Sleep phase and gastro-oesophageal reflux in infants at possible risk of SIDS

J Y PATON, U M MACFADYEN, AND H SIMPSON

Department of Child Health, University of Leicester, Leicester

**SUMMARY** The association between gastro-oesophageal reflux and sleep state in 24 infants with confirmed or suspected gastro-oesophageal reflux was studied by monitoring both the pH in the lower oesophagus and polygraphic tracings made during sleep at night. Gastro-oesophageal reflux during the night was confirmed in 20 infants. Three hundred and sixteen precipitous drops of more than one unit of pH were recorded during the studies, 186 during periods of wakefulness. Of 130 drops in pH during sleep, 62 (48%) began during active sleep and 62 during indeterminate sleep. Of the latter, 56 (90%) were associated with brief gross body movements. Only five of the drops in pH (4%) began during quiet sleep. Gastro-oesophageal reflux stopped during active sleep on 56 occasions (43%), in indeterminate sleep in 62 (47%), and in quiet sleep in 12 (9%). Episodes of gastro-oesophageal reflux starting or ending in quiet sleep were uncommon. The occurrence of gastro-oesophageal reflux during active sleep may partly explain why reflux during sleep is a risk factor for pulmonary disease.

Gastro-oesophageal reflux occurs less often during sleep than wakefulness in children.\(^1\) Despite this, gastro-oesophageal reflux during sleep is an important risk factor for aspiration of gastric contents.\(^2\)\(^3\) The occurrence of gastro-oesophageal reflux also seems to vary with sleep phase, though published data on sleep state at the time of reflux is conflicting.\(^4\)\(^6\) Experimental work in animals and infants has shown that sleep state influences pulmonary protective reflexes.\(^7\)\(^11\) Information on sleep phase and the occurrence of gastro-oesophageal reflux may therefore be important in explaining why gastro-oesophageal reflux during sleep is potentially hazardous. We have investigated the association between gastro-oesophageal reflux and sleep state in 24 infants with known or suspected reflux, by monitoring both the pH in the lower oesophagus and polygraphic tracings during sleep.

**Patients and methods**

Four groups of infants defined by their clinical presentation were selected for study (table 1). Of the 24 infants, nine had presented after apparently life threatening events and a further 12 after milder but none the less alarming events—for example, minor choking episodes or short apnoeic episodes that responded immediately to stimulation. A further

<table>
<thead>
<tr>
<th>Table 1 Clinical details of infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Apparently life threatening events</td>
</tr>
<tr>
<td>Siblings</td>
</tr>
<tr>
<td>Choking or apnoea*</td>
</tr>
<tr>
<td>Suspected tracheobronchial aspiration</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*One infant studied on three occasions; †length of gestation not known in two.
Sleep phase and gastro-oesophageal reflux in infants at possible risk of SIDS

ther two were siblings of infants who had died of SIDS, and the last infant was thought to have recurrent pulmonary aspiration. All symptomatic infants had been investigated fully to exclude infective, metabolic, neurological, and anatomical causes of apparently life threatening events, choking, and apnoea.

The infants were selected for study either because they had or were thought to have gastro-oesophageal reflux. Of the 24, 17 had previously had radionuclide scans. Severe gastro-oesophageal reflux (to the level of the upper oesophagus) had been found in 14, moderate gastro-oesophageal reflux (into the lower oesophagus) in one, and neither in the remaining two. The other seven infants who were studied without preliminary scanning presented with histories and findings similar to those who had had scans, and for that reason were considered likely to have appreciable gastro-oesophageal reflux.

The ethical committee of the Leicester Royal Infirmary approved the experimental protocol. Verbal informed consent was obtained from the parent or guardian of each infant. The significance of differences between groups was assessed by the \( \chi^2 \) test, a probability of \(<0.05\) being accepted as significant.

**MONITORING OF THE \( \text{pH} \) IN THE LOWER OESOPHAGUS**

The \( \text{pH} \) in the lower oesophagus was measured with a Radiometer GK2801C micro glass \( \text{pH} \) electrode and a Radiometer PHM75 \( \text{pH} \) meter. The output from the \( \text{pH} \) meter was interfaced to a Servoscribe flat bed recorder running at a paper speed of 10 mm/minute.

