Low melatonin excretion during mechanical ventilation in the intensive care unit

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ABSTRACT

Biochemical markers for the circadian rhythm were studied in patients treated at the ICU (intensive care unit) of two regional hospitals. A normal rhythm is characterized by a relatively higher melatonin and a lower cortisol excretion at night. Disturbances affect sleep, mood and cognitive performance. All urine excreted between 07:00 and 22:00 hours (day) and between 22:00 and 07:00 hours (night) was collected and sampled throughout the entire ICU period (median, 10 days) in 16 patients for the excretion of 6-SMT (6-sulphatoxymelatonin), which is a metabolite of melatonin, and free cortisol. The overall excretion of 6-SMT was slightly lower and the cortisol excretion higher than reported for healthy reference populations. Mechanical ventilation was associated with a markedly lower 6-SMT excretion (median, 198 ng/h) compared with periods without such help (555 ng/h; \(P \leq 0.0001\)), whereas infusion of adrenergic drugs increased the 6-SMT excretion (\(P < 0.01\)). Five patients (31 %) showed a virtually absent melatonin excretion for 24 h or more. The diurnal rhythms were consistently or periodically disturbed in 65 % and 75 % of the patients. These alterations cannot be explained by excessive exposure to light at night. In conclusion, there was hyposecretion of melatonin during mechanical ventilation, an overall high cortisol excretion and a disturbed diurnal rhythm of both of these hormones in most patients treated in two ICU departments.

INTRODUCTION

Sleep–wake disturbances are frequently recognized as a problem for patients in the ICU (intensive care unit). Neurophysiological methods demonstrate sleep fragmentation and suppression of Stage 3, Stage 4 and REM (rapid eye movement) sleep [1–4]. Therapeutic procedures, personal care and nurse–patient communication may cause such disturbances [1] and the illness is probably another major cause [2,5].

More recently, the pattern of melatonin secretion has been associated with sleeping disturbances in the ICU. Both melatonin and cortisol are biological markers of the circadian rhythm, the former showing a peak at night and the latter at noon. Shilo et al. [6] measured the urinary concentration of a melatonin metabolite, 6-SMT (6-sulphatoxymelatonin), during 24 h in 14 ICU patients. They found a disturbed melatonin excretion pattern in all patients, and most of them showed no nocturnal rise. Mundigler et al. [7] reported a high 6-SMT excretion without nocturnal peak in ICU patients with sepsis, whereas the nocturnal peak was preserved after transthoracic oesophagectomy [8]. However, no previous studies have followed the biochemical markers of the circadian cycle for more than a few days in ICU patients.

In the present study, we measured melatonin and cortisol excretion throughout the entire ICU stay (median, 10 days) in 16 patients. The purpose was to identify

Key words: circadian rhythm, cortisol, intensive care unit, melatonin, 6-sulphatoxymelatonin (6-SMT).
Abbreviations: APACHE II, Acute Physiology And Chronic Health Evaluation 2; CPAP, continuous positive airway pressure; ICU, intensive care unit; 6-SMT, 6-sulphatoxymelatonin.

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Table 1  Demographic data and APACHE II score on admission to the ICU

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>APACHE II score</th>
<th>Days in ICU</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>62</td>
<td>Septic shock after gastrointestinal surgery</td>
<td>22</td>
<td>32</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>86</td>
<td>SIRS after acute aortic aneurysm surgery</td>
<td>24</td>
<td>47</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>87</td>
<td>Sepsis + abdominal pain and previous myocardial infarction</td>
<td>23</td>
<td>30</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>58</td>
<td>Multiple rib fractures, pneumothorax and subdural haematoma</td>
<td>26</td>
<td>10</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>68</td>
<td>Sepsis after ileus operation</td>
<td>17</td>
<td>11</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>76</td>
<td>Re-operation for suture rupture after gastrectomy</td>
<td>17</td>
<td>10</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>41</td>
<td>Guillain–Barrés paralysis</td>
<td>4</td>
<td>34</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>44</td>
<td>Pneumonia</td>
<td>12</td>
<td>14</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>70</td>
<td>Aortic aneurysm and chronic obstructive lung disease</td>
<td>7</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>46</td>
<td>Transferred from another hospital 2 weeks after multi-trauma</td>
<td>3</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>78</td>
<td>Lung and kidney insufficiency after aortic aneurysm surgery. Previous dialysis</td>
<td>17</td>
<td>7</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>74</td>
<td>Spontaneous bladder and colonic perforation, sutured surgically</td>
<td>18</td>
<td>12</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>79</td>
<td>Myocardial infarction and cardiogenic shock</td>
<td>24</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>83</td>
<td>Cerebrovascular lesion with aspiration pneumonia</td>
<td>21</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>61</td>
<td>Pneumonia and chronic obstructive pulmonary disease</td>
<td>15</td>
<td>4</td>
<td>Yes</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>88</td>
<td>Lung embolus after surgery for acute fracture of the femur</td>
<td>25</td>
<td>3</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Factors that correlate with the rate of excretion of these hormones and their diurnal variation. Disturbances of melatonin secretion promote fatigue and, in turn, poor co-operation with the nursing staff during mobilization.

