

**ANAESTHESIA, SLEEP AND
DYSSOMNIAS- PART 2
ANAESTHESIA TUTORIAL OF THE WEEK
269**

27TH AUGUST 2012

Dr Paul James, Specialty Trainee Anaesthetics
Nottingham and East Midlands School of
Anaesthesia
Correspondence to paul_t_james@yahoo.co.uk



QUESTIONS

Before continuing, try to answer the following questions. The answers can be found at the end of the article.

1. Which of the following statements are true regarding narcolepsy?
 - a. The population incidence is 0.01%
 - b. There is an autoimmune component to the disease
 - c. Onset of narcolepsy is in late adulthood
 - d. Narcolepsy is characterised by excessive sleepiness and cataplexy

2. Regarding Restless legs syndrome;
 - a. There is a strongly positive relationship with cardiovascular disease
 - b. Symptoms improve during pregnancy
 - c. Restless legs syndrome is worsened by the use of all anti-emetics
 - d. Patients with restless legs syndrome may be on oral dopamine agonists

3. Central alveolar hypoventilation syndrome;
 - a. Shows a familial preponderance
 - b. Can occur following strokes
 - c. There is an association with Hirschsprung's disease
 - d. Requires long term nocturnal ventilation

INTRODUCTION

Part one of this tutorial discussed the normal physiology of human sleep and explores the relationship between anaesthesia and sleep. This tutorial will discuss dyssomnias and the associated anaesthetic implications.

DYSSOMNIAS

These are the major, or primary, sleep disorders associated with disturbed sleep at night or impaired wakefulness. Dyssomnias produce either excessive sleepiness, or problems with initiating or maintaining the sleep state. They are a heterogeneous set of conditions that have their origins in different pathological processes (see table1). Many have a direct impact on the conduct and recovery of anaesthesia, and on the provision of post-operative analgesia, and are discussed here.

Table 1. Classification of sleep disorders

INTRINSIC SLEEP DISORDERS	CIRCADIAN RHYTHM DISORDERS	EXTRINSIC SLEEP DISORDERS
Psychophysiological insomnia	Jet lag	Inadequate sleep hygiene
Sleep state misperception	Shift work disorder	Environmental sleep disorder
Idiopathic insomnia	Irregular sleep wake pattern	Altitude insomnia
Narcolepsy	Delayed sleep phase syndrome	Adjustment sleep disorder
Recurrent Hypersomnia	Advanced sleep phase syndrome	Insufficient sleep syndrome
Idiopathic Hypersomnia	Non 24 hour sleep-wake syndrome	Limit-setting sleep disorder
Post Traumatic Hypersomnia		Sleep-onset association disorder
Obstructive Sleep Apnoea		Food allergy insomnia
Central sleep apnoea syndrome (CSAS)		Nocturnal eating (drinking) syndrome
Central alveolar hypoventilation syndrome (CAHS)		Hypnotic-dependent sleep disorder
Periodic limb movement disorder		Stimulant-dependent sleep disorder
Restless legs syndrome		Alcohol-dependent sleep disorder
		Toxin-induced sleep disorder

NARCOLEPSY

Narcolepsy is a disorder of excessive sleepiness. Typically it is associated with the phenomenon of cataplexy (sudden loss of bilateral muscle tone provoked by strong emotion, with retention of normal consciousness, respiration and memory). It is further characterised by the presence of hypnagogic hallucinations (hallucinations occurring at the onset of sleep) and sleep paralysis (the inability to perform voluntary actions at the onset of sleep or awakening). These two symptoms, along with cataplexy and excessive sleepiness, comprise the tetrad of narcolepsy.

The incidence of narcolepsy in European populations is roughly 0.05%. Narcolepsy has its typical onset in adolescence and young adulthood, but there is often a delay to diagnosis. There is no sex preponderance amongst sufferers, but a strong genetic link. The majority of people diagnosed with narcolepsy and cataplexy are known to have a specific HLA gene variant called DQB1*0602. Almost all patients with narcolepsy and cataplexy can be demonstrated to have a lack of hypocretin (orexin) in the dorsal and the lateral hypothalamus. The HLA association, as well as other recent results from genetic studies, suggests a possible autoimmune basis for the hypocretin cell destruction and thus narcolepsy.

