NOCTURIA IN PATIENTS ON LONG-TERM STEROID THERAPY

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SUMMARY

1. About half of our asthmatic patients on long-term treatment with prednisone developed nocturia.
2. This is due to reversal of the normal circadian rhythm of water and electrolyte excretion and is partially corrected within 48 hr of stopping treatment.
3. The disturbance in water and electrolyte excretion appeared to be due to a decrease in proximal tubular reabsorption of sodium at night. This was not directly related to a change in the secretion of cortisol, aldosterone or antidiuretic hormone.

Nocturia is known to occur in Cushing's syndrome and in Addison's disease (Doe, Vennes & Flink, 1960) and is a recognized feature of Conn's syndrome (Lennon, Ruetz & Engstrom, 1961) but has not been described in patients on long-term treatment with steroids. Few complain spontaneously of nocturia yet enquiry has revealed that it is a common symptom. Of eighty-seven patients receiving maintenance doses of 5 or 10 mg of prednisone for asthma, forty-one (47%) stated that they passed more urine by night than by day. These patients had been accustomed to routine collection of 24 hr urine specimens for tests of pituitary and adrenal function. The symptom is not confined to patients with asthma; patients with rheumatoid arthritis given steroids also develop nocturia but the incidence has not been established in this disease.

The onset is variable. Some patients notice nocturia on starting steroids while in others it appears after a period of treatment. To elucidate the mechanism of this phenomenon, detailed studies were carried out on a few patients receiving prednisone.

PATIENTS AND METHODS

Five patients with well-controlled asthma and without hypertension or evidence of renal disease were admitted to hospital for study. They were not confined to bed but were given a

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constant diet containing 100 mEq sodium and 80 mEq potassium and a constant intake of fluid each day. Food and fluid were consumed before 22:00 hr and prednisone was given in doses of 5 mg at 09:00 hr and 21:00 hr. Throughout the study, urine was collected in three periods every day: 08:00–16:00 hr, 16:00–00:00 hr and 00:00 hr–08:00 hr.

A period of 3 days was allowed for equilibration on the constant metabolic regime and the pattern of water and electrolyte excretion studied over the next 4 or 5 days. Inulin clearance was then measured by day and 36 hr later by night while the patients were receiving prednisone. Prednisone was then stopped and 48 hr after administration of the last dose, inulin clearance was repeated at night. A total of three inulin clearances were thus performed in the four patients in whom these measurements were made (see Results). One accurate clearance period was undertaken on each occasion. A priming dose of inulin was given and a constant infusion maintained for 4 hr. Breakfast was withheld until mid-day during the first measurement of inulin clearance. Blood was taken and an accurately timed specimen of urine passed by normal voiding was collected under paraffin during the last 2 hr of infusion for measurement of inulin clearance, electrolytes, urine pH, bicarbonate, titratable acid and ammonia excretion.

Forty-eight hr after restarting prednisone, each patient received 0.3 mg 9-flourohydrocortisone at midnight to study its effect on electrolyte excretion. Two days later, an intramuscular injection of 5 units of pitressin tannate in oil was given at midnight and osmolality measured on each separate urine specimen passed up to 08:00 hr the following morning.

Sodium and potassium were measured with an E.E.L. (Evans Electroselenium Ltd, Halstead, Essex) flame photometer, calcium and magnesium with an E.E.L. absorption spectrophotometer, and chloride using an E.E.L. chloride meter. Phosphate and creatinine were measured by Autoanalyser (Technicon), bicarbonate and titratable acid by the method of Gyory & Edwards (1967), and ammonia by the microdiffusion method of Conway (1951). A direct reading pH meter (Electronic Instruments Ltd, Richmond, Surrey) was used to measure urinary pH and the technique described by Astrup (1961) to measure venous pH, PCO₂ and standard bicarbonate. The method of Bacon & Bell (1948), as described by Varley (1963), was used to measure inulin and an Advanced osmometer (Advanced Instruments Inc., Mass, U.S.A.) to determine the osmolality of blood and urine.

Urinary 17 hydroxycorticosteroids (17 OHCS) were measured by a modification (Liddle, Richard & Peterson, 1955) of the method of Silber & Porter (1954) and plasma 17 OHCS by a modification (Hatfield & Shuster, 1959) of the method described by Peterson, Karrer & Guerra (1957). Aldosterone excretion was estimated by the method of Thomas & Oake (1969) where aldosterone 1,2-H³ (supplied by the Radiochemical Centre, Amersham) was added to urine to assess recovery.

RESULTS

Analysis of the 8 hr urine specimens showed that the urine volume at night was greater than that passed by day (Fig. 1); the total volume excreted between midnight and 08:00 hr varied between 600 and 1200 ml. A similar pattern of excretion was found for sodium, potassium and chloride and the maximum excretion of calcium and phosphate also occurred at night (Table 1).