**METHODS**

Between November 2000 and October 2001, the circadian rhythm was assessed in 16 patients (seven females and nine males) aged between 41 and 88 (median, 71) years throughout a period of intensive care at two Swedish hospitals, South Hospital in Stockholm and the Regional Hospital in Gällivare. After Ethics Committee approval, inclusion in the study was effected within 48h (usually < 24h) after admission to the ICU. The patient gave his/her informed consent before inclusion or, if possible, on a later occasion. The criterion for inclusion was an expected stay at the ICU of at least 2 days. Patients with a markedly impaired kidney function (serum creatinine > 250 µmol/l) were excluded. The severity of illness was assessed using the APACHE II (Acute Physiology And Chronic Health Evaluation 2) scoring system (Table 1).

The illumination in the patient’s room was monitored in the first seven patients by a Universal Photometer model S2 (Hagner, Solna, Sweden). Continuous measurements were made at a frequency of 0.5/min for up to 1 week. Photometer data were stored in a Satellite U universal logger 4232 (Mitec Instrument AB, Säfftte, Sweden) and then analysed on a standard PC. The light detector was placed as close to the upper part of the patient’s bed as possible, but so as not to interfere with the daily care of the patient. The position and the angle of the detector were adjusted to mimic the illumination at the patient’s eyes. The resulting curves were analysed to ensure that a day and night illumination pattern had been maintained for the patients studied.

Melatonin secretion is normally increased at bedtime and remains high until early morning. In contrast, cortisol secretion falls. Both hormones express a circadian rhythm which is driven by an endogenous oscillator situated in the hypothalamus [9]. To discriminate between the day/night phases of melatonin and cortisol excretion, the patients had an indwelling urinary bladder catheter from which all urine was collected between 07:00 and 22:00 hours (day) and between 22:00 and 07:00 hours (night) during the entire stay in the ICU (see Table 1). The catheter was wrapped throughout its length with black plastic to protect the urine from light. The volume was measured (median excretion rate, 106 ml/h) and two samples were frozen to -18 °C for later analysis.

In the first sample, the concentration of a metabolite of melatonin, 6-SMT, was measured by RIA using an 125I-labelled tracer and antibody against sheep 6-SMT [10,11] (Stockgrand Ltd, Guildford, Surrey, U.K.). The urinary excretion of 6-SMT correlates closely with the melatonin concentration in plasma [12,13], even in the presence of a low creatinine clearance [14], and represents the average plasma level during the period of urine collection. A reference population excreted 400 ng/h 6-SMT between 07:00 and 22:00 hours, and 1500 ng/h between 22:00 and 07:00 hours [6], which is similar to patients (age, 56 years) with chronic disease who are free from acute illness [7]. Age-matched controls yielded a slightly lower reference value, 350 ng/h, for an entire 24 h period [14].

The second urine sample was analysed by an immunoassay in which the sampled cortisol competes with horseradish peroxidase-labelled cortisol for a limited
number of binding sites [15] (Nordic Biosite, Täby, Sweden). The product of urine volume and cortisol concentration measured in this way provides a good approximation of the metabolically active cortisol fraction in plasma. According to the manufacturer of the kit, the normal range for the cortisol excretion is 0.5–8 µg/h.

Both assays had a relative specificity of 100% for the measured substrate. The coefficient of variation was 3.5% or less, and all samples were analysed in duplicate, the mean value being used in the calculations.