Before each study the \( \text{pH} \) probe was sterilised by immersion in a freshly prepared 1:80 sodium hypochlorite solution for at least one hour. It was then calibrated and rinsed in distilled water before it was positioned in the infant's oesophagus. A two-point in vitro calibration using standard commercial precision buffers (Radiometer \( \text{pH} \) 7.383 and \( \text{pH} \) 1.1) maintained at 37°C was always carried out immediately before use and repeated at the end of the study to check instrument drift. The mean (SD) measured \( \text{pH} \) of the \( \text{pH} \) 7.38 standard buffer at the end of the studies (that usually took about four hours) was 7.42 (0.10) giving a mean \( \text{pH} \) drift of 0.04 \( \text{pH} \) units over the course of the studies—that is, 0.01 \( \text{pH} \) unit/hour. The largest recorded drift from the calibration value of \( \text{pH} \) 7.38 was 0.14 \( \text{pH} \) units. The \( \text{pH} \) probe was therefore both stable and accurate.

The \( \text{pH} \) probe was placed in the lower oesophagus using the nomogram developed by Strobel et al.\(^{12}\) for infants and children that relates height to the distance between the mouth and the lower oesophageal sphincter. Before each study the infant’s length (cm) was measured using a Harpenden stadiometer, the distance to the lower oesophageal sphincter was calculated using the nomogram, and the probe was passed orally to 87% of this length (to ensure placement above the lower oesophageal sphincter) and taped in place. The infants were then given their usual feeds after which they drifted off to sleep.

In studies of the \( \text{pH} \) in the lower oesophagus gastro-oesophageal reflux is usually defined as a fall in \( \text{pH} \) to below 4. In infants, however, the gastric \( \text{pH} \) can take up to two hours to fall below 4.\(^{13}\) The \( \text{pH} \) of refluxing gastric contents may therefore be above 4, especially just after a feed. In the present studies the infants were given normal feeds of either breast milk or formula (both of which have a \( \text{pH} \) of about 6.5) and no attempt was made to acidify the feeds to facilitate detection of reflux. To take account of the possibility of the occurrence of 'non-acid' reflux, gastro-oesophageal reflux was defined as a fall in \( \text{pH} \) of more than one unit, irrespective of whether or not the \( \text{pH} \) fell below 4.

The end of a drop in \( \text{pH} \) was defined as a rise in \( \text{pH} \) of at least one unit (from the lowest level recorded in the drop) to above 4. For drops in \( \text{pH} \) of about 4 the insistence on a rise of one unit ensured that tiny variations were not counted as separate episodes of reflux. All drops in \( \text{pH} \) regardless of their duration were recorded. Those lasting less than 15 seconds were classified as 'spikes' and those longer than or equal to 15 seconds were classified as 'episodes'. The imposing of an arbitrary view on the minimum duration of a drop in \( \text{pH} \) was therefore avoided. The recorder paper speed (15 seconds was equivalent to 2.5 mm) made this distinction easy.

**POLYGRAPHIC SLEEP MONITORING**

The studies were carried out between 2200 and 0500 in a quiet dimly lit laboratory with a mean ambient temperature of 23°C.

At the beginning of a study at night the \( \text{pH} \) probe was passed orally to the appropriate position and the electrodes for monitoring cardiorespiratory variables were positioned. The infant was then given the usual evening feed and settled to sleep, lightly clothed and unrestrained, and usually in the left lateral position. As soon as the infant was asleep electrodes for electrooculography, electromyography, and electroencephalography were positioned. The outputs from the transducers were recorded on an Mingograph 8 channel jet recorder (Elema Schonander) run at 1 cm/second. Despite the presence of monitoring equipment the infants usually slept throughout the period of study.

Each sleep record was divided into successive 30
second epochs that were then analysed visually and scored as either awake, indeterminate or transitional sleep, quiet sleep, or active sleep, by one experienced observer. Epochs where more than half showed evidence of body movement were classified as indeterminate sleep. The scoring criteria were based on the definitions suggested by Rechtschaffen and Kales\(^\text{14}\) and Anders \textit{et al.}\(^\text{15}\). In the present studies transitional epochs were subdivided depending on whether or not the epoch showed evidence of gross body movements.

\textbf{Results}

The 24 infants were studied on 28 occasions, three infants being studied more than once. The mean duration of the 28 studies was 268 minutes (median 268, range 195–369) and the mean duration of sleep 200 minutes (median 210, range 89–216). The mean duration of wakefulness, which usually occurred at the beginning of each study after the infant’s feed, was 68 minutes (median 66, range 14–181). There were 316 drops in pH of more than one unit, 186 during wakefulness and 130 during sleep. Gastrooesophageal reflux was observed during sleep in 20 infants. In the 28 studies, 43% of sleep was active, 38% quiet, and 19% indeterminate. Table 2 shows the number of drops in pH/100 minutes of a given sleep state incorporating data from all 28 studies. Most drops in pH occurred during indeterminate sleep (double the number during active sleep) and fewest during quiet sleep. The proportion of spikes to episodes was similar in each sleep state, episodes being usually at least twice as common as spikes.