Partial correction of this reversal in circadian rhythm occurred when prednisone was stopped for 48 hr but the abnormal pattern was re-established within 48 hr of restarting the drug (Fig. 2).
Nocturia due to steroid therapy

There was a significant difference (t-test) between results on and off prednisone for the group as a whole in respect of the volume of urine passed from 16:00 hr to 00:00 hr (period 2), \( P < 0.02 \), volume of urine from 00:00 to 08:00 hr (period 3), \( P < 0.02 \), sodium excretion in period 2, \( P < 0.02 \), sodium excretion in period 3, \( P < 0.01 \), and potassium excretion in period 3, \( P < 0.02 \). Despite the shift, there was no significant change in overall water or electrolyte balance. Frozen specimens of urine were not preserved for D.B. so that further analysis was not possible. The influence of 9 \( \alpha \)-fluorohydrocortisone on nocturia was assessed in this patient but she did not participate in any other studies. Measurements of urine osmolality in the other four patients, expressed as a mean figure for each 8 hr period over 4 or 5 days, showed that the urine was more dilute by night than by day (Fig. 3). This was associated with a decrease in free water reabsorption and in one patient (D.H.), in whom the urine was more dilute than plasma, free water appeared in the urine.

![Fig. 1. Urine volume in patients receiving prednisone. Each column represents a period of 8 hrs, the dark column indicating the urine output at night.](image-url)
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Inulin clearances were low in the patients studied (Fig. 4) but in only one patient (P.W.) was there evidence that the inulin clearance was greater by night than by day with a fall in filtration rate at night when prednisone was omitted. In the others, changes were minimal with no consistent pattern on or off treatment. In these three patients, bicarbonate excretion was high at night and the output of ammonium (NH₄) and titratable acid (TA) was low whereas more NH₄ and TA was passed by day and there was little or no bicarbonate (Fig. 5). The urine was therefore more alkaline by night than by day, i.e. the reverse of normal. On stopping prednisone, excretion of bicarbonate ceased at night and the normal preponderance of NH₄ and TA was seen so that the urine was more acid. Venous pH, Pco₂ and standard bicarbonate were normal.

**Table 1.** Urine volume and electrolyte excretion in patients receiving prednisone

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Period* (hours)</th>
<th>Urine volume (ml)</th>
<th>Na (mEq)</th>
<th>K (mEq)</th>
<th>Cl (mEq)</th>
<th>Ca (mg)</th>
<th>PO₄ (mg)</th>
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<tbody>
<tr>
<td>D.H.</td>
<td>62</td>
<td>F</td>
<td>152.5</td>
<td>53.5</td>
<td>08.00-16.00</td>
<td>636 (205)</td>
<td>28 (14)</td>
<td>22 (2)</td>
<td>24 (14)</td>
<td>55 (26)</td>
<td>70 (20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.00-00.00</td>
<td>440 (61)</td>
<td>15 (6)</td>
<td>21 (3)</td>
<td>14 (7)</td>
<td>49 (21)</td>
<td>148 (40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>00.00-08.00</td>
<td>994 (204)</td>
<td>58 (18)</td>
<td>24 (3)</td>
<td>41 (12)</td>
<td>82 (28)</td>
<td>174 (55)</td>
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<td>D.B.</td>
<td>61</td>
<td>F</td>
<td>147.5</td>
<td>62.4</td>
<td>08.00-16.00</td>
<td>547 (159)</td>
<td>29 (12)</td>
<td>18 (8)</td>
<td>24 (6)</td>
<td>46 (21)</td>
<td>102 (69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.00-00.00</td>
<td>503 (87)</td>
<td>23 (10)</td>
<td>18 (9)</td>
<td>30 (4)</td>
<td>48 (23)</td>
<td>106 (59)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>00.00-08.00</td>
<td>1119 (173)</td>
<td>49 (12)</td>
<td>31 (11)</td>
<td>70 (10)</td>
<td>58 (13)</td>
<td>236 (70)</td>
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<td>D.S.</td>
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<td>F</td>
<td>145.0</td>
<td>53.0</td>
<td>08.00-16.00</td>
<td>283 (71)</td>
<td>21 (10)</td>
<td>21 (3)</td>
<td>14 (5)</td>
<td>86 (19)</td>
<td>47 (12)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.00-00.00</td>
<td>525 (173)</td>
<td>25 (5)</td>
<td>24 (2)</td>
<td>30 (4)</td>
<td>127 (15)</td>
<td>76 (19)</td>
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<td>00.00-08.00</td>
<td>678 (189)</td>
<td>56 (10)</td>
<td>24 (4)</td>
<td>44 (5)</td>
<td>130 (18)</td>
<td>89 (40)</td>
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<td>P.W.</td>
<td>61</td>
<td>F</td>
<td>155.0</td>
<td>90.0</td>
<td>08.00-16.00</td>
<td>364 (160)</td>
<td>17 (10)</td>
<td>18 (6)</td>
<td>14 (8)</td>
<td>85 (19)</td>
<td>247 (55)</td>
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<td>16.00-00.00</td>
<td>472 (128)</td>
<td>29 (9)</td>
<td>13 (5)</td>
<td>23 (13)</td>
<td>130 (20)</td>
<td>319 (79)</td>
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<td></td>
<td></td>
<td></td>
<td>00.00-08.00</td>
<td>928 (143)</td>
<td>55 (8)</td>
<td>37 (6)</td>
<td>45 (7)</td>
<td>198 (26)</td>
<td>473 (123)</td>
</tr>
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<td>W.C.</td>
<td>47</td>
<td>F</td>
<td>155.0</td>
<td>66.7</td>
<td>08.00-16.00</td>
<td>470 (200)</td>
<td>22 (10)</td>
<td>20 (8)</td>
<td>28 (22)</td>
<td>32 (16)</td>
<td>205 (79)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.00-00.00</td>
<td>396 (151)</td>
<td>20 (6)</td>
<td>20 (5)</td>
<td>20 (4)</td>
<td>30 (20)</td>
<td>203 (47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>00.00-08.00</td>
<td>960 (87)</td>
<td>57 (7)</td>
<td>28 (5)</td>
<td>57 (6)</td>
<td>66 (10)</td>
<td>373 (88)</td>
</tr>
</tbody>
</table>