The results of the 6-SMT and cortisol analyses were expressed as the median and interquartile range for the excreted amounts/h of day or night. Statistics were used to test for differences in the rates depending on the use of mechanical ventilation [assisted/controlled ventilation or CPAP (continuous positive airway pressure)], administration of certain drugs (adrenergic agents, propofol, benzodiazepines, opiates and cortisol) and the development of fever. Univariate analysis was performed using the Mann–Whitney or Kruskal–Wallis tests. Multivariate analyses comprised stepwise multiple regression and three-way ANOVA and were performed using the log-transformed 6-SMT and cortisol excretion rates. $P < 0.05$ was considered significant.

RESULTS

The 16 patients had an APACHE II score of between 3 and 26 (median, 18) on admission and spent 3–47 (median, 10) days in the ICU. Four patients died (Table 1).

The ICU environment had normal day/night cycles of light, except for a few occasional short exposures to light at night in connection with emergency treatments. The peak illumination at noon varied between 250 and 500 lux and the illumination at night was about 50 lux (Figure 1).

The overall median 6-SMT excretion was 252 ng/h (interquartile range, 120–615) with marked variations depending on clinical state and medical treatment. Five patients (31%) had a 6-SMT excretion during at least one 24 h period of less than 40 ng/h, or only 10% of the normal excretion in the daytime.

![Figure 1](image1) Representative recording of the illumination in the area of the patient’s head during the first 6 days in patient 1

Collection periods with mechanical ventilation were associated with a lower 6-SMT excretion [198 (78–456) ng/h] than during collection periods when such assistance was not given [555 ng/h (305–1066); $P < 0.0001$]. This difference was independent of whether assisted/controlled ventilation or CPAP was used and persisted throughout the ICU stay (Table 2 and Figure 2).

6-SMT excretion was also lower during fever, but higher when adrenergic drugs were infused (Table 2 and Figure 3). The cortisol excretion, which amounted to 22 (11–42) µg/h, was higher during cortisone and lower

![Figure 2](image2) Urinary excretion of 6-SMT for different periods of the ICU stay depending on the mode of ventilation

Time periods with adrenergic therapy were excluded.

![Table 2](image3) Univariate analysis of factors affecting to the excretion of 6-SMT and cortisol during intensive care

Values are medians (25th–75th percentiles). The Mann–Whitney (two groups) or Kruskal–Wallis (three groups) test was used in the statistical analysis.
Figure 3 Urinary excretion of 6-SMT in patients 1 and 2 who both remained for more than 1 month in the ICU. Upper panel, depression of 6-SMT during mechanical ventilation while the circadian rhythm is then partially restored. Lower panel, depression of 6-SMT during mechanical ventilation, followed by a brisk rise during infusion of noradrenaline (norepinephrine). The excretion is normal during weeks 3 and 4.

Figure 4 Urinary excretion of 6-SMT (left-hand panel) and cortisol (right-hand panel) in three ICU patients. Top, very low 6-SMT excretion and disturbance of the day/night variations during mechanical ventilation. Middle, normal 6-SMT excretion, but disturbed rhythm, during mechanical ventilation. Cortisol excretion is initially very high, which is probably due to preceding surgery, but the rhythm is preserved. Bottom, disturbed circadian rhythm of both 6-SMT and cortisol.

Table 3 Multivariate analysis of factors that significantly affect the excretion rates of 6-SMT and cortisol during intensive care

Stepwise multiple regression was used to calculate F values. The F value indicates the strength of the factor.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Factor</th>
<th>F value</th>
<th>Direction of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-SMT</td>
<td>Mechanical ventilation</td>
<td>66</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Benzdiazepine treatment</td>
<td>18</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Adrenergic treatment</td>
<td>10</td>
<td>Increase</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Cortisone treatment</td>
<td>39</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Propofol treatment</td>
<td>5</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

6-SMT excretion showed a consistently disturbed day/night rhythm in seven patients, partially disturbed (usually during mechanical ventilation) in five patients, and a normal rhythm in four patients (Table 4 and Figure 3). For the cortisol excretion, five patients were judged to have a consistently disturbed day/night rhythm, five a partially disturbed, and six had a normal rhythm (Table 5 and Figure 4). The degree of the disturbance did not correlate with the age of the patient or with the APACHE II score.

