Case 4

Management of poor sleep on Intensive Care

Clinical Problem

This expanded case summary has been chosen to explore the management options for improving sleep patterns on the Intensive Care Unit (ICU). It will focus on pharmacological options, primarily melatonin.

A fifty nine year old man presented to ICU five days after admission to hospital with an infectious exacerbation of Chronic Obstructive Pulmonary Disease (COPD) complicated by a spontaneous pneumothorax. His medical history included COPD, previous lobectomy for tuberculosis, peripheral vascular disease, ischaemic heart disease, spinal stenosis and excess alcohol consumption. Escalating oxygen requirements led to intubation and ventilation on the day of admission to ICU. He deteriorated further into multi organ failure requiring inotropic support and renal replacement therapy.

Management

On day 2 of his ICU stay he developed an ischaemic right foot. On day 3 he had a failed trial of extubation and consequently had a tracheostomy. His multi organ failure gradually resolved with the main ongoing problems being a slow respiratory wean and ischaemic foot. On day 11 a computed tomography angiogram showed occlusion of his right common femoral artery and he was therefore transferred to an ICU with vascular surgery on site. On day 12 he underwent femoral endarterectomy.

His respiratory wean was complicated by recurrent pneumothoraces and then a persistent air leak via a bronchopleural fistula. Delirium and poor sleep were ongoing but fluctuant problems. Non pharmacological management included standard unit procedures such as an afternoon rest period, maintenance of day/night cycles of lighting and noise and nurse led attempts at orientation to time and place. Pharmacological management included chlordiazepoxide, haloperidol, trazadone and olanzapine. His recovery from this was hampered by a move to a side room, made necessary by a routine swab growing Methicillin Resistant Staphylococcus Aureus. On day 14 his delirium became severe enough to require full re-sedation with propofol, this was then switched off on day 16 with a clonidine infusion being instigated instead.

His initial response to the clonidine was good, however at night time he deteriorated again with very poor sleep and marked agitation. The delirium and unpredictable sleep patterns interfered with attempts at respiratory weaning. A trial of melatonin (2 milligrams (mg) nocte) was therefore undertaken.

At the time of my last clinical interaction with him he remained on ICU, self ventilating with external Continuous Positive Airway Pressure via his tracheostomy. He still...
required multi modal anti-delirium medication. The melatonin had no appreciable impact on his sleep pattern.

Discussion

Poor sleep is a well known problem for ICU patients. It includes decreased sleep time, decreased Rapid Eye Movement (REM) time and fragmentation of sleep into short periods day and night. Possible causes and consequences are listed in the tables below.

<table>
<thead>
<tr>
<th>Table 1 - Factors associated with poor sleep on ICU</th>
<th>Table 2 – Possible consequences of poor sleep</th>
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<tbody>
<tr>
<td>• ICU environment (e.g. noise, light, temperature)</td>
<td>• Impaired immune response</td>
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<tr>
<td>• Patient care activities (e.g. pressure area relief)</td>
<td>• Altered metabolic and endocrine systems</td>
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<td>• Medications</td>
<td>• Increase in pain sensitivity</td>
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<td>• Ventilator asynchrony</td>
<td>• Impaired attention, mood and psychomotor performance</td>
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<tr>
<td>• Pain</td>
<td>• Increased daytime sleepiness</td>
</tr>
<tr>
<td>• Neurotransmitter and hormonal imbalance</td>
<td>• Delirium</td>
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<td></td>
<td>• Impaired weaning</td>
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Maintaining good sleep patterns and an appropriate day/night cycle may be beneficial for the prevention and management of delirium. Strong evidence of a causal relationship is lacking but it is still generally considered good practice to try to maintain normal sleep patterns to aid delirium management and for patient comfort. The significance of delirium is highlighted by its negative effect on both mortality and long term cognitive function recovery, therefore any methods which may reduce its incidence are an important facet of ICU care.

Non-pharmacological options

Non-pharmacological options include appropriate nursing care, particularly in timing of interventions, and environmental control of lighting and noise. These are not necessarily easy to achieve on a busy ICU. Attention to ventilator synchrony in ventilated patients may also aid sleep. High quality trials of such interventions are difficult but the rationale appears sound. At a minimum patient comfort is likely to be improved by such measures.

Pharmacological options

Benzodiazepines are frequently used for poor sleep outside of a critical care setting, these agents are however associated with increased delirium in ICU patients and therefore are probably not appropriate for sleep management on ICU. Other pharmacological options in common usage include olanzapine, trazadone and haloperidol. Melatonin is also used, although less frequently in my personal experience. In the case described above all of these agents were used.
A review of the evidence to support the use of melatonin shows only three randomised trials.

