>Nondippers (n = 7)</td>
<td>67 (11)</td>
<td>65 (6)</td>
<td>65 (5)</td>
<td>72 (9)</td>
</tr>
<tr>
<td>Magnitude of respiratory sinus arrhythmia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects (n = 11)</td>
<td>18 (6)</td>
<td>16 (4)</td>
<td>21 (6)</td>
<td>19 (9)</td>
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<tr>
<td>Dippers (n = 6)</td>
<td>21 (6)</td>
<td>14 (5)</td>
<td>17 (6)</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Nondippers (n = 7)</td>
<td>23 (7)</td>
<td>18 (5)</td>
<td>20 (6)</td>
<td>22 (9)</td>
</tr>
</tbody>
</table>

*Values are mean (SD) beats per minute.
tude of the fall in PEF (r = -0.49, p>0.09 and 
and r = -0.23, p>0.4, respectively). There was no correlation 
between any of the ECG variables at 4:00 AM and 
the magnitude of the fall in PEF (minimum heart rate, 
and r = -0.22, p>0.4; mean heart rate, r = -0.28, p>0.3; 
maximum heart rate, r = -0.33, p>0.2; RSA, 
r = -0.31, p>0.2).

Details of corticosteroid therapy in the asthmatic 
patients are given in Table 1. There was no difference 
between the midnight cortisol levels of the five long-
term users of beclomethasone dipropionate and those 
of the remainder of the asthmatic patients (p>0.2, 
Mann-Whitney U test).

**DISCUSSION**

The occurrence of extremely low midnight plasma 
cortisol levels in the asthmatic patients with morning 
dipping clearly requires careful analysis in the light of 
their use of corticosteroid medications. As only two 
dippers had received short courses of systemic cortico-
steroids some years prior to the study, it is primarily 
the effect of inhaled beclomethasone dipropionate on 
the hypothalamic-pituitary-adrenal (HPA) function that is 
of direct relevance in the interpretation of our results. 
Lawn et al recently suggested that children using 
relatively large doses of beclomethasone dipropionate 
(300 to 1300 μg/day) may have nocturnal suppression of 
corticosteroid secretion. Neither clinical data with 
special reference to dipping nor plasma ACTH levels 
were reported, and the possibility cannot be excluded 
that these findings reflect the occurrence of a similar 
phenomenon to that documented in the present study, 
this being, however, directly related to the disease, 
rather than to the drug therapy. While other authors 
have reported the occurrence in children of some 
depression of plasma cortisol levels by beclomethasone 
dipropionate used in doses ranging from 300 to 800 
μg/day, the majority of the studies performed in 
children, using it in similar doses, including those 
related to nocturnal adrenal function, have provided 
no support for the occurrence of HPA suppression. 
Studies in adults using the drug have demonstrated the 
ocurrence of HPA suppression with 1,600 to 2,000 μg/
day. The dippers were adults, only two-thirds of 
whom were using relatively small doses of bec-

lomethasone dipropionate (200 to 500 μg/day, mean 
300 μg/day). There is no convincing evidence of HPA 
suppression in adults in association with doses of this 
magnitude nor any effect on nocturnal cortisol 
levels.

Another important finding militating against a HPA-
depressant effect of beclomethasone dipropionate in 
the dippers is the finding in them of normal plasma 
ACTH levels. The ACTH is secreted in a pulsatile 

fashion with a delay between the occurrence of a pulse 
and the subsequent cortisol response. It is difficult, 
therefore, to clearly interpret the relationship between 
the levels of these two hormones when obtained from 
one blood sample. Although the response of the 
plasma cortisol level to insulin and the metyrapone test 
are more sensitive tests of HPA function, the finding of 
plasma ACTH levels in the normal range makes it 
considerably less likely that suppression by bec-
lomethasone dipropionate was the underlying cause 
for the low midnight cortisol levels in the asthmatic 
dippers.

That beta-adrenergic receptor "subsensitivity" may 
be an underlying pathogenetic mechanism in bron-
chial asthma remains a popular postulate, and it has 
long been thought likely that corticosteroid depriva-
tion may be associated with a degree of adrenergic 
blockade. Glucocorticoids potentiate the relaxant 
response of respiratory tract smooth muscle to cate-
cholamines, and reverse the tachyphylaxis to the 
bronchodilator response of beta-adrenergic-agonists 
after three to five hours. These properties may be 
related to an "upregulation" in number of beta-recep-
tors, as well as to an increase in their affinity for 
agonists, occurring after as little as four hours. 
An exaggerated midnight plasma cortisol trough could 
theoretically, therefore, precipitate airway narrowing 
within a few hours by the induction of a relative state 
of beta-adrenergic "subsensitivity."

If morning dipping is directly related to excessively 
low midnight plasma cortisol levels, it should be 
preventable by cortisol therapy, and Soutar et al have 
suggested that an infusion of corticosteroids has no 
protective effect against morning dipping. However, 
the fluorometric method of plasma corticosteroid 
determination used to assess the adequacy of their 
doses is insensitive and subject to spurious elevation 
related to various medications. Clearly, a similar 
study should be undertaken using a radioimmunoassay 
to measure plasma cortisol levels.

In contrast to Barnes et al, we were unable to 
demonstrate a statistically significant diurnal variation 
in the plasma epinephrine levels in any group of 
subjects. Although the asthmatic dippers appeared to 
demonstrate the greatest degree of variation in this 
variable, it is unlikely that the small changes which 
occurred were closely related to the large fluctuations 
in simultaneously recorded PEF in this group.

It has been suggested that the nocturnal nadirs in 
plasma cortisol and epinephrine levels may have a 
direct effect on the airway smooth muscle of asthmatic 
patients and also predispose to the release of mast cell 
mediators. Although an increase in mast cell-associated 
neutrophil chemotactic activity has been shown to 
occur in association with both exercise and allergen-
induced bronchospasm, the present data provide no 
support for the occurrence of a similar phenomenon in 
relation to morning dipping.

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The relationship between vagal tone and the fluctuations in airway caliber which occurred in the asthmatic dippers is less easy to assess. Only the dippers exhibited significant variations in heart rate during the study. The most marked was that in maximum heart rate which produced corresponding changes in the RSA. As heart rate is, at any time, the net result of both sympathetic and parasympathetic factors, it is clearly difficult to attribute the diminution in maximum heart rate which occurred at midnight and 4:00 AM in the dippers purely to an increase in vagal tone, particularly as vagal neural output has been clearly shown to be directly related to the RSA which actually diminished at these times. However, the possibility cannot be excluded that a nocturnal increase in vagal tone was related to the early morning diminution in airway caliber in the asthmatic dippers.

Of the different variables investigated, the plasma cortisol level demonstrated the most significant degree of variation in all groups during the study period, the fluctuations being most pronounced, moreover, in those subjects with the greatest changes in airway caliber, namely the asthmatic dippers. The nondippers, on the other hand, exhibited patterns more closely resembling those of normal subjects in the magnitudes of the changes which occurred in both plasma cortisol levels and airway caliber. The midnight plasma cortisol level was the only variable in our study which differed significantly between the different groups of subjects, being extremely low in the dippers and showing, in addition, a strong negative correlation with the magnitude of the fall in PEF in the asthmatic patients. We suggest, therefore, that an exaggerated nocturnal nadir in cortisol levels may directly precipitate morning dipping in some patients with asthma. It must be emphasized, however, that the dippers had a greater impairment of pulmonary function than the nondippers, resulting in the use by a greater number of them of regular beclomethasone dipropionate therapy.

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