Effects of obstructive sleep apnea, inhalational anesthesia and fentanyl on the airway and ventilation of children.

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**Running title:** Opioid induced apnea in OSA

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Abstract:

To assess effects of anesthesia and opioids, we studied 13 children with obstructive sleep apnea (OSA, age 4.0 ± 2.2 yr, mean ± SD) and 24 age matched controls (5.8 ± 4.0 yr). Apnea indices of children with OSA were 29.4 ± 18 hr⁻¹, median 30 hr⁻¹. Under inhalational anesthetic, closing pressure at the mask was 2.2 ± 6.9 cmH₂O vs -14.7 ± 7.8 cmH₂O, OSA vs controls (p<0.001). After intubation, spontaneous ventilation was 115.5 ± 56.9 vs 158.7 ± 81.6 ml/kg/min, OSA vs controls (p=0.02), despite elevated pCO₂ (49.3 vs 42.1 mmHg, OSA vs controls, p<0.001). Minute ventilation fell after fentanyl (0.5 mcg/kg i.v.), with central apnea in 6/13 OSA cases vs 1/23 controls (p<0.001). Consistent with the finding of reduced spontaneous ventilation, apnea was most likely when end-tidal CO₂ exceeded 50 mmHg during spontaneous breathing under anesthetic. Thus, children with OSA had depressed spontaneous ventilation under anesthesia, and opioids precipitated apnea in almost 50% of children with OSA who were intubated, but breathing spontaneously under inhalational anesthesia.

Key Words: obstructive sleep apnea, children, ventilation, closing pressure, anesthesia, analgesia, fentanyl
Background

Obstructive sleep apnea (OSA) describes the repetitive collapse of the upper airway during sleep. Factors that can predispose to the condition include a small upper airway size (11), abnormal neuromuscular control (25), and there may be an inherited factor in the disease (21). During childhood, OSA is commonly associated with compromise of the airway size by adenotonsillar hypertrophy, and adenotonsillectomy is the treatment of choice (10).

Physiological abnormalities in subjects with OSA include a more collapsible upper airway compared to subjects with primary snoring, or controls without symptoms, whether this is measured during wakefulness or natural sleep (6, 11, 13). Many adults with a diagnosis of OSA have abnormal ventilatory responses (7), and in severe cases, respiratory failure encroaches into the waking state. However, compared to control subjects, the ventilatory responses for children with OSA have only been abnormal under specialised conditions (12, 8). For example, they have diminished responses to repeated hypercapnia when awake (8), and reduced arousal in response to CO2 when asleep (13).

Sedatives and anesthetic agents are known to exacerbate abnormalities of neuromuscular and of respiratory control. There is, however, little specific evidence for or against the use of sedatives and opioids in the perioperative period of children with OSA (4). To date, there are only anecdotal reports of respiratory depression in response to sedatives such as chloral hydrate (1), and respiratory depression of children in the perioperative period (9) including hypoxia (21, 5, 10, 14, 17). Ostermeier summarised 18 cases of respiratory depression in the postoperative period for patients with OSA, but included only one child, who had airway obstruction and bradycardia after chloral hydrate (19).

We hypothesised that, although subtle, the ventilatory control abnormalities present in children with OSA would increase their risk for respiratory depression during anesthesia. To examine whether children with OSA are more sensitive to the respiratory depressant effects of anesthesia and/or
opioid analgesics when compared to a control group, we measured ventilation after anesthetic induction, and then repeated the measurement after an intravenous dose of fentanyl. We found that children with OSA have respiratory depression despite elevated CO₂ when compared to control subjects under anesthesia, and that opioid analgesics compounded this, causing apnea in approximately half of the OSA group.

Methods

Patient selection

Consecutive patients from The Children’s Hospital at Westmead (Royal Alexandra Hospital for Children) were recruited if they were undergoing adenotonsillectomy for OSA that had been confirmed by overnight sleep study. Control subjects comprised children having surgery, who had no symptoms of sleep disordered breathing. Questionnaires regarding symptoms of sleep breathing abnormalities were collected in all cases (2). The study was approved by the Ethics Committee of the Hospital, and informed, written consent was obtained from the parents or the child, prior to each child’s participation in the study. For this preliminary investigation, we estimated that 18 subjects were needed in each group to show that a statistically significant effect size of one standard deviation between groups.

