Alveolar hypoventilation treated with medroxyprogesterone

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SUMMARY Two children aged 1 and 20 months developed alveolar hypoventilation syndrome. They suffered severe apnoeic episodes and periodically required assisted ventilation. Their ventilatory response to carbon dioxide was lower than that of normal children and the transcutaneous oxygen tension during sleep was well below the normal range. Treatment with medroxyprogesterone acetate resulted in an improved response to carbon dioxide, and assisted ventilation was no longer needed. Oxygen and carbon dioxide tensions improved but were still slightly abnormal during sleep. There were no clinical side effects of treatment but one infant had slight pituitary suppression.

Congenital failure of automatic control of ventilation is a rare but well known disorder in childhood.1 Diminished responsiveness to CO₂ may be found in these infants, although neither the underlying structural abnormality nor the pathophysiology is entirely clear. Infants with primary alveolar hypoventilation may die suddenly and sleep hypoventilation has been proposed as a cause of sudden infant death syndrome.2 This proposition is supported by the finding that some babies with episodes of apnoea have hypercarbia and a blunted CO₂ response during sleep.3 Although the proposed association between sudden infant death and sleep hypoventilation is controversial,4 the increased interest in respiratory monitoring of infants with symptomatic sleep apnoea may lead to the detection of an increased number of cases of hypoventilation. This report deals with two infants with symptomatic apnoea and severe sleep hypoventilation diagnosed during a respiratory monitoring programme for babies at increased risk of sudden infant death.

Treatment of children with congenital central hypoventilation syndrome has usually been confined to artificial ventilation during sleep or phrenic nerve pacing. The long term outcome has generally been poor.5–6 Various respiratory stimulating drugs like theophylline and doxapram have also been tried with uncertain success.7 We found medroxyprogesterone acetate effective in the treatment of two patients described here. Medroxyprogesterone is known to increase ventilation in the healthy adult8 and has also been reported to increase ventilation in infants with hypoventilation.9 We present a more detailed analysis of long and short term effects of medroxyprogesterone on respiratory, endocrinological, and developmental parameters.

Patients

Case 1. This patient, the second child of a 24 year old mother, was delivered vaginally and without any complications at term. At 5 hours of age she was referred for observation after a cyanotic attack; capillary carbon dioxide tension (Pco₂) was 13.4 kPa. She recovered rapidly and was discharged home the following day without further investigations. At home the mother observed several apnoeic spells, sometimes associated with cyanosis. On two occasions, at 4 and 5 weeks of age, the infant was admitted for observation because of episodes of respiratory arrest. Blood gases were not checked on either occasion. A few hours after subsequent discharge she had prolonged respiratory arrest and had to be given mouth to mouth resuscitation. On arrival at the hospital she was found to have right cardiac enlargement with pulmonary infiltrates and cerebral oedema. She was artificially ventilated and seemed to recover within a few days. A week later, at 2 months of age, she was referred to our unit for investigation. Her blood gas values were essentially normal when she was awake but hypoxia and hypercarbia were observed during sleep. Because
artificial ventilation during sleep proved necessary, a tracheostomy was performed and this was maintained until she was 18 months old. Her respiratory functions were tested repeatedly during this time. Various respiratory stimulants were tried but only medroxyprogesterone acetate improved her ventilation enough to make artificial ventilation unnecessary. After three control trials with medroxyprogesterone she was decannulated and put on continuous oral treatment. She was discharged home at 20 months of age having spent 18 months in hospital (the last four, only during the night).

Case 2. This patient, the first child of a 22 year old mother, was delivered vaginally after an uncomplicated pregnancy. The neonatal period was uneventful. The infant was wholly breast fed up to 3 months of age and partially to 5 months. At about 3 months of age tracheal hypersecretion was noted and subsequently the child developed night sweats, constipation, and fluctuations in body temperature. The symptoms were aggravated during the following months. Weight and length stayed slightly below normal on a standard growth chart. Mental development was well ahead but motor development was moderately retarded. At 20 months of age, in conjunction with an upper respiratory tract infection, she suddenly became limp and apnoeic. Within minutes she was brought to a paediatric emergency unit where she developed cardiac arrest and general convulsions soon after arrival. She stayed on artificial ventilation for a few days, and during the initial investigation meningitis, septicaemia, and epilepsy were excluded. After extubation a mild spastic diplegia was noted; this resolved during the subsequent months. Further investigation at a university clinic showed no endocrinological or metabolic abnormalities and no disorders of the gastrointestinal tract. Three months after the first attack, and during another upper respiratory tract infection, she again became apnoeic. An upper airway obstruction was suspected and a tonsilloadenoidectomy was performed. Two months later she developed cardiorespiratory arrest during another upper airway infection. She was found to have right cardiac enlargement, pulmonary infiltrates, cerebral oedema, and recurrent general seizures on admission to hospital and was transferred to a paediatric intensive care unit for tracheostomy and ventilatory support. Due to difficulties in weaning the girl off the ventilator she was transferred to our unit for respiratory investigation.