In table 3 the data are further subdivided into those drops in pH during which the lowest pH remained above 4 and those during which it went below 4. For each of the indices shown the number of drops in pH was greater during wakefulness than during sleep. When the duration of episodes was considered, a similar trend between wakefulness and sleep was found, but proportionally more drops in pH of more than one minute were noted during sleep (table 4).

Although drops in pH of more than one unit occurred more often during wakefulness than during sleep for each of the indices presented, there were also differences between wakefulness and sleep in the lowest pH recorded in one drop and in the duration of the drops. Table 5 gives the actual number of spikes and episodes that occurred during wakefulness and sleep (uncorrected for time differences). Significant changes occurred in the spike: episode ratio, the proportion of spikes and episodes during which the pH fell below 4, and in the proportion of episodes that exceeded one minute in duration between wakefulness and sleep, indicating

<table>
<thead>
<tr>
<th>Table 2</th>
<th>No of drops in pH/100 minutes in each sleep state (28 studies in 24 infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>Sleep state</td>
</tr>
<tr>
<td></td>
<td>Active</td>
</tr>
<tr>
<td>Duration of phase (minutes)</td>
<td>1197</td>
</tr>
<tr>
<td>Percentage of time in sleep state</td>
<td>43</td>
</tr>
<tr>
<td>No of drops in pH/100 minute phase:</td>
<td></td>
</tr>
<tr>
<td>Spikes (lasting &lt;15s)</td>
<td>4-69</td>
</tr>
<tr>
<td>Episodes (lasting ≥15s)</td>
<td>5-01</td>
</tr>
<tr>
<td>Total No of drops in pH</td>
<td>9-70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Occurrence of drops in pH during wakefulness and sleep (28 studies in 24 infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH drops in</td>
<td>Lowest pH</td>
</tr>
<tr>
<td>Spikes (lasting &lt;15s)</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Episodes (lasting ≥15s)</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Total</td>
<td>&gt;4</td>
</tr>
</tbody>
</table>

pH <4=fall of pH ≥1 unit of pH to a lowest pH below 4; pH >4=fall of pH ≥1 unit of pH but lowest pH not below 4.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Duration of episodes during wakefulness and sleep (28 studies in 24 infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>No of episodes/100 minutes</td>
</tr>
<tr>
<td>&lt;1 minute</td>
<td>2-85</td>
</tr>
<tr>
<td>≥1 minute</td>
<td>2-14</td>
</tr>
</tbody>
</table>

...
Sleep phase and gastro-oesophageal reflux in infants at possible risk of SIDS

Table 5 Differences in severity and duration of drops in pH in wakefulness and sleep

<table>
<thead>
<tr>
<th>Drops in pH</th>
<th>Lowest pH</th>
<th>No of pH drops</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Awake</td>
<td>Asleep</td>
<td></td>
</tr>
<tr>
<td>Spikes</td>
<td>&gt;4</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>Episodes</td>
<td>&gt;4</td>
<td>51</td>
<td>14</td>
</tr>
<tr>
<td>Spikes</td>
<td>&lt;4</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>Episodes</td>
<td>&lt;4</td>
<td>45</td>
<td>78</td>
</tr>
<tr>
<td>Spikes</td>
<td>&gt;4, &lt;4</td>
<td>90</td>
<td>38</td>
</tr>
<tr>
<td>Episodes</td>
<td>&gt;4, &lt;4</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>Spikes</td>
<td>&gt;4</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>Episodes</td>
<td>&lt;4</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>Spikes</td>
<td>&gt;4</td>
<td>51</td>
<td>14</td>
</tr>
<tr>
<td>Episodes</td>
<td>&lt;4</td>
<td>45</td>
<td>78</td>
</tr>
<tr>
<td>Spikes and episodes</td>
<td>&gt;4</td>
<td>107</td>
<td>25</td>
</tr>
<tr>
<td>Episodes</td>
<td>&lt;4</td>
<td>79</td>
<td>105</td>
</tr>
<tr>
<td>Episodes &lt;1 minute</td>
<td>&gt;4, &lt;4</td>
<td>55</td>
<td>16</td>
</tr>
<tr>
<td>Episodes &gt;1 minute</td>
<td>&gt;4, &lt;4</td>
<td>41</td>
<td>76</td>
</tr>
</tbody>
</table>

pH <4 = fall of pH >1 unit of pH to a lowest pH below 4; pH >4 = fall of pH >1 unit of pH but lowest pH not below 4. Spikes lasted <15s, and episodes lasted >=15s.

a comparative increase in the severity of reflux during sleep.