Questionnaire data was collected on the day of surgery. Children in the control group generally had surgery unrelated to the upper airway. Questionnaires were used to confirm that control subjects had minimal risk for OSA, and the sleep study prior to surgery was used to confirm the presence of OSA. Previous studies have shown that in children from the general population, rather than from a sleep-unit, questionnaire responses can distinguish children who are unlikely to have OSA using the “OSA score” (2). Any “control” subject with chronic snoring was excluded, because of the inability of questionnaire to distinguish primary snoring from OSA in children (3). Analyses were made between the groups of children with vs without OSA.
Anesthesia and study protocol

No premedication was used. Anesthesia was induced using an inhaled mixture of 30% oxygen, 60% nitrous oxide and 5% halothane, then an intravenous cannula was inserted. The expired concentration of halothane was stabilized at 1% prior to commencing the study protocol (Datex As3 Capnograph, Scandinavia). Closing pressure was measured using a sealed nasal mask, with the head in a neutral position and the mouth closed. Upper airway closing pressure was measured by manually occluding the mask inlet for an average of 10 spontaneous breath efforts, while the anesthetist maintained the mask and head positions. The flow signal was monitored for a plateau indicating airway closure. Where obstruction occurred above atmospheric pressures, positive pressure was introduced into the circuit via a t-piece and reservoir bag, containing 30% oxygen, 60% nitrous oxide, and the percentage of halothane required to maintain a 1% expired concentration just prior to the test. Pressure at the mask was monitored in real-time on the digital data display.

Anesthesia was then deepened, and an uncuffed endotracheal tube or laryngeal mask inserted to provide an unobstructed airway. Laryngeal mask airway was used in 14 (61%) of the 23 control cases, and 1 (7%) of the 13 children with OSA. Expired halothane concentration was then stabilised again at 1%, and minute ventilation and end tidal CO₂ (Datex AS3 Capnograph, Scandinavia) were digitally recorded (Amlab, Sydney). An intravenous injection of 0.5 mcg kg⁻¹ of fentanyl was given, then these measurements of ventilation were repeated. End tidal CO₂ at baseline was calculated as the mean plateau value over 9.6 ± 1.9 min (range 4.6-13.3).

Signal Acquisition, Calibration, and Measurement of Ventilation.

For the purpose of this study real time signals for CO₂ and flow were acquired directly from analogue outputs of the Datex AS3. Pressure signals were acquired in real time using a Validyne DP45-28 pressure transducer and CD101 carrier demodulator. All signals were digitised using a
signal processor (Amlab International, NSW, Australia). The pressure range of the DP45-28 is +/- 0.6 to 90 in H2O full scale, with accuracy +/- 0.25% at full scale. The Validyne carrier demodulator (CD101) has a linearity of +/- 0.05%. The specifications of the Datex AS3 are a range of 0 to 10% for CO2, with accuracy of ± 0.2 vol %, rise time 360 ms, and sample rate 200 ml/min. Using the same sampling tubing, flow rate, and Datex AS3, the measured delay in our circuit (with relation to the other data) to a step change in CO2 was 2.2 sec.

Flow measurements were made using a Datex (AS3) and either the Pedi-lite™ or D-lite™ sensor. The Pedi-lite™ sensor has a range of 0.25 ml to 25 L/min, a deadspace of 2.5 ml, and is used for patients weighing 3 to 30 kgs. The D-lite™ sensor has a range of 1.5 to 100 L/min, deadspace of 9.5 ml, and was used for children >20 kgs. Since either sensor was suitable for children weighing 20-30 kg, the choice between the two was made on the basis of other children in the same recording session.

All equipment was allowed to stabilised thermally for 30 min prior to calibration, and subsequent data collection. A two-point calibration was made before each test, using zero and 10 L/min flow rates, taking the sampling rate of the CO2 analyzer into account. Signals for flow and for pressure were checked using a calibration analyser (RT-200, Timeter Instrument Corp, Allied Healthcare Products Inc, St. Louis, MO). The Timeter Calibration Analyser (Timeter RT200) is a traceable reference instrument, Serial NoS17F, with pressure resolution of 0.1 cmH2O, and accuracy of +/- 0.5% of the reading. The same instrument was used for flow calibration, with resolution of 0.1 L/min, and accuracy of +/- 1% of the reading.