Presentation of a narcoleptic patient for anaesthesia heralds many potential complications. There is no consensus as to the best technique, with most evidence coming from case reports. The theoretical difficulties faced by the anaesthetist are as follows:

- Increased sensitivity to anaesthetic agents
- Delayed emergence from general anaesthesia
- Post-operative hypersomnia and apnoea
- Post-operative sleep paralysis
- Cataplexy during positioning for regional anaesthesia
- Interactions between treatments for narcolepsy and anaesthetic agents

From case reports many techniques have been successfully utilised, but the current trend is to use short acting, rapidly metabolised agents, propofol and remifentanyl (Pelaez et al¹) or desflurane (Doyle and Wilkinson²), to avoid delayed emergence. Equally it would seem prudent to employ regional anaesthesia and analgesia wherever possible in these patients, and avoid the use of benzodiazepines.

Many narcoleptic patients are taking medication which may interact with anaesthetics. Amongst these are amphetamines and modafinil. Amphetamine use leads to depletion of catecholamines, which manifests itself as an inability to mount a sympathetic response to hypotension. In such a patient group, direct acting agents such as adrenaline or phenylephrine should be used to treat hypotension. Modafinil is used as a 'wake-promoting' drug. It has been proven to improve recovery from anaesthesia in normal individuals, but further implications on anaesthesia are not clear. The use of BIS monitoring has been recommended by Neustein³ and others, to guide the administration of anaesthesia.

CENTRAL SLEEP APNOEA SYNDROME (CSAS)

Several separate entities are grouped under CSAS in the international classification of sleep disorders manual. These include Cheynes-Stokes breathing – central sleep apnoea (CSB-CSA), high altitude periodic breathing, idiopathic (primary) central sleep apnoea and central sleep apnoea due to other medical conditions.

CSAS manifests as periodic cessation of breathing during sleep, leading to abnormal ventilation and gas exchange. This is in contrast to obstructive sleep apnoea (OSA) where there is ongoing respiratory effort during apnoeic spells.

CSAS results from impaired central respiratory drive and has been shown to have both hypocapnic (primary CSA, CSB-CSA) and hypercapnic forms (primarily neurodegenerative or neuromuscular in origin). During NREM sleep respiratory drive is controlled by chemical stimuli, most significantly carbon dioxide. The "apnoeic threshold" is the PaCO₂ below which, apnoea's occur. In CSAS this threshold is reached following transient hyper-ventilation which may follow obstruction or retention of secretions. The occurrence of apnoea is followed by inevitable hyperpnoea and a cycle of unstable breathing follows.

Hypercapnic sleep apnoea's occur in those that have an attenuated response to hypercapnia, such as those with chronic ventilatory failure. The transition to normal sleep is accompanied by an elevation in carbon dioxide even in the normal individual; in those with superimposed conditions the patients become carbon dioxide narcotised and apnoea's can then occur. Thus central apnoea due to hypercapnia is due to the removal of the wakefulness stimulus to breathe or to phasic REM related hypoventilation⁴. Both types have been treated effectively with intermittent non-invasive ventilation. Hypercapnic CSAS may also respond to agents that act as respiratory stimulants such as acetazolamide and progesterone.

Central sleep apnoea syndrome is a relatively uncommon condition that affects roughly 0.5 to 1 % of the population. There is predominance for males and the incidence increases with age. The sex difference is lessened as females become postmenopausal. The patient complains of insomnia, excessive daytime sleepiness and frequent arousals

Relevance to anaesthesia is both in the pathophysiological effects of the condition, and the effects of anaesthesia on the patient. Persistent or unrecognised sleep apnoea's can lead to respiratory failure,

right heart failure, hypertension, ischemic heart disease, polycythaemia and neuropsychological sequelae.

