Altered arousal response in infants exposed to cigarette smoke

A B Chang, S J Wilson, I B Masters, M Yuill, J Williams, G Williams, M Hubbard

Aims: A failure of the arousal mechanism is a key feature in the apnoea theory for sudden infant death syndrome (SIDS). In infants studied at an age when the incidence of SIDS is highest, we evaluated whether in utero smoke exposed infants have altered arousal response to standardised auditory stimuli, and/or sleep pattern, as recorded on overnight complex sleep polysomnography.

Methods: A standardised sequence of audiology stimuli was applied binaurally to 20 in utero smoke and non-smoke exposed infants aged 8–12 weeks during a rapid eye movement (REM) and NREM epoch, in a controlled (temperature, position, pacifier use, noise) sleep environment. Infants were monitored for 10–12 hours using complex sleep polysomnography.

Results: Five infants exposed to in utero tobacco smoke did not have behavioural arousal response, whereas all non-smoke exposed infants aroused during NREM (p = 0.016). There was, however, no difference in REM sleep, and the groups did not differ in routine overnight complex sleep polysomnography parameters.

Conclusion: At the age when the incidence of SIDS is at its peak, infants of smoking mothers are less rousable than those of non-smoking mothers in NREM sleep; this may partly explain why such infants are more at risk of SIDS.

METHODS

Two groups of infants were recruited by approaching all available mothers consecutively on the postnatal wards on the days of recruitment and by asking mothers attending for their infants’ routine six week check. Infants were eligible for the study if their mothers smoked either ante- and postnatally (smoke exposed, SE) or not at all (non-smoke exposed, NSE). The babies had to be full term with no perinatal complications and no significant cardiorespiratory disease, history of apnoea, or neurological problems. The study was approved by the local hospital’s human ethics committee.

All infants were aged 8–12 weeks at the time of study (March to October 1999), free from intercurrent and recent (less than four weeks) infection, and not on any medication. Questionnaires were completed by a paediatrician (MH) and consisted of questions about the preconceptional and postnatal history, maternal and paternal age, marital and social status, socioeconomic score (Daniel score) based on employment, maternal and paternal age, feeding practice, sleep position, and cigarette consumption of the father and mother, both ante- and postnatally. In addition the mothers all completed the Edinburgh postnatal depression screen. Each baby underwent a full paediatric examination and an overnight 10–12 hour complex sleep polysomnography study (sleep study). Studies were performed in a controlled sleep laboratory environment (including temperature control, 22–24°C) with continuous recording of electroencephalogram (EEG, C3–A2 left central lead and O2–A1 right occipital lead), electro-oculogram (EOG, left LOC–A2 and right ROC–A2), nasal airflow (Vacumetrics, USA), abdomen and chest wall activity, respiratory movements (Vacumetrics, USA), audio recordings and video recordings.

Abbreviations: ABR, auditory brain stem evoked response; ALTE, apparent life threatening event; EEG, electroencephalogram; EOG, electro-oculogram; NREM, non-rapid eye movement; NSE, non-smoke exposed; REM, rapid eye movement; SE, smoke exposed; SIDS, sudden infant death syndrome; SPL, sound phase level
movement using respiratory inductance plethysmography (Respitrace, USA), and pulse oxygen saturation (CSI Oximeter 504US, USA) on a computerised system (LaMont-NCI Systems, Sydney, Australia).

The infants slept alone in a cot, without a pacifier, in the supine position for arousal stimulus application. The first auditory stimulus was applied 10 minutes into the first epoch of NREM sleep and a minute after any obvious sigh or movement. The auditory stimulus of increasing intensity was applied by two speakers positioned exactly 20 cm from each ear. A warble tone oscillating in a sinusoidal waveform 10 times per second between 1200 Hz and 2800 Hz was applied for six seconds. The sound level was increased from 63 dB sound phase level (SPL) in seven steps to 86.2 dB SPL. The level of sound was calibrated with a Bruel and Kjaer sonometer at the same distance. The noise was activated away from the bed, ensuring no local movement/noise stimulus around the cot. The signal was recorded on the polysomnograph and continued through each step, with at least one minute between steps until full behavioural arousal occurred or until the maximum stimulus was applied. This protocol was then repeated 10 minutes into the next epoch of REM sleep. The subject was then left uninterrupted for the remainder of the study while data were collected. Auditory brain stem evoked responses (ABR) were obtained the day after the study commenced and binaurally to thresholds. Infants were excluded from the study if a change in EEG, heart rate, and respiratory rate were present, there was no significant difference between the groups for maternal age, alcohol consumption, family history of SIDS, or depression score (only one smoking mother scored positively on the questionnaire).

Not all infants had detectable change in the various outcome measures (change in respiratory rate, heart rate, EEG, behavioural response) after the maximum stimulus was applied (table 2). In NREM sleep five infants from the SE group did not have a behavioural arousal. This group was significantly more afebrile as defined by the Daniel score. There was no difference between the groups for maternal age, alcohol consumption, family history of SIDS, or depression score (only one smoking mother scored positively on the questionnaire).