The Amlab (Amlab International, NSW, Australia) is a commercially available digital signal processor with an accuracy of 0.0001%. Data was acquired at a sampling frequency of 100Hz. The Amlab processor was calibrated to read the same as the RT-200 calibration analyser. The CO2 signal was calibrated using the Datex Quick Cal™ Calibration Gas (at 5%CO2 and 0%), with the Amlab digital signal processor then calibrated to read the same values. Real time, calibrated data, was
stored in digital format using Amlab data acquisition software, then exported for further analysis. Signal analysis was performed by Anadat (RHT-Infodat, Montreal, Canada), which is another commercially available digital signal analysis package. This software package includes a program for deriving respiratory variables on a breath-by-breath basis, from the calibrated flow signal (Abreath, V 5.2, RHT-Infodat, Montreal, Canada). The output variables include minute ventilation ($V_E$), tidal volume ($V_t$), respiratory frequency ($f$), and inspiratory and expiratory breath times ($T_i$ and $T_e$). Minute ventilation was corrected for body weight (ml/kg/min) to account for the large variability in age and weight of the children being studied.

Sleep studies

All overnight polysomnograms (sleep studies) were performed in the Sleep Unit of the Children’s Hospital at Westmead, in the usual manner for the unit. Briefly, conditions were adapted to approximate the child’s usual sleep habits, and studies commenced at the child’s usual bedtime. Sleep staging was performed with a minimum of 5 channels, and respiratory analysis utilised a minimum of 7 variables.

Sleep staging was derived from electroencephalogram (EEG; $C_3/A_2$ $O_2/A_1$), electrooculogram (EOG; left outer canthus/A2, and right outer canthus/A1), and submental electromyogram (EMG). Electrocardiogram (EKG) was included. Respiratory effort was recorded using inductance plethysmography, and surface EMG of the diaphragm. Plethysmography included abdominal, thoracic, and sum (Respirtrace®, Non Invasive Monitoring Systems, Inc., Miami Beach, Florida). Apneas and adequacy of ventilation were recorded through airflow, oxygen saturation, and transcutaneous CO$_2$ (TcpCO$_2$). Airflow was recorded via nasal oxygen cannulae (intermediate infant nasal cannula, No. 1615, Salter Labs, Arvin, California) connected to a pressure transducer with or without thermister recording because airflow measurement provides more reliable detection of respiratory events in OSA (17). Respiratory events were analysed using a combination of airflow
and respitrace (12). Gas measurements were made transcutaneously using oxygen saturation (SaO₂, Ohmeda Biox 3700e Pulse Oximeter, Datex-Ohmeda, Homebush, Australia) and transcutaneous CO₂ (TcpCO₂, TINA TCM3, Radiometer, Denmark).

Sleep study data were acquired on a digital system (Compumedics, Melbourne), and analysed for sleep stages, and the frequency and severity of apneas and hypopneas. Respiratory events were considered significant if they lasted ≥ 2 respiratory cycles, based on the respiratory rate of the preceding minute, and they were associated with SaO₂ desaturation of ≥3%, and/or they were terminated by an arousal. Treatment is generally recommended by our clinicians if the respiratory disturbance index (RDI) exceeds ≥5 respiratory events hr⁻¹, and includes obstructive events. Full arousals were defined as an abrupt shift in EEG for ≥1 s, with the exception of an occurrence of spindles. Currently, our laboratory does not consider the occurrence of a spindle to indicate arousal, because of the risk that spindles occurring as a normal part of sleep could be incorrectly marked as respiratory-related events. Movement arousals were defined as disturbances on ≥2 independent channels with EEG remaining unaffected for at least 1 s. The primary outcome measure of the sleep study was the apnea index (number of all apneas per hour of sleep time). The obstructive apnea index (ORDI, number of mixed, obstructive apnea and hypopnea per hour of sleep time), and respiratory disturbance index (RDI = number of apnea and hypopnea per hour of sleep time, including central apnea, and sleep stage specific indices) were also recorded. Other outputs included the arousal index (number of all arousal types per hour of sleep time), TcpCO₂ (mean and range), heart rate (mean and range), and SaO₂ (mean, range, and number of desaturations >2%, >4%, and >5% per hour of sleep time). All measurements of oxygen saturation were made after the study had been reviewed, and movement artefact excluded.
Statistical Analyses

Multivariate analysis, or repeated measures ANOVA (SPSS Inc., Version 10.0.5, Chicago, Illinois) were used to analyse differences between the two groups and the responses to fentanyl. Group comparisons were made assuming equal variance. Chi-square analysis was used to assess the difference in incidence of central apnea after fentanyl. Results are shown as mean ± standard deviation unless otherwise stated. A p value of < 0.05 was considered statistically significant. Subgroup analyses for groups with diagnoses in addition to OSA were not performed, because of the small sample size in this study.

