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The effects of a single mild dose of morphine on chemoreflexes and breathing in obstructive sleep apnea

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ABSTRACT

The effect of morphine on breathing and ventilatory chemoreflexes in obstructive sleep apnea (OSA) is unknown. It has been assumed that acute morphine use may induce deeper respiratory depression in OSA but this has not been investigated. We evaluated awake ventilatory chemoreflexes and overnight polysomnography on 10 mild-moderate OSA patients before and after giving 30 mg oral controlled-release morphine. Morphine plasma concentrations were analysed. We found a 30-fold range of morphine plasma concentrations with the fixed dose of morphine, and a higher plasma morphine concentration was associated with a higher CO_2 recruitment threshold (VRT) ($r = 0.86$, $p = 0.006$) and an improvement in sleep time with $Sp_{O_2} < 90\%$ (T90) ($r = -0.87$, $p = 0.005$) compared to the baseline. The improvement in T90 also significantly correlated with the increase of VRT ($r = -0.79$, $r = 0.02$). In conclusion, in mild-to-moderate OSA patients, a single common dose of oral morphine may paradoxically improve OSA through modulating chemoreflexes. There is a large inter-individual variability in the responses, which may relate to individual morphine metabolism.

1. Introduction

Opioids are commonly used in a number of clinical settings, including treatment of pain, trauma, cancer and in opioid maintenance treatment program. The number of opioid prescriptions has increased dramatically in the past decade. In the USA, the therapeutic use of methadone and oxycodone increased by 824% and 660%, respectively, between 1997 and 2003 (US Department of Justice and Drug Enforcement Administration, 2005). In Australia, the number of Pharmaceutical Benefits Scheme (PBS) opioid prescriptions increased three-fold, from 2.4 million in 1992 to 7.0 million in 2007 (Leong et al., 2009). Meanwhile, mortality rates from unintentional drug overdose have also increased substantially, with deaths attributed primarily to prescription opioid analgesics (more than 90%) (Centres for Disease Control and Prevention, 2007; Hall et al., 2008; Okie, 2010). In Australia, there was a three-fold increase in the number of hospitalisations as a result of unintentional overdose by opioids other than heroin and methadone from 1998/99 to 2006/07 (National Hospital Morbidity Database, 2008). Death from opioids is nearly always due to respiratory arrest (Caplehorn and Drummer, 1999; Gutstein and Akil, 2005). Acute opioid use can reduce vital ventilatory chemoreflexes and cause severe hypoventilation (Bailey et al., 2000), with the immediate cause of death often being pulmonary oedema secondary to prolonged hypoventilation (Caplehorn and Drummer, 1999).

During sleep, respiration is naturally depressed and mainly under automatic neural-chemical control (Douglas, 2000). Acute opioid use significantly reduces protective chemoreflexes, and patients have an increased risk of respiratory arrest during sleep (Dempsey et al., 2010). As a common disease, obstructive sleep apnea (OSA) is characterised by repetitive pauses in breathing during sleep due to the collapse and/or narrowing of the upper airway, and is usually associated with a reduction in blood oxygen saturation. The effect of opioids on OSA is unknown. No carefully designed clinical trial has investigated the effect of opioids in OSA (Chung et al., 2008; Macintyre et al., 2011). Current knowledge is based on observational case studies and retrospective

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analysis, and most have involved multiple drugs during perioperative procedures, limiting firm conclusions. At the same time, OSA has become a major concern for anaesthesia care providers (Benumof, 2002; Chung et al., 2008). Significant adverse respiratory outcomes have been reported in cases of obese patients with OSA during perioperative management (Benumof, 2002; Agro et al., 2004). The American Society of Anesthesiologists has issued practice guidelines for the perioperative management of OSA patients to reduce the risk of adverse outcomes (Gross et al., 2006). However, relevant recommendations were primarily based on the consensus of consultants' opinions (Gross et al., 2006; Chung et al., 2008). Similarly, sleep-disordered breathing was listed as a likely contributor to all opioid-related deaths mainly based on an expert panel's opinion (Webster et al., 2011). In contrast, a few recent reviews and reports have questioned whether OSA is an independent risk factor for perioperative adverse events (Sabers et al., 2003; Ahmad et al., 2008; Ankichetty et al., 2011; Macintyre et al., 2011; Weingarten et al., 2011). These reviews suggest that these adverse events may be related to co-existing obesity (Weingarten et al., 2011). Therefore clinical experimental trials are needed to investigate the effect of opioids on breathing during sleep including how these effects may relate to actual plasma drug levels. In the present study, we hypothesised that a commonly used single dose of oral morphine would impair awake ventilatory chemoreflexes and breathing during sleep in OSA patients and this would be related to plasma morphine levels.