A rational approach to anaesthesia in these patients might include the following considerations: in the preoperative phase information should be gathered about the condition, including physiological effects, and relevant investigations. The ECG may show evidence of right ventricular hypertrophy, left ventricular hypertrophy or associated ischaemic heart disease. Echocardiography if available may help diagnose right sided heart failure. Pulmonary function tests are frequently normal and should only be done if one suspects underlying disease. Blood tests may reveal polycythaemia, in which case medical treatment or venesection may be considered.

Susceptibility to apnoea's with central depressants should be assumed, and they should be avoided. If the patient usually uses some form of non-invasive ventilation, provisions should be made for this to continue both pre and post operatively.

Choice of anaesthetic technique to some extent depends on the surgical procedure, but regional anaesthesia would seem to be favourable. Caution must be exercised in the use of opioids with neuraxial techniques. Ostermeier et al⁵ describe 3 cases of respiratory arrest in patients with sleep apnoea's having had epidural opioids. Combined techniques with neuraxial anaesthesia and focused nerve blocks might circumvent the need for opioids. Continuous nerve catheters may also have a role to play. Simple analgesics such as paracetamol and NSAIDs can be effective adjuvants. If general anaesthesia is required, a technique that ensures a prompt return to consciousness is the best choice. Extubation should be undertaken when the patient is fully awake and fully reversed from any neuromuscular blockade.

The postoperative period carries the greatest risk. Patients with CSAS are vulnerable to respiratory depression and apnoea's, particularly in association with opioid analgesia. Supplemental oxygen should be used, and considerations made for an extended period of post-operative monitoring. This may take the form of admission to critical care facilities.

CENTRAL ALVEOLAR HYPOVENTILATION SYNDROME (CAHS)

Central alveolar hypoventilation syndrome (CAHS) is a rare condition. It involves abnormal autonomic control of breathing, leading to hypoventilation and prolonged apnoea. CAHS becomes more marked during slow wave sleep, where the normal responses to hypoxia and hypercapnia are absent.

Better known as 'Ondine's curse', in reference to the 15th Century German folk tale in which Ondine (Undine), a water nymph, cursed her adulterous husband to cease breathing if he fell asleep. First described in 1962 by Severinghaus and Mitchell, it is predominantly a congenital condition. There is however a late onset, as well as an acquired form of the disease. This form occurs following cerebral lesions such as brainstem infarcts, tumours, intracerebral haemorrhage, infections and neurodegenerative conditions.

The congenital form is intrinsically linked to a mutation of the paired-like homeobox 2B (PHOX2B) gene. This region normally carries a 20 alanine repeat sequence. Affected individuals have been shown to have an expansion of up to 50% at this region, and severity of the disease is proportional to the size of expansion. There are a very few children living with this congenital abnormality. In 2009 estimates were given at around 1000⁶. The late onset form reflects variants of the mutation with lesser symptoms and diagnosis in adulthood, probably leading to a larger number of sufferers. Diagnosis is made in the congenital form in the absence of primary lung, cardiac or central disease. There is an association with other diseases displaying autonomic nerve system dysregulation, such as Hirschsprung's disease and tumours of neural crest origin. Pulmonary artery hypertension frequently occurs and is the result of increased pulmonary vascular resistance secondary to hypoxic pulmonary vasoconstriction. The progression of pulmonary hypertension can be halted by avoidance of hypoxia, either through nocturnal mechanical ventilation or diaphragmatic pacemakers.

The goal of anaesthesia in these patients, as with the other dyssomnias, is to minimise respiratory depression. Thorough pre-operative assessment is key, including addressing any reversible medical

problems. Those with diaphragmatic pacemakers present further challenges, similar to those in patients with cardiac pacemakers.

Where applicable regional anaesthesia should be employed. When general anaesthesia is unavoidable, intubation and ventilation is mandatory. Short acting agents are preferred for obvious reasons, and avoidance of opioids (including neuraxial opioids) is paramount. Addition of regional techniques can help achieve this goal. Post-operative care should be planned, with early involvement of critical care services.