Results

At the end of the data collection period, a total of 42 children had participated in the study. Results are presented for 38 children (13 with OSA and 25 age-matched controls). Two “OSA” cases were excluded from the analysis, 1 because the sleep study showed partial airway obstruction but no apnea and the other because the sleep study was undertaken in another centre, so sleep state and respiratory analyses (to confirm the presence of OSA) were not available. Two “control” cases were excluded because they had a history of chronic snoring. The OSA score of the groups were -3.2 ± 0.5 (-3.8 to -1.7) and 2.0 ± 1.8 (-0.3 to 4.0) (p < 0.001, control vs OSA, respectively). Thus, questionnaires were completed for all control cases, and confirmed that the children did not snore or snored occasionally, and did not have other sleep breathing problems. All children used as control subjects had OSA scores low enough to exclude OSA, and all children with OSA fell into the range where sleep studies would be recommended (2).

The nature of our recruitment meant that these children were characteristic of our sleep unit population, including 50% with an associated diagnosis likely to increase their risk for OSA (24). These diagnoses included Down syndrome (n=3), “Charge” syndrome (n=1), obesity (n=1) and
cerebral palsy (n=1), with the remainder having no associated abnormalities other than enlarged tonsils and adenoids. Surgical procedures being undertaken in the control group included: herniotomy (n=3), hydrocele (n=4), circumcision (n=5), orchidopexy (n=4), cholecystectomy (n=1), other urological surgery (n=2), burns (n=1), excision of lip cyst (n=1), adenoidectomy (n=1), and insertion of grommets (middle ear drainage n=1). Three were reported to have asthma, and one was born prematurely.

There was a male predominance in both OSA and control groups 78.3 vs 69.2% males, control and OSA, respectively. The mean age of the subjects was 4.0 ± 2.2, and 5.8 ± 4.0 yr, in the OSA and control groups, respectively. The proportion of obese subjects was 30 and 23% in the control and OSA groups, with obesity defined as weight >95th percentile for age and gender using World Health Organisation (WHO) reference values (26). As a group, the control subjects tended to be on a higher weight percentile. Table 1.

The median obstructive apnea index of the OSA group was 30.6 (mean 21.7, SD 15.9, range 4.5-67 obstructive events per hour of sleep time). Details of the sleep studies are shown in Table 2.

Respiratory measurements

Closing pressures were higher in children with OSA (2.2 vs -14.2 cmH2O, OSA vs controls, respectively, p<0.001). Figure 3a. Closing pressures also correlated with RDI, R^2 = 0.58, p<0.005, excluding one extreme outlier (case 10, one of 3 children with Down syndrome, who had a high closing pressure of 12 cmH2O, but relatively low RDI of 13.2 hr^{-1}). Figure 3b.

During spontaneous breathing, at baseline and after anaesthetic induction, end tidal pCO2 was elevated in the OSA group (49.3 ± 5.6 vs 42.1 ± 4.9 mmHg, OSA vs controls, respectively, p<0.001). Despite this, minute ventilation (corrected for weight) was lower in children with OSA (115.5 ± 81.6 vs 158.7 ± 81.6 ml/kg/min, OSA vs controls, respectively, p=0.02). Table 3. The T_i/T_tot ratio was lower in children with OSA at baseline with an unloaded upper airway (0.32 ± 0.01
vs 0.37 ± 0.01s, OSA vs control, respectively, p<0.001). Other respiratory parameters were not
different between the OSA and controls at baseline. Measurements included tidal volume (= V_t, 4.7 ± 2.8 vs 4.7 ± 2.7 ml/kg/min, OSA vs control, respectively, NS), inspiratory flow (11.7 ± 9.0 vs 13.0 ± 9.6 l/s, OSA vs control, respectively, NS), and respiratory frequency (34.8 ± 11.1 vs 37.8 ± 10.1 min⁻¹, OSA vs control, respectively, NS).

Response to fentanyl

A single intravenous dose of fentanyl induced depression of respiratory parameters in all
children. Tables 3 and 4. Complete apnea was induced in 6 of 13 children with OSA (46%) but only
one of the 23 controls (5%, chi-square p<0.001), with no spontaneous respiratory efforts for 3.7 ±
4.0 min (range 30 s to 11.5 min). Assisted ventilation was provided during the apneic period. All
children with a baseline end-tidal CO₂ >50 mmHg had central apnea after fentanyl. The control
subject who experienced apnea had a spontaneous CO₂ of 45.7 mmHg, and no other diagnosis that
would explain the predisposition to apnea. Neither the degree of respiratory depression, nor the
occurrence of apnea after fentanyl, was affected by the presence of another diagnosis. Although
numbers were small, the proportion of children with abnormalities was not different in the apneic
group (3/6 =50%) compared to the study group (6/13 = 46%). Apnea indices on the sleep study were
not predictive of fentanyl induced apnea (Table 2).