* Figures for each 8 hr period represent the mean values on 4 or 5 consecutive days with SD in parentheses.

0.3 mg of 9 α-flurohydrocortisone was given at midnight to five patients while on prednisone and this relatively large dose produced no change in sodium excretion or urine volume at night in four patients. In the other patient sodium was retained with a corresponding increment in potassium excretion but there was little change in urine volume. Following injection of pitressin, the maximum urinary osmolality was greater than 800 m-osmol in each patient. The haematocrit, plasma proteins, serum electrolytes and serum osmolality were normal and did not vary significantly during the day or night. Measurements of plasma and urinary 17 OHCS showed that there was adrenal suppression without any consistent pattern in cortisol output throughout the 24 hr; there was no change on stopping prednisone (Fig. 6). As in normal subjects, aldosterone excretion was greater by day than by night in three of the four patients studied (Table 2).
FIG. 2. Changes in urine volume and electrolyte excretion on withdrawal of prednisone. (Clear column—urine volume; hatched column—sodium; stippled column—potassium.)
Fig. 3. Osmolar clearance and free water reabsorption in patients on prednisone. Each column represents the mean for 8 hr periods over 4 or 5 days; values for urinary osmolality are also shown.

Fig. 4. Inulin clearance in patients on and off treatment with prednisone.
FIG. 5. Hydrogen ion excretion (●) and urinary pH (○) in patients on and off treatment with prednisone.

FIG. 6. Plasma and urinary 17 hydroxycorticosteroids in patients on and off treatment with prednisone.
TABLE 2. Aldosterone excretion in patients receiving prednisone

<table>
<thead>
<tr>
<th>Subject</th>
<th>Period (hours)</th>
<th>Aldosterone (µg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.C.</td>
<td>08.00-00.00</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td>00.00-08.00</td>
<td>2.0</td>
</tr>
<tr>
<td>D.S.</td>
<td>08.00-00.00</td>
<td>21.0</td>
</tr>
<tr>
<td></td>
<td>00.00-08.00</td>
<td>1.5</td>
</tr>
<tr>
<td>D.W.</td>
<td>08.00-00.00</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>00.00-08.00</td>
<td>2.0</td>
</tr>
<tr>
<td>D.H.</td>
<td>08.00-00.00</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>00.00-08.00</td>
<td>8.5</td>
</tr>
</tbody>
</table>

* Mean of duplicate determinations.

DISCUSSION

Large doses of cortisone (Rosenbaum et al., 1952) and of prednisolone (Imrie, Mills & Williamson, 1963) are known to produce acute reversal of circadian rhythm in normal subjects. Since this change in circadian rhythm may also occur in patients with oedema, Rosenbaum and his colleagues questioned whether salt retention was in some way responsible for the effect of cortisone; but the finding that reversal still occurred in normal subjects put on a salt-restricted diet excluded this explanation. The fact that partial correction of the disturbance in circadian rhythm occurred in our patients without change in water or electrolyte balance is further evidence against a mechanism involving retention of sodium and an increased body sodium mass. That prednisone may have induced a shift in the distribution of sodium, potassium or water between the body compartments is unlikely because the serum electrolytes, osmolality, hematocrit and plasma proteins showed no significant change throughout the 24 hr.