Methods

Respiratory recordings. The protocol for the investigation was approved by the local ethical committee and informed consent was obtained from the parents. Polygraphic recordings of respiratory movements, electrocardiograph, transcutaneous oxygen pressure (TcPo2), transcutaneous carbon dioxide pressure (TcPCO2), end tidal PCO2, and tidal flow were performed during a night’s spontaneous sleep. The signals obtained were graphically displayed on an eight channel, high speed recorder (Mingograph Siemens Elema, Sweden). Sleep states were classified by direct observation using the criteria described by Prechtl.10

Respiratory movements were monitored with a chest impedance plethysmography unit (HP 81 Hewlett-Packard) or with a chest and abdomen induction plethysmography device (Respitrace Ambulatory Monitoring, USA).

Oxygen pressure and PCO2 were measured with a transcutaneous gas monitor (TCM 20 Radiometer, Copenhagen). End alveolar PCO2 was determined using an infrared chamber CO2 analyser (Datex, Helsinki). Tidal flow was recorded during a representative period of quiet sleep and during the CO2 response test with a heated Fleisch tube or an electrospirometer flow head (Mercury Corporation, Glasgow). The flow was directly measured at the tracheostoma and electronically integrated to give volume recordings.

Procedures. Oxygen pressure and PCO2 were sampled from the tracings every minute during a representative sleep state. The numerical values were grouped in 0.5 kPa intervals. The percentage of sleep time spent in each PO2 and PCO2 interval was calculated and presented as a cumulative graph as previously described by Slutsky and Strohl.15 This mode of presentation is especially valuable in patients with obstructive sleep apnoea, where a median value would not reflect the presence of hypoxic episodes, but proved equally helpful in assessing the ventilatory changes in patients with central hypoventilation.

During the CO2 response test end alveolar CO2 values and integrated flow data were sampled every 15 to 20 seconds. All tests were performed during quiet sleep. All gas volumes and partial pressures are expressed at body temperature pressure saturated (BTPS).

Endocrinological investigation. Resting values of follicle stimulating hormone and luteinising hormone and the concentrations of these hormones after intravenous gonadoliberin (60 µg/m²) were studied before and during treatment in the first infant and during treatment in the second.
Pituitary function was assessed by the 'rapid' metyrapone test. Length and weight development were followed on a standard Swedish growth chart; psychomotor development was assessed by a child physiotherapist using a modified Griffiths test.

Results

Case 1

Respiratory recordings

During quiet sleep the infant's breathing pattern became highly irregular and frequent tracheal suctioning was necessary because of hypersecretion. End tidal Pco2 was about 6 kPa when awake and increased to 8 kPa during active sleep and to more than 10 kPa during quiet sleep. This pattern remained virtually unchanged during the first months (Fig. 1). Transcutaneous Pco2 correlated well with the end alveolar Pco2 (r=0.96). When left without ventilatory support TcPo2 rapidly decreased to below 4 kPa. When hypoxia was relieved by oxygen administration a further increase in Pco2 was observed. Oral theophylline (6 mg/kg) produced no change in blood gases. Naloxone (0.2 mg/kg) caused a reduction in end tidal Paco2 from 8.3 to 5.6 kPa and increased the TcPo2 from 3.1 to 7.0 kPa, but the effect disappeared within minutes. After doxapram injection (1.25 mg/kg), Pco2 decreased from 8.3 to 5.9 kPa and Po2 increased from 3.1 to 4.3 kPa: this response lasted for about three hours.