After fentanyl, group differences in respiratory parameters remained consistent with the baseline
data. For example, end tidal CO₂ levels were higher in children with OSA than controls (55.4 ± 2.8
vs 48.7 ± 1.4 mmHg in OSA vs controls, respectively, p<0.02), and the T_i/T_t ratio was lower in
children with OSA (T_i/T_t 0.25 vs 0.30, OSA vs control, respectively, p=0.01). The respiratory rate
RR after fentanyl was not different in children with OSA compared to control subjects (23.4 ± 9.6
vs 24.6 ± 11.4 min⁻¹ OSA vs controls, NS). There was a trend for respiratory rate, as a proportion of
baseline, to be lower in children with OSA compared to control subjects (63.7 vs 78.6 %, p=0.06).
Relative effects of OSA vs fentanyl

Two-way ANOVA showed that the respiratory depressant effects of fentanyl were present for all children, but not different between groups (OSA vs controls). Differences attributable to fentanyl are shown in Table 4. For example minute ventilation fell in all children (159.4 ± 57.4 vs 114.5 ± 55.9 ml/kg/min before vs after fentanyl, p<0.01), and spontaneous CO₂ levels increased. Figure 4 illustrates the change in end-tidal CO₂ for control and OSA subjects, before vs after fentanyl. Figure 5 shows minute ventilation as combined data for both groups, before vs after fentanyl.

Two-way ANOVA showed that overall, the inspiratory duration (Ti) was not different between groups (0.71 ± 0.09 vs 0.69 ± 0.03, OSA vs control, NS). In addition, Ti did not change significantly before vs after the administration of fentanyl (0.69 ± 0.06 vs 0.71 ± 0.03, NS).

Multivariate analyses were also performed for inspiratory drive (Vt/Ti), and showed that fentanyl had a significant effect (14.7 ± 1.9 vs 12.6 ± 2.0 ml/kg, before vs after fentanyl, p=0.03), but no effect was attributable to OSA (11.9 ± 3.1 vs 15.4 ± 3.3 ml/kg, OSA vs control, NS), and there was no interaction between the two. When minute ventilation was normalised to end tidal CO₂, the differences in minute ventilation between the diagnostic groups (OSA vs controls) and fentanyl (before vs after) were independently significant. Thus, respiratory depression was present in children with OSA (2.7 ± 1.3 vs 4.2 ± 4.3 ml/kg/min/mmHgCO₂, OSA vs controls, p=0.01), and in the presence of fentanyl (4.5 ± 4.3 vs 2.7 ± 2.2 ml/kg/min/mmHgCO₂, before vs after, p=0.004).

Discussion

We examined the effects of opioids on ventilatory parameters of children with proven OSA, in the common clinical context of an inhalational anesthetic, and found respiratory depression in children with OSA. After securing the airway, children with OSA had reduced minute ventilation and
elevated CO₂ in the presence of inhalational anesthesia, as compared to controls. The addition of an opioid analgesic (fentanyl) led to central apnea in approximately half of the OSA group.

Although questionnaires can distinguish control subjects from children with possible, or likely OSA, sleep studies are necessary to confirm the presence of OSA once a child is identified as symptomatic of OSA (2). Carroll et al found a 1:4 chance of misdiagnosis (positive and negative) of OSA once children presented to a sleep unit, so all children in the present study had OSA proven by an overnight sleep study (3). The OSA scores of our OSA group reflect the characteristics of a sleep-unit population. Other clinical characteristics were also consistent with the population of our pediatric sleep unit, that is, children with moderate to severe disease often have an associated clinical condition (24). We deliberately recruited such an unselected group, to ensure that the results would be applicable to clinical populations in general. Since our ventilatory measurements were made after bypassing the upper airway, the presence of anatomical abnormalities would not be expected to confound the measured outcomes.

Upper airway closing pressures were above atmospheric levels in 8 of 13 (62%) of the OSA subjects when measured under anesthesia. This highlights the ready collapsibility of the airway of children with confirmed OSA, under routine inhalational anesthesia (6, 11, 13), which is important if anesthesia is to be introduced for any routine procedure in this group of patients. In this study, no muscle paralysis or local anesthetic was used, and the children were breathing spontaneously. According to standard procedure for this measurement, if the airway collapses above atmospheric pressure, positive pressure was introduced into the circuit (14). The closing pressure values below atmosphere likely reflected some component of upper-airway muscle activity (13, 6). Closing pressures measured above atmosphere, for children with OSA and after introduction of positive pressure into the circuit, were likely to have been biased towards a passive airway (no muscle activity) through muscle relaxation (13). The interactions of muscle activity, airway resistance, and airway size are complex. Henke demonstrated that upper airway muscles have no significant role in
maintaining patency in non-snoring young adults, suggesting that the recruitment of upper airway
muscles in subjects with OSA is a response to inspiratory load, and/or hypercapnia (12). Thus, the
conditions for upper airway muscle activity may have differed between the OSA group and controls,
with the bias introduced by a positive pressure environment possibly leading to additional loss of
upper-airway muscle activity in OSA subjects at the time of measurement. As far as we are aware,
this is the first documentation of closing pressures during inhalational anesthetic, without muscle
relaxant, for adults or children with and without OSA.