Most recently Bourne and colleagues\(^5\) undertook a double blind, placebo controlled, randomised control trial (RCT) in 24 patients. They selected patients weaning from a ventilator via a tracheostomy. Of note they excluded patients with an alcohol intake of greater than 50 units/week which would apply to the patient described above. Randomisation and blinding was thorough, with an attempt to quantify baseline environmental factors also made. A dose of 10mg Melatonin was chosen. Haloperidol was allowed for agitation but not other sedatives. A number of assessments of sleep quality and duration were made, but polysomnography, which has been described as the gold standard measurement\(^1\), was not used.

As may be expected of a small trial there were significant differences in baseline characteristics of the two groups. An attempt to correct for this using linear regression was made, but using a self created single variable of “high risk” patients. Other quality issues included a failure to recruit the intended 34 patients and some sets of missing data, as always RCT’s on ICU are fraught with difficulty. The only statistically significant result was of a reduced Area Under the Curve (AUC) for bispectral index. The authors acknowledge that the clinical significance is unproven but they feel it may represent better and longer sleep. I am not aware of BIS being a validated tool for assessment of sleep. Side effects were only reported by a single patient and treatment appeared well tolerated. Based on plasma concentration data the authors suggest a dose of 1-2mg in the ICU population rather than 10mg as used in most studies. In my opinion this study, despite being of reasonable design and execution, has failed to support the use of melatonin.

Two further RCT’s by Ibrahim and colleagues\(^6\) and Shilo and colleagues\(^7\) have been published. Ibrahim found no difference in observed sleep duration in a trial of 32 patients broadly similar to the Bourne patient population. Shilo’s trial of only 8 patients showed no significant difference between groups.

In summary there is currently no evidence to support the use of melatonin on ICU.

Of the other agents listed there are some trials outside of ICU with potential evidence of benefit. A randomised, double blind, placebo controlled crossover trial\(^8\) in healthy volunteers showed an increase in sleep time for olanzapine, when compared to haloperidol, risperidone and placebo. A randomised, crossover, single blinded trial in paediatric burn patients\(^9\) showed increase in sleep time when haloperidol was used. The applicability of these trials to the ICU population is tenuous. Trials in an ICU population have not been published.

The use of α2 agonists such as clonidine and dexmedetomidine seems to be gaining in popularity on ICU. A randomised controlled trial comparing propofol with dexmedetomidine in elective coronary artery bypass grafting patients\(^10\) showed statistically significant worse sleep (as assessed by patient questionnaire rather than a more objective measure) in the dexmedetomidine group. It is difficult to extrapolate this to weaning patients who do not require deeper levels of sedation. This study raises the question of whether low dose propofol sedation at night would have been an appropriate management strategy in this case. However, a small study\(^11\) of using
night time propofol for sleep in ventilated patients on assist modes found worse quality sleep in the propofol group. This adds to an earlier study\textsuperscript{12} comparing midazolam with propofol showed no significant increase in sleep quality in either group when compared to baseline.

Trazadone has not been studied in the ICU population either to promote sleep or as an anti-delirium agent. A review undertaken of studies using trazadone for insomnia in non-hospitalised patients\textsuperscript{13} found inadequate evidence to support it’s use. The review also highlighted concerns with side effects including psychomotor impairment.

**Lessons Learnt**

High quality trial data is always difficult to obtain in ICU populations, in this instance it is made even more difficult by the need to assess subjective endpoints such as quality of sleep. The lack of evidence may be due to paucity and small size of studies. In my opinion the existing trial evidence does not form a strong argument for or against the use of drugs felt to aid sleep. The decision to use pharmacological sleep aids and the choice of agent is therefore one to be based upon familiarity, cost and perceived effectiveness.

A causal relationship between poor sleep and delirium has not been shown. However, it is likely that the pathophysiology of the two conditions is similar and they frequently co-exist\textsuperscript{1}. As such agents that are felt to combat both conditions seem most appropriate for night-time administration. My personal choice would be one of haloperidol as first line and olanzapine as second line. My experience of α\textsubscript{2} agonists has also been favourable. I acknowledge the absence of evidence supporting these decisions. Non-pharmacological management and high quality nursing care remains very important.

An ideal large RCT would compare melatonin, haloperidol, an α\textsubscript{2} agonist, olanzapine and placebo and utilise endpoints including polysomnography and patient/nurse questionnaires. It would perhaps also be interesting to add bedside delirium assessments such as the Confusion Assessment Method for ICU (CAM-ICU). There has been an increased interest in detecting and treating delirium on ICU recently and such a trial would be very helpful to clinicians on all ICU’s. It would however be very difficult to undertake. In the absence of the above pragmatism and experience must be relied upon.
References