Oral medroxyprogesterone acetate produced a significant reduction in the end tidal Paco2 (Figs. 1 and 2(b)) and an increase in TcPo2 (Fig. 2(a)). The effect became evident within two days and seemed to last up to a week after stopping the drug. At the higher dosage range (4 mg/kg/day) there was a clear increase in Po2 both when the child was asleep and awake, though this became less evident when the dose was reduced (Fig. 3). Carbon dioxide pressure correlated inversely with the dose of medroxyprogesterone. Peak plasma concentrations were
reached after five days’ treatment and no medroxyprogesterone could be detected in plasma four days after stopping the drug. The increase in ventilation seemed both to precede the steady state plasma concentration and to persist beyond the actual treatment period. An altered response to CO₂ was observed during treatment: the response curve shifted to the left but no change in the slope was detected (Fig. 4(b)).

By clinical criteria, medroxyprogesterone treatment seemed to obviate the need for respiratory support during sleep and the sleep disturbances, psychomotor unrest and hypersecretion, were not observed during treatment.

Endocrinological studies
Baseline gonadotrophin concentrations were normal for age before and after medroxyprogesterone. Gonadoliberin challenge test showed a slight inhibition of follicle stimulating hormone and luteinising hormone release during treatment. The metyrapone-induced release of adrenocorticotropic hormone was, however, inhibited during treatment. Her weight and length were —1 SD both before and during treatment. Retardation in length may have occurred, since the mother is unusually tall (190 cm). A reddish vaginal discharge and a slight tendency to oedema were observed at the higher dosage (2.5 to 4 mg/kg/day), though these symptoms resolved when the dose of medroxyprogesterone was reduced below 2 mg/kg/day. The greatest increase in the child’s temperature during treatment was 0.2°C.

Psychomotor development
The patient’s psychomotor development was initially delayed but was found to be nearly normal after her general condition had improved. She was crawling at 1 year and walking at 16 months. There was a noticeable delay in speech which improved dramatically once a speech plate was installed in the tracheal cannula; at 18 months she was using two syllable words. A modified Griffiths score was within the normal range for this age.

Case 2
Respiratory investigation
Before treatment pronounced slow breathing was observed during quiet sleep with spontaneous breathing frequency between 8 and 15 breaths per minute. Frequent central respiratory pauses of 15 to 20 seconds duration were followed by a decrease in the heart rate and TcPo₂.

The blood gas pattern was characterised by hypoxia and raised end tidal Pco₂ (Fig. 5). The sleep pattern was disturbed by motor unrest, profuse perspiration, and tracheal hypersecretion. Oral theophylline, with plasma concentrations between 25 and 35 µmol/l (4.5–6.4 µg/ml), increased the spontaneous respiratory rate to about 25 and the median P0₂ during quiet sleep increased from 4 kPa to 7.7 kPa. The general condition of the infant improved but central apnoeic episodes were still present and end tidal Pco₂ during quiet sleep was persistently above 6 kPa.

Medroxyprogesterone was given twice daily in a total dose of 2 mg/kg/24 hours, together with a small dose of theophylline 5 mg/kg. During sleep the theophylline concentration was below 17 µmol/l (3.1 µg/ml). End tidal Pco₂ returned to normal during treatment (Fig.5(b)). The CO₂ response curve shifted to the left and the slope became slightly steeper (Fig. 4(a)). Arousal occurred at Pco₂ values

![Graph](image-url)  
Fig. 4  Carbon dioxide response during quiet sleep with and without treatment with medroxyprogesterone in patients 1 and 2.

Patient 1 was artificially ventilated before the test.
greater than 7 kPa. Minute ventilation during sleep was virtually unchanging at 100 ml/min/kg.

The transcutaneous \( P_{O_2} \) was still slightly below normal values (Fig. 5(a)) but no further hypoxic episodes were observed.

**Endocrinological studies**

Baseline gonadotrophin concentrations were normal for age during treatment. The concentrations of follicle stimulating hormone and luteinising hormone were normal to high after gonadorelin challenge, with no indications of pituitary suppression. Baseline cortisol decreased from a normal concentration of 190 \( \mu \)mol/l (6-9 \( \mu \)g/100 ml) to 88 \( \mu \)mol/l (3-2 \( \mu \)g/100 ml) during treatment. No inhibition in the release of adrenocorticotrophic hormone was observed.