A new finding of this study was that respiratory depression was present in children with OSA
after anesthetic induction, compared to controls, at baseline. We were not able to determine the
mechanism underlying this difference, and it may be due to abnormal airway responsiveness, to
abnormal respiratory control mechanisms, or to a combination of both. The profile of abnormalities
in children with OSA was similar to that seen in the control subjects after fentanyl. Elevation of
pCO₂ and lower minute ventilation as compared to controls suggests that there was a central
component to the respiratory depression that we observed in the OSA group. Inspiratory loading
may induce similar respiratory changes, but would usually also prolong Ti, which was not observed
in the OSA group. Respiratory control abnormalities appear to be subtle in children with OSA, and
one previous study showed that children rapidly reduce minute ventilation in response to an upper-
airway load (18).

Previously documented respiratory abnormalities in children with OSA, include failure to
arouse from sleep in response to high CO₂, depression of responses to CO₂ when the stimulus is
cyclical (13, 8), and tolerance of higher CO₂ levels under anesthesia. The pattern of respiratory
depression for children with OSA in this study, compared to control subjects, included depression of
baseline ventilation and the occurrence of apnoea after fentanyl. Similar changes to those we
observed in our baseline measurements have been noted in adults in response to the opiate μ-
receptor (23), including the finding of a shorter Ti, which was present in children with OSA under
anaesthetic and was consistent before and after fentanyl. This altered pattern of ventilation, with shorter Ti has been previously observed in children with OSA after repeated hypercapnia (8). In our study an artificial airway by-passed any upper-airway obstruction and there had been no prior chemical stimulus (eg. CO₂) when this shift in ventilatory pattern was first observed; the airway was kept patent during the test period, excluding the brief occlusion used to measure airway closing pressure.

Children with OSA appear to have specific sensitivity to opioids. The respiratory depression caused by the opioids was marked in children with OSA under anaesthesia. The low dose of opioid (fentanyl) used in this study caused equivalent respiratory depression in all children, whether or not they had OSA, but precipitated central apnea in 46% of the OSA group. Consistent with this, the best predictor for opioid induced central apnea was that the child had elevated end tidal CO₂ to levels >50 mmHg during spontaneous breathing after anesthetic induction. The depression of respiration in the OSA group was independent of that caused by fentanyl, although the features of the respiratory depression for children with OSA at baseline were similar to those caused by 0.1 mcg/kg of fentanyl in the control subjects.

Limitations of the study

Minute ventilation was measured in this study, but only after the children had had their airway secured. We did not examine for further changes in upper-airway responsiveness in the presence of hypoxia or hyperoxia. It remains possible that differences in upper-airway load, upper-airway responses, and/or the responses to relative hyperoxia in the presence of an anaesthetic contributed to the differences we observed between the groups.

Laryngeal mask airways (LMA’s) were used for the majority of control subjects in this study, whereas ETT’s were used for the majority of subjects with OSA. This raises a number of issues including: 1. Possible differences in the resistive load of the two circuits, 2. Ventilatory responses to
stimulation of the larynx vs the supraglottic region, 3. Activity of the larynx affecting the ventilatory responses, and, 4. Possible leak around an uncuffed endotracheal tube.

Ventilation was measured after securing the airway, but it remains possible that the difference in resistance of the LMA vs ETT circuits contributed to the differences observed at baseline. We measured and found a small difference in the resistive loads of the two systems. At 6L/min, the fresh gas flow used during the studies, the pressure drop across the LMA was 0.1 cmH\(_2\)O, compared to 0.5 cmH\(_2\)O for the ETT. One previous study examined the effects of resistive load in children with OSA (18). An inspiratory resistive load of 15 cmH\(_2\)O, (30 times greater than our measured load), was required before there was a 30% reduction in minute ventilation in that study. In the current series, the OSA group had a 37% reduction in minute ventilation compared to the controls.