Data about the sleep phase at the beginning and end of each drop in pH were also analysed. At the start of each drop in pH the infant was usually in the active or the indeterminate sleep state (48% in each case). It was rare for a drop in pH to start during quiet sleep (4%). Similarly, most episodes ended when the infants were in the active (43%) or the indeterminate sleep state (47%); only 9% ended during the quiet sleep state and 1% in wakefulness. Occasionally episodes started in one sleep phase (active sleep), lasted through the next phase (quiet sleep) and ended in a third (active sleep). When the indeterminate state was examined separately, 90% of the drops in pH that started and 82% of the drops in pH that ended in this phase were in epochs with gross body movements. The cardiorespiratory effects of gastro-oesophageal reflux will be reported elsewhere.

Discussion

Previous reports on the association between sleep state and the occurrence of gastro-oesophageal reflux have been conflicting. Jeffery et al reported gastro-oesophageal reflux studied by monitoring of the pH in the lower oesophagus together with polygraphic tracings made during sleep in 20 infants who had had apparently life threatening events. Of 190 episodes of gastro-oesophageal reflux, 140 (74%) occurred during brief periods awake, 31 (16%) during active sleep, and 19 (10%) during indeterminate sleep. None occurred during quiet sleep. In contrast, Walsh et al studied 14 infants with similar problems and identified 63 episodes of gastro-oesophageal reflux. Of these precipitous drops in pH, 39 (62%) occurred during wakefulness, 18 (29%) during quiet sleep, and six (10%) during active sleep. Ariagno et al described a group of 45 infants who had had apparently life threatening events but in whom accurate sleep phasing had not been done; a less precise analysis of sleep state based on activity had been carried out. Of 356 precipitous drops in pH, 261 (73%) occurred during periods awake, 82 (23%) during periods of intermittent activity (presumably equating to active sleep), and only 13 (4%) during periods of minimal activity (probable quiet sleep). Therefore, though there is agreement that gastro-oesophageal reflux is seen most often during periods of wakefulness or brief arousals during sleep, there is no consensus on the sleep phase during which it occurs.

The results of this study confirm that gastro-oesophageal reflux occurs most commonly when infants are awake. The proportion of drops in pH occurring when they are awake compared with when they are asleep in the present study (4:2:1) is similar to that found by Jeffery et al (5:3:1). The occurrence of gastro-oesophageal reflux during sleep in our study was similar to the results of Jeffery et al. Gastro-oesophageal reflux was uncommon during quiet sleep and occurred most often during the indeterminate and active sleep phases. Jeffery et al found that drops in pH during sleep occurred most often during active sleep, whereas in our study they
occurred twice as often during indeterminate sleep. This discrepancy may merely reflect differences between the studies in the definition of epochs containing movement. If gastro-oesophageal reflux in epochs with movement was designated as occurring during periods of wakefulness, then the number of episodes during indeterminate sleep would be significantly lower. The information in the study of Jeffery et al6 is not sufficiently detailed to permit a precise comparison. The reason for the differences between the present findings and those of Walsh et al5 concerning gastro-oesophageal reflux during quiet sleep is not clear.

We found a highly significant difference in the duration and acidity of drops in pH between wakefulness and sleep. The change was from drops of shorter duration (spikes) and lesser acidity in wakefulness to longer drops of greater acidity during sleep. This observation (increasing acidity of reflux during sleep) may be spurious. Most of the period of wakefulness occurred at the start of monitoring in the interval between the last feed and the onset of sleep; the increasing acidity of gastro-oesophageal reflux during sleep may therefore reflect only the fall in gastric pH that occurs in infants as digestion progresses after a milk feed.13 Sutphen and Dillard,10 using intragastric monitoring of pH, have recently confirmed that the intragastric pH in the two hour period after a formula feed was greater than 4 for 44% of the time.

The prolongation of reflux during sleep may reflect more genuine physiological changes. In adults, Dent et al17 reported that reflux occurring during sleep tended to be prolonged because the main mechanism of clearance of