The patient’s length was \(-2\) SD while weight was normal for age. No clinical side effects of medroxyprogesterone were observed at doses up to 4 mg/kg/24 hours. No increase in basal temperature was observed.

**Psychomotor development**

At the first examination at 2 years of age the girl would not walk without support. At three years of age after 2 months of treatment her motor development was judged as normal by a physiotherapist.

**Discussion**

Both children had hypoxia and hypercapnia during sleep, particularly during quiet sleep, with near normal \( P_{O_2} \) and \( P_{CO_2} \) values while awake. This is characteristic of congenital central hypoventilation syndrome as described by several investigators.\(^1\) \(^5\) \(^14\)

Both children had some \( CO_2 \) sensitivity which seemed sufficient to sustain their breathing during long periods. Patient 1 had no associated abnormalities while patient 2 exhibited signs of a generalised autonomic dysfunction, which did not, however, resemble those of classic dysautonomia syndrome.

The diagnosis of hypoventilation was established by polygraphic recording of respiration, \( TcP_{O_2} \), end tidal \( P_{CO_2} \), and by determining the ventilatory \( CO_2 \) response using a pneumotachograph. Transcutaneous electrodes were valuable in quantitatively assessing the degree of hypoventilation and the efficiency of treatment since this procedure caused minimal disturbance of the infant. The reliability of transcutaneous gas measurements have been proved in several studies.\(^15\) \(^16\)

As previously reported the \( TcP_{CO_2} \) was higher than blood or end tidal \( P_{CO_2} \) measurements. The possibility that \( TcP_{O_2} \) readings during hypoxia were low because of a decreased peripheral blood flow cannot, however, be fully excluded.\(^17\)

Furthermore, the relation between end tidal \( P_{CO_2} \) and \( TcP_{CO_2} \) was slightly changed during high dose medroxyprogesterone treatment, possibly because peripheral blood flow was affected. This could either be caused by the progesterone per se or by the increase in \( P_{O_2} \) and subsequent increase of skin blood flow.

Most children with central hypoventilation syndrome are treated with ventilators at night.\(^1\) \(^5\)

Theophylline is not usually effective in these cases. Occasionally, constant positive airways pressure\(^18\) has been reported to improve respiration in adults, but had no effect in this case study. Doxapram stimulated respiration, but was not used continuously because of the severe side effects associated with its use.\(^7\)

Diaphragm pacing by electrical stimulation of the phrenic nerve has been tried in a few infants with central hypoventilation syndrome, but the long term prognosis has not been very promising and phrenic nerve pacing is not recommended before the age of 10 years.\(^6\) \(^19\)

Medroxyprogesterone has been used occasionally, with some beneficial effects, in cases of central hypoventilation syndrome.\(^7\) Neither the ventilatory effects nor the possible endocrinological side effects are well documented. In our patients an appreciable improvement was obtained both in respect of end tidal \( P_{CO_2} \) and \( TcP_{O_2} \) values and the general condition of the patients during the treatment.
When drug treatment was interrupted the condition of the patient deteriorated. Medroxyprogesterone treatment improved ventilation in respect of PCO₂ and PO₂ but these values did not become normal. The general condition of both patients, however, was improved to such an extent that they were no longer dependent on assisted ventilation during the night. The tracheostoma in the first patient could be permanently closed, but this has not yet been possible in the second.

Based on ventilatory studies in the cat, Tok and Loeschke suggested that the effect of progesterone on breathing is mediated via muscarinic receptors in structures in a superficial layer on the ventral surface of the medulla oblongata, possibly sensing (H⁺). Skatrud et al. showed a stimulatory effect of medroxyprogesterone in normal boys, but although treatment did not alter the slope of the ventilatory CO₂ response curve, it had a threshold-lowering additive effect which is in agreement with our findings. This indicates that medroxyprogesterone probably has no effect where there is complete absence of a ventilatory CO₂ response (Fleming, personal communication) but can effectively strengthen reduced CO₂ responsiveness in our two patients.

The suppression of pituitary gonadotrophins and adrenocorticotrophic hormone noted during treatment are not considered to be major side effects at this age. The glucocorticoid effects, however, indicate that in situations of physical stress, additional cortisol should be given to account for the moderate suppression of the pituitary-adrenal axis.

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