OBSTRUCTIVE SLEEP APNOEA (OSA)

OSA is probably the most common of sleep disorders, and the most likely to be encountered. There is a wealth of literature on the anaesthetic management of these patients. It is included here briefly for completeness sake, with suggestions for more in-depth reviews included in the further reading. Management plans should include avoidance of respiratory depressants, preparation for difficult face mask ventilation, difficult endotracheal intubation and continuation of pre and post-operative nasal CPAP.

RESTLESS LEG SYNDROME

The patient with restless leg syndrome (RLS) displays an urge to move their legs. This is usually associated with lower limb paraesthesia or dysaesthesia, coupled with voluntary and involuntary motor symptoms. These occur at rest and worsen at night, leading to sleep disturbance. Additionally 75% of patients are afflicted by periodic leg movements. This involves involuntary leg twitching which occurs at 10 to 60 second intervals throughout sleep⁷. Restless leg syndrome is associated with up to 25% of pregnancies, iron deficiency and renal failure. It is more common in middle age, and in women. More often than not it has a chronic course. It has been shown that up to 10% of the population of the U.S suffer from RLS, and as many as 2% experience moderate or severe symptoms⁸. Recent systematic review has highlighted a strongly positive relationship with cardiovascular disease. There is also a probable association with diabetes and impaired glucose tolerance.

Symptoms are exacerbated by immobilisation, and are relieved by walking. Aetiology is elusive, but there is a strong suggestion of abnormal brain iron levels leading to an overactive dopaminergic system. There is a familial preponderance. Sufferers experience a reduced total sleep time, increased nocturnal waking and shifts in sleep phases. The most successful pharmacological treatment takes the form of oral dopamine agonists.

The implications for the anaesthetist are multiple. In sufferers perioperative movements may be deleterious to the surgical outcome. In procedures normally performed under local anaesthesia, necessitating stillness, alternative techniques should be sought. Serum ferritin levels mirror the severity of the condition, thus bleeding may worsen the condition. Raux et al⁹ suggest monitoring post-operative serum ferritin levels, with replacement either orally or intravenously in those with levels below 50mg/ml. They also advocate a transient increase in dopamine agonists in bed ridden patients. Consideration should be given to subcutaneous or transdermal treatment if the oral route is not available.

RLS can be triggered by metoclopramide, droperidol and prochlorperizine, and their use for prevention of nausea and vomiting should be avoided in these patients. The use of domperidone and 5HT-3 receptor antagonists (e.g. ondansetron) is safe.

IDIOPATHIC and RECURRENT HYPERSOMNIA

Most hypersomnias have an organic cause, such as tumours, encephalitis and stroke or can be attributed to other sleep disorders such as restless legs or narcolepsy. The cardinal symptoms of idiopathic hypersomnia, in the absence of organic pathology, are non-imperative sleep, excessive daytime sleepiness, prolonged night time sleep, difficulty awakening, sleep drunkenness on waking (automatic behaviour, confusion, and repeated returns to sleep) and prominent mood disorders, such as depression. There are distinct differences to narcolepsy. Absence of cataplexy, electrophysiological

evidence of REM sleep disturbance and prolonged unrefreshing naps allow a positive diagnosis. Idiopathic hypersomnia is a rare disorder, and the prevalence is unclear.

There is some suggestion that it affects 2 to 5 people per 100,000¹⁰. Idiopathic hypersomnia is associated with dysautonomia, which involves orthostatic hypotension, syncope, headache, and Raynaud-type phenomena.

Recurrent hypersomnia, also known as Kleine-Levin syndrome (KLS), is even less prevalent. It occurs most frequently in adolescence, and boys are 3 times more likely than girls to be affected. It is characterised by recurrent episodes of hypersomnia, behavioural or cognitive disturbances, compulsive eating behaviour and hyper sexuality. These episodes last a few days to several weeks, and recur weeks or months apart. Aetiology remains elusive, although case reports exist of patients having had precipitating infections, such as gastroenteritis or upper respiratory tract infections. General and local anaesthesia have been reported as precipitants. There is little familial clustering, and there is no definitive genetic association.