It is possible that LMA’s would precipitate different respiratory reflex responses to endotracheal tubes. Previous studies have compared the reflex responses induced by laryngeal vs tracheal stimulation with water, CO\(_2\) or cool air, and found no difference (20). Responses to supraglottic and glottic stimulation are also equivalent (20, 22). Activity of the larynx would only influence the responses of children for whom an LMA was used, because dilatation of the larynx would be expected at higher CO\(_2\) values. However, this effect would have most influence in the control group, whereas higher CO2 values were observed in the group with OSA.

Although non-cuffed endotracheal tubes were used, the possibility of leak affecting the ventilatory measurements was minimised by the fact that they were made during spontaneous (i.e. negative inspiratory pressure) ventilation. A leak around the endotracheal tube would not be expected to affect the CO\(_2\) levels measured, but may have affected the measurement of minute ventilation.

The sampling rate of the CO\(_2\) analyser was relatively high for the size of the children being studied. However, the calibration for all flow measurements accounted for, and should have eliminated any change in flow rates attributable to this sampling. The sampling rate of the analyser
may have introduced a small systematic error into our studies, and no additional correction was added for this after the data was acquired. This would not have affected the direction, although it may have had a slight effect on the magnitude of the differences we observed.

Summary and Clinical Relevance

We studied children with OSA in the common clinical environment of inhalational anaesthesia. In that setting we found that children with OSA have respiratory depression compared to age-matched control subjects, when breathing spontaneously under anaesthetic with the upper-airway secured. Further studies would be required to elucidate the relative contribution of respiratory control and/or upper-airway abnormalities to this response. A small dose of opioids caused additional respiratory depression. Thus, in the presence of inhalational anesthesia and an endotracheal tube, fentanyl led to central apnea requiring respiratory support in 46% of children with OSA. We conclude that children with OSA are particularly sensitive to respiratory depression caused by opioids.
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References


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Group characteristics at baseline, mean (standard deviation), of children with obstructive sleep apnea (OSA) and age matched control subjects.
Table 2. Indices of the Overnight sleep studies

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Case</th>
<th>RDI</th>
<th>ORDI</th>
<th>REM OAI</th>
<th>SaO2 mean</th>
<th>SaO2 min</th>
<th>Desaturation episodes</th>
<th>Av Desat</th>
<th>CO2 low</th>
<th>CO2 high</th>
<th>CO2 range</th>
<th>Study</th>
<th>Diagnosis</th>
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<td>3.46</td>
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<td>95</td>
<td>71</td>
<td>580 206 131</td>
<td>5</td>
<td>not recorded</td>
<td>42.6</td>
<td>T&amp;A</td>
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<tr>
<td>3.68</td>
<td>2</td>
<td>4.5</td>
<td>3.5</td>
<td>7.1</td>
<td>98</td>
<td>92</td>
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<tr>
<td>2.11</td>
<td>3</td>
<td>28.1</td>
<td>22.9</td>
<td>78.0</td>
<td>97</td>
<td>52</td>
<td>479 237 205</td>
<td>11</td>
<td>44 58 14</td>
<td>59.9*</td>
<td>T&amp;A</td>
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<td>2.36</td>
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<td>97</td>
<td>80</td>
<td>561 167 89</td>
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<td>45.9</td>
<td>DS</td>
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<td>5</td>
<td>9.7</td>
<td>9.2</td>
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<td>97</td>
<td>88</td>
<td>198 31 16</td>
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<td>45 58 13</td>
<td>54.9*</td>
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<tr>
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<td>13.5</td>
<td>7.3</td>
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<td>63</td>
<td>175 29 12</td>
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<td>57.4*</td>
<td>DS</td>
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<td>7</td>
<td>41.8</td>
<td>30.8</td>
<td>68.1</td>
<td>96</td>
<td>67</td>
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<td>7</td>
<td>44 61 17</td>
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<td>26.9</td>
<td>95</td>
<td>75</td>
<td>482 121 80</td>
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<td>56.0*</td>
<td>CP</td>
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<td>33.0</td>
<td>29.8</td>
<td>62.2</td>
<td>95</td>
<td>45</td>
<td>429 158 114</td>
<td>9</td>
<td>48 70 22</td>
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<td>T&amp;A</td>
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<td>87</td>
<td>358 54 22</td>
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<td>54 61 7</td>
<td>45.9*</td>
<td>DS</td>
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<td>92.7</td>
<td>98</td>
<td>54</td>
<td>645 337 266</td>
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<td>not recorded</td>
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<td>T&amp;A</td>
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<td></td>
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<tr>
<td>1.45</td>
<td>12</td>
<td>14.3</td>
<td>6.3</td>
<td>35.3</td>
<td>94</td>
<td>87</td>
<td>536 66 30</td>
<td>3</td>
<td>42 55 13</td>
<td>47.3</td>
<td>CHARGE</td>
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<td>43.1</td>
<td>31.1</td>
<td>34.6</td>
<td>98</td>
<td>84</td>
<td>395 145 91</td>
<td>4</td>
<td>44 59 15</td>
<td>48.3</td>
<td>T&amp;A</td>
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</tr>
<tr>
<td>3.98</td>
<td>-</td>
<td>29.4</td>
<td>21.7</td>
<td>49.1</td>
<td>96.1</td>
<td>72.7</td>
<td>416.7 135.1 93.5</td>
<td>5.4</td>
<td>44.8 59.8 15.0</td>
<td>50.3  MEAN</td>
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<td></td>
</tr>
</tbody>
</table>