Prednisone did, however, produce marked changes in renal function. Despite the increase in osmolar clearance, the urine was more dilute by night than by day. This was partly attributable to a decrease in free water reabsorption but it is also possible that more free water was produced in the distal tubule as the result of an increase in solute load arriving from the proximal segment. The maximum excretion of potassium as well as sodium occurred by night suggesting that the solute load delivered to the distal tubule was increased. This could have been due to an increase in filtered load or decrease in proximal tubular reabsorption.

Inulin clearances were low. This is probably because all but one of the women selected for study were over the age of 60; the values obtained correspond roughly with those recorded by Davies & Shock (1950) in normal subjects of corresponding age. In only one patient was the filtration rate greater by night than by day with a fall at night when prednisone was stopped. This contrasts with the results recorded by Berlyne et al. (1968) who studied nocturia due to reversal in circadian rhythm in patients receiving steroids after renal homotransplantation. They found that creatinine clearances were higher by night than by day in all their patients (Mallick & Berlyne, 1969).
Although variations in inulin clearance were minimal in our other patients, they showed a reversal in the normal circadian pattern of acid secretion. Their asthma was well controlled even when prednisone was stopped and no abnormality in venous pH, PCO₂ or standard bicarbonate was detected. Thus the excess of bicarbonate excreted at night was probably due to a reduction in proximal tubular reabsorption and not the result of any change in filtered load. This change was probably secondary to a decrease in proximal tubular reabsorption of sodium since chloride excretion was also increased. The lack of response to 9-flurohydrocortisone in four patients and the increase in potassium excretion in one suggests that a large quantity of sodium had reached the distal tubule and provides further evidence for a disturbance in proximal tubular function.

Exactly how prednisone produces this disturbance in proximal tubular function is not clear. It may have a direct effect on tubular function or influence the normal pattern of secretion or activity of some other hormone. Experiments on the isolated kidney of animals have shown that a rise in renal artery perfusion pressure produces an increase in sodium excretion without change in filtration rate (Tobian et al., 1964; McDonald & de Wardener, 1965); but if prednisone has this effect it should lead to an exaggeration of the normal circadian rhythm rather than reversal, as the drug was given morning and evening.

As already stated, the urine was more dilute by night than by day with a decrease in free water reabsorption indicating reversal of normal output of ADH, but any change in ADH secretion is probably the result of the increase in osmolar clearance rather than the cause of nocturia because the highest rate of urine flow coincided with the highest rate of electrolyte excretion. Two patients with malignant hypertension and nocturia studied by Berlyne et al. (1965) were resistant to the action of pitressin at night, but the increase in osmolality in response to pitressin in our patients indicated that their renal tubules were not resistant to ADH.

Aldosterone has little effect on proximal tubular function and it has been shown that the maximum secretion of aldosterone occurs during the day in normal subjects and is related to posture (Muller, Manning & Riondel, 1958). A normal pattern of aldosterone output was recorded in three of our four patients. Measurements of plasma and urinary 17 OHCS showed that cortisol production was suppressed with no distinctive pattern of secretion throughout the 24 hr. In normal subjects, the morning rise in cortisol production coincides with the increase in electrolyte excretion but this does not mean that they are interdependent. Martel et al. (1962) have shown that when normal subjects change their sleeping habits reversal of electrolyte excretion precedes by several days any change in cortisol production. Doe, Vennes & Flink (1960) found that cortisol given in doses of 5 mg every 3 hr throughout the day re-established a normal circadian rhythm of electrolyte excretion in patients with Addison’s disease despite a constant excretion of cortisol metabolites. This suggests that cortisol plays a permissive role and does not control the normal excretory pattern.

There has been speculation, but as yet no proof, regarding the existence of a previously unrecognized hormone which may influence sodium reabsorption by the proximal tubule (de Wardener, 1969). If prednisone inhibits the secretion or action of such a hormone it would appear to do so directly since there was no discernible change in fluid distribution or electrolyte balance in our patients, merely a shift in the maximum output during the day.

The observations reported here suggest that nocturia on steroid therapy is related to decreased sodium reabsorption at night. Since there was no disturbance in electrolyte balance,
sodium may have been retained during the day. It must be admitted that sodium retention could have been the primary disorder and the increased excretion of water and electrolytes at night a compensatory phenomenon. Further work is necessary to decide the primary event.

Although few patients complained of nocturia, the patients studied were appreciative of uninterrupted sleep when prednisone was stopped. Giving prednisone as single dose in the morning did not prevent nocturia; this study would indicate that control of nocturia is achieved only by termination of steroid therapy.

ACKNOWLEDGMENT

We would like to thank Dr D. A. Williams for allowing us to study his patients with asthma.

REFERENCES