Treatment with stimulants similar to those used in narcolepsy has been tried for both disorders, but the results are not encouraging.

The rarity of both conditions is evident by the limited number of case reports describing management of anaesthesia in such patients. A considered approach should be taken in the same vein as described above for other dyssomnias. Many sufferers will be taking stimulant medication and these should be factored into management plans.

Theoretical complications of general anaesthesia in a KLS patient include triggering a sleeping episode, increased sensitivity to anaesthetic agents, apnoeic episodes and prolonged extubation time.

IMPORTANT POINTS

- Sleep is vital, producing an array of physiological effects, and being a product of a complex gamut of neuro-chemical processes.
- Anaesthesia, analgesia and operative stress can all affect normal sleep patterns
- Anaesthetic management of patients with dyssomnias should involve a thorough pre-operative assessment, an anaesthetic technique designed to minimise effects on the disease process, and consideration of post-operative critical care management

ANSWERS TO QUESTIONS

Further explanation can be found in the text.

1. F, T, T, T
2. T, F, F, T
3. T, T, T, T

FURTHER READING

Brown E, Lydic R, Schiff D. General anesthesia, sleep and coma. *N Engl J Med.* 2010; 363: 2638-50. <http://www.esst.org/adds/ICSD.pdf> - Manual of sleep disorders.

Bright S. Obstructive sleep apnoea and anaesthesia. *Anaesthesia tutorial of the week.* 152
21st september 2009.

Raux M. Case Scenario: Anesthetic implications of restless legs syndrome. *Anesthesiology.* 2010; 112 (6):1511-1517.

Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, Keens TG, Loghmanee DA, Trang H. An official ATS clinical policy statement: central hypoventilation syndrome genetic basis, diagnosis, and management. *Am J Respir Crit Care Med.* 2010; 181: 626–644.

Leschziner G, Gringas P. Restless legs syndrome. *BMJ.* 2012; 344: 38 – 41.

REFERENCES

1. Pelaez R, Hortal FJ, Bastida E, Barrio JM, Riesgo MJ. Narcolepsy and Cardiac Surgery : Can anesthesia with propofol and remifentanyl be safe? *J. Cardiothor. Vasc. Anaesth.* 2004; 18 (2): 201-203.
2. Doyle A, Wilkinson D. Day case general anaesthesia in a patient with narcolepsy. *Anaesthesia.* 2008; 63: 880-882.
3. Neustein S. Administration of desflurane with bistrectal index monitoring in a patient with narcolepsy undergoing anesthesia, *Acta Anaesth. Belg.* 2009; 60: 247-249.
4. Chowdhuri S, Safwan B. Central sleep apnoea. *Indian J Med Res.* 2010; 131: 150-164. Online at <http://icmr.nic.in/ijmr/2010/february/0205.pdf> (accessed August 2012)
5. Ostermeier et al. Three sudden postoperative respiratory arrests associated with epidural opioids in patients with sleep apnea. *Anest Analg* 1997; 85: 452-60.
6. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, Keens TG, Loghmanee DA, Trang H. An official ATS clinical policy statement: central hypoventilation syndrome genetic basis, diagnosis, and management. *Am J Respir Crit Care Med.* 2010; 181: 626–644.
7. Pearce JMS. Restless leg syndrome. *Eur Neurol.* 2005; 53:206–207.
8. National institute of Neurological disorders and stroke factsheet. Online at http://www.ninds.nih.gov/disorders/restless_legs/detail_restless_legs.htm (accessed August 2012)
9. Raux M. Case Scenario: Anesthetic implications of restless legs syndrome. *Anesthesiology.* 2010; 112 (6):1511-1517.
10. Bassetti C, Aldrich MS. Idiopathic hypersomnia. *Brain.* 1997; 120:1423–1435.