RDI = respiratory disturbance hypopnea index, ORDI = obstructive apnea/hypopnea index, REM OAI = obstructive apnea index (events per hour) during REM sleep, SaO2 mean, and SaO2 min = mean, and minimum saturation recorded during the sleep study, respectively. \(>2\%\), \(>4\%\) and \(>5\%\) = number of desaturation episodes of 2%, 4%, and 5% or more, respectively. Av Desat = average desaturation following a respiratory event, CO2 low, CO2 high, and CO2 range = minimum, maximum and range of transcutaneous CO2 values (maximum minimum) during sleep, respectively. BL = baseline. * subjects who had central apnea with fentanyl. T&A = adnotonsillar hypertrophy, DS = Down Syndrome, CHARGE = charge association, CP = cerebral palsy.
Table 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OSA</th>
<th>CONTROLS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous $V_E$ (ml/kg/min)</td>
<td>115.5 (81.6)</td>
<td>158.7 (81.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>$f$ (min$^{-1}$)</td>
<td>34.8 (11.4)</td>
<td>35.4 (12.6)</td>
<td>NS</td>
</tr>
<tr>
<td>$V_t$ (ml/kg)</td>
<td>4.4 (4.1)</td>
<td>3.8 (3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline end tidal CO$_2$ (mmHg)</td>
<td>49.3 (5.6)</td>
<td>42.1 (4.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>$V_E$ Normalised to CO$_2$ (ml/kg/min/mmHg)</td>
<td>2.9 (1.4)</td>
<td>3.2 (1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Closing Pressure (cmH$_2$O)</td>
<td>1.6</td>
<td>-14.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fall in baseline ventilation after fentanyl (ml/kg/min)</td>
<td>78.6 (54.5)</td>
<td>65.0 (128.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values shown are mean (standard deviation).
<table>
<thead>
<tr>
<th>Response to Opioids</th>
<th>Before Fentanyl</th>
<th>After Fentanyl</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_E$ (ml/kg/min)</td>
<td>159.4 (57.4)</td>
<td>114.5 (55.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Normalised $V_E$ (per mmHg)</td>
<td>4.5 (4.3)</td>
<td>2.7 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spontaneous $CO_2$ (mmHg)</td>
<td>51.7 (8.9)</td>
<td>57.2 (11.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Changes in respiratory parameters of all children in responses to an intravenous dose of fentanyl, regardless of the presence or absence of OSA. The values presented are mean (standard deviation). P value refer to results of two-way ANOVA.
Figure 1. Raw data demonstrating the method used to determine closing pressure in a subject with OSA. The absence of flow was confirmed in the first trace, while airway pressure is shown in the second. The pressure at which the airway collapsed, was measured at –3.2 cmH2O.

Figure 2. A. Closing pressure measured at a facemask of children with OSA and control subjects after anesthetic induction, but before intubation. B. = RDI and closing pressures, with regression line, for children with OSA. See text for statistical analysis.

Figure 3. Effects of OSA and fentanyl on end tidal CO2 (mmHg), during spontaneous breathing after anesthetic induction for children with and without OSA, before and after fentanyl.

Figure 4. Minute ventilation of all subjects at baseline (after induction with inhalational anesthetic) compared to anesthetic plus fentanyl. Values for control and OSA subjects were combined because the effect of fentanyl was independent of the effect of diagnostic category. See text for statistical analyses.
A

Pressure (cmH\textsubscript{2}O)

-40
-35
-30
-25
-20
-15
-10
-5
0
5
10
15

Control

OSA

B

AH\textsubscript{I} / hr sleep time

Y = 2.32X + 30.49