In REM sleep five infants from the SE group did not have a behavioural arousal. This group was significantly less likely to have behavioural arousal after application of maximal stimuli when compared to the NSE infants (p = 0.016). However, no difference between groups was found in REM sleep. There was also no difference between the groups for change in EEG, heart rate, or respiratory rate. In infants where a change in EEG, heart rate, and respiratory rate were present, there was no significant difference between the groups in the SPL required to produce the threshold changes.

In routine sleep study parameters, no difference was found between the groups in central apnoea index, obstructive apnoea index, time in REM sleep, total sleep time, and respiratory desaturation index in both REM and NREM sleep phases (table 3).

**DISCUSSION**

In this study of infants at an age when the incidence of SIDS is highest, it has been shown that infants exposed to utero...
tobacco smoke have reduced arousal response when compared to infants not exposed to in utero smoke during NREM but not REM sleep. However, the groups did not differ in routine overnight complex sleep polysomnography parameters.

SIDS is the single most common cause of post neonatal death in previously well infants. In utero smoke exposure is also associated with altered respiratory physiology in infancy, such as reduced airway calibre and increased airway responsiveness, and decreased arousal response to hypoxic stimulus but not altered ventilatory response to hypercapnia or hypoxia. The arousal response is a protective mechanism by which infants increase their activity to prevent life threatening asphyxia, for example, movements to sustain access to fresh air. Studying newborns and infants aged 4–17 weeks, Franco et al showed that during REM sleep, infants of smokers had reduced arousability (median threshold in smoke exposed was 70 dB (range 50–100) versus 60 (50–90) in non-smoke exposed infants). They did not, however, study the NREM phase and used a higher maximum SPL for changes in outcomes.

We used a different sequence of stimulus to other groups. Although any stimulus produces a similar sequence of movement arousal regardless of type, care must be taken to avoid additional stimuli during testing. We chose an auditory stimulus calibrated and delivered at a distance of 20 cm from the level of the infant's ears and operated from a computer distant to the infant to minimise such errors. It is more difficult to standardise air jets into the nostrils and auditory stimuli delivered very close to the ear, as both require proximity of the tester. While airjet delivery can be standardised, it is difficult to assure standardised flow and/or pressure at the receptor level as the infant's nasal anatomy and patency will influence physical characteristics of airflow delivered. Furthermore, auditory stimuli delivered to one or other ear at random may heighten inequalities in hearing between each ear. Three of our 20 babies had unilateral conductive hearing loss, as there is a strong relation between smoking and incidence and duration of secretory otitis media.

Some studies have shown higher rates of obstructive apnoeas in smoke exposed infants which we did not find.
However, arousal is said not to be important in the termination of obstructive and central events in children with obstructive sleep apnoea. The criticism with many studies involving polysomnography in infants is the difficulty in interpreting results form infants of a wide age range, as sleep characteristics and arousability change markedly over the first six months of life. Some studies have used premature babies who are at an increased risk of SIDS, but who also pose difficulties when deciding whether to use postnatal or post-gestational age, as neither corresponds to the full term equivalent. We have used a narrow age range of infants during a period when the risk of SIDS is highest. Our infants were all full term, without any perinatal illness, were studied in a temperature, noise, and light controlled environment during specified sleep stages, and their mothers were not depressed. None were sleep deprived, slept prone during the study, received sedation, or used a pacifier, all of which have been shown to alter arousability. Other studies have not controlled for all these factors.

SIDS is strongly associated with maternal smoking, with a dose response effect. This risk remains significant after controlling for other confounders such as age of mother, parity, prematurity, low socioeconomic status, sleep position, and protective effect of breast-feeding. In addition, studies confirm that postnatal household exposure has an independent additive effect. Most hypotheses relating SIDS to maternal smoking discuss an effect of maternal smoking on fetal oxygenation and fetal brain development. 3H]-nicotine binding sites in mid-gestational fetuses are heavily concentrated in the tegmental nuclei, which are involved in cardiopulmonary integration, arousal, attention, REM sleep control, and somatic motor function. This study adds to the body of evidence that in utero smoke exposure is detrimental to the infant’s neurorespiratory system, which governs arousals. We conclude that at the age when the incidence of SIDS is at its peak, infants of smoking mothers are less rousable than those of non-smoking mothers in NREM sleep, and this may partly explain why such infants are more at risk of SIDS.

ACKNOWLEDGEMENTS

We greatly appreciate Dr Michael O’Callaghan’s comments on the study design and Mary O’Neill’s practical assistance in the project. Support: South Australia SIDS Foundation.

REFERENCES

1 Hunt CE. Sudden infant death syndrome and other causes of infant mortality: diagnosis, mechanisms, and risk for recurrence in siblings. Am J Respir Crit Care Med 2001; 164:346–57
Altered arousal response in infants exposed to cigarette smoke

A B Chang, S J Wilson, I B Masters, M Yuill, J Williams, G Williams and M Hubbard

Arch Dis Child 2003 88: 30-33
doi: 10.1136/adc.88.1.30

Updated information and services can be found at:
http://adc.bmj.com/content/88/1/30

These include:

References
This article cites 34 articles, 9 of which you can access for free at:
http://adc.bmj.com/content/88/1/30#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Child health (3922)
Health education (555)
Health promotion (611)
Smoking (150)
Smoking and tobacco (150)
Infant health (811)
SIDS (96)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/