2. Methods

This experiment was conducted as a part of a proof-of-concept study examining the potential for the antibiotic minocycline to reverse opioid-induced respiratory depression. Data on minocyclcine are not reported. The study was conducted at the Clinical Sleep Laboratory of Royal Prince Alfred Hospital (RPAH), a major teaching hospital of the University of Sydney. The study protocol was approved by Sydney South West Area Health Service (SSWAHS) Ethics Review Committee (Protocol No. X10-0268 & HREC/10/RPAH/476). Written consent forms were signed by all patients. The Australian & New Zealand Clinical Trial Registry number is ACTRN12610001074088.

2.1. Patients and procedure

Thirteen men with mild-moderate OSA were recruited from the sleep clinics of the Royal Prince Alfred Hospital and the associated Woolcock Institute of Medical Research from October 2010 to December 2010. Only men were included due to potential ventilatory chemoreflex changes in women during the menstrual cycle (White et al., 1983). We excluded regular opiate users and those who had a history of adverse effects from opioids or minocycline, history of drug abuse, current CPAP users, current or recent severe physiological or psychological illness including severe cardiovascular (hypertension) or CNS diseases, and those with another severe sleep disorders, or concurrent use of other medications that might interfere with the study drugs.

All patients underwent a baseline visit with overnight polysomnography (PSG) and awake ventilatory chemoreflex tests. Only those patients with apnea-hypopnea index (AHI) $\geq$10 and oxygen saturation (Sp_{O_2}) nadir between 70 and 90% were included and asked to come back for the intervention study.

In the intervention visit, patients finished dinner at 5 pm, and took a single oral dose of 30 mg slow-release morphine (MS Contin, Mundipharma Pty Limited, Sydney, Australia) at 5:30 pm. The drug will reach peak concentration at about 3 h post-dose and have around a 12 h duration of effect. Between 9 and 9:30 pm, patients were tested for awake ventilatory chemoreflexes. Between 9:30 and 10 pm, 5 ml of venous blood was taken for drug concentration analyses. At 10 pm (lights off time), the PSG sleep study started and was recorded continuously until 7 am the next morning.

2.2. PSG

In-lab standard full PSGs (Alice 5, Philips Respironics, Andover, MA, USA) were monitored, including 4 channels of electroencephalogram (EEG), 2 channels of electrooculogram (EOG), chin electromyelogram (EMG), anterior tibial EMG, electrocardiogram (ECG), body position, nasal pressure, chest and abdomen movements, and Sp_{O_2}. PSG recordings were scored using Rechtschaffen and Kales criteria (Rechtschaffen and Kales, 1968), by an experienced sleep technologist who was blinded to treatment allocation. Respiratory events and arousals were scored according to standard Chicago and ASDA criteria respectively (American Sleep Disorders Association, 1992; AASM Task Force, 1999). AHI was calculated by dividing the total number of apneas and hypopneas by the total sleep time (hours). Oxygen desaturation index (ODI) was calculated by dividing the total number of $\geq$3% Sp_{O_2} dips by the total sleep time (hours).

2.3. Ventilatory chemoreflex testing

Central chemosensitivity, CO_2 ventilatory recruitment threshold (VRT) and basal minute ventilation (V_E) were measured using a fully computerised system using Duffin's modified chemoreflex test (Duffin, 2010, 2011). An advantage of the Duffin's modified rebreathing method is that VRT can be directly measured rather than being estimated using an extrapolated line. Central chemosensitivity was determined by testing the slope of iso-oxic hyper-oxic (holding oxygen constant at 150 mmHg) ventilatory response to CO_2, as a 10 min test while the patient was awake (Fig. 1). The procedure included a 5 min hyperventilation and a 5 min of rebreathing through a closed circuit. During the hyperventilation, end-tidal P_{CO_2} was controlled between 19 and 25 mmHg. The computer then switched the valve and the patient rebreathed for 5 min through a bag containing a mix gas of 6% of CO_2 and 94% O_2. The P_{O_2} in the circuit was held constant at 150 mmHg. The computer continuously analysed O_2 consumption over the past 3 breaths and used a prediction model to determine how much O_2 to feed into the circuit. The VRT and central chemosensitivity (the slope of P_{CO_2} plotted against minute ventilation) were analysed through purpose-built software. An example is shown in Fig. 1.

2.4. Drug analyses

Plasma morphine concentrations were analysed at the laboratory of the Discipline of Pharmacology, The University of Adelaide. Plasma morphine concentrations were measured by LC/MS using a previously validated procedure (Somogyi et al., 2008). The intra- and inter-assay validation data showed accuracy > 90% and precision < 15% on quality control samples. The lower limits of quantification were 1 ng/ml.

2.5. Statistical analysis

The main outcomes of interest were respiratory depression related parameters including overnight Sp_{O_2} nadir, percent of sleep time with Sp_{O_2} < 90% (%T90), central chemosensitivity and VRT between baseline and morphine night. Descriptive data were expressed as mean ± SD, unless otherwise stated. Pair-wise comparisons were tested by paired *t*-test or Wilcoxon signed-rank test depending on normality of data distribution. Associations were