DISCUSSION

The overall excretion of 6-SMT in ICU patients was slightly lower than in reference populations [6,7,14]. The
increase expected to occur at night was often absent, indicating loss of diurnal rhythm. Several of the ICU patients showed periodical presence of both the normal excretion rate and expected day/night variation, but the diurnal rhythm was most typically disturbed when the overall excretion was low. In contrast, the excretion of cortisol over 24 h was more than 5 times higher than the average for a healthy population. The lower values at night, which is part of the normal sleep/wakefulness pattern, were usually absent.
The excretion rates of both 6-SMT and cortisol differed depending on treatment factors and medical condition (Table 2). Adrenergic drugs clearly increased 6-SMT excretion and, as expected, cortisone treatment increased urinary cortisol levels. Importantly, 6-SMT excretion was decreased by more than 50% during mechanical ventilation, sometimes even to below the level of detection. The difference from those who breathed spontaneously was independent of the time period of the ICU stay and whether assisted/controlled ventilation or CPAP had been applied. These patients showed both hyposecretion of melatonin and a disrupted diurnal rhythm.

The choice of sedative seemed to have little influence on the 6-SMT level, although these drugs were used more often during mechanical ventilation. If anything, benzodiazepines (mostly midazolam) was associated with a slightly higher 6-SMT excretion. Similar covariance was seen with body temperature. Exogenous melatonin lowers the body temperature [16], but the body reacts to fever by increasing melatonin secretion, which is why high levels can be found in patients with sepsis [7]. In our study, however, fever was associated with low 6-SMT levels. Since the correlation between melatonin and body temperature disappeared in the multivariate analyses, fever was probably more likely to develop in those who were ventilated. A few patients showed an increase in 6-SMT excretion when they developed fever, but this pattern was inconsistent. Furthermore, the relatively high between-patient variation was probably also boosted by factors that were not anticipated by us, or were difficult to evaluate statistically. For example, a ‘trauma response’ seemed to increase the early cortisol excretion in those who were transferred to the ICU after surgery, such as patient 6 (Figure 4).

Apart from in infants, who became breathless and blue during sleep [17], there is little previous evidence that melatonin levels are low during critical illness. The mechanism remains to be elucidated. The strongest known inhibitor of melatonin secretion is bright light, which also helps to synchronize the circadian rhythm [18,19], but our patients were subjected to a normal day/night rhythm of light [20]. More likely causes include the underlying disease and the mixture of treatments associated with mechanical ventilation. The stressful situation, as evidenced by the high cortisol excretion, as well as environmental noise, may have contributed [21].

These patients may have suffered from hyposecretion of melatonin. In animal models, such hyposecretion impairs mitochondrial oxidative phosphorylation [22] and the capacity to survive endotoxinaemia [23]. Melatonin has antioxidant actions which prevent ischaemia-induced renal damage [24,25]. In humans, case reports suggest that damage to the pineal gland results in drowsiness, which can be reversed with exogenous melatonin [26,27]. Supplementation with melatonin may also help to coordinate and enhance the secretion of growth hormone and prolactin [27].

Disturbances of the circadian rhythm and sleep in ICU patients have been well demonstrated by electrophysiological methods [1–4]. In the present study, it was not an issue as to whether urine was collected during the daytime or at night, as it should if the biological rhythms were intact. Disruption of the circadian rhythm is known to affect sleep, mood and cognitive performance [28–30]. Although a precise assessment of this rhythm would ideally include phase-angle shifts [7], the frequent hyposecretion of melatonin and the disturbed melatonin/cortisol patterns suggest that melatonin could be a useful medication in the ICU, in particular during mechanical ventilation. Shilo et al. [31] improved sleep/wakefulness patterns by providing exogenous melatonin to eight patients with respiratory failure. The benefits of such therapy could be a less sleepy patient, who co-operates better with the nursing staff during mobilization. The consumption of sedatives might decrease, since melatonin is a hypnotic agent [16,30].

It is concluded that hyposecretion of melatonin is very common during mechanical ventilation in the ICU, suggesting a need for exogenous supplementation.

ACKNOWLEDGMENTS

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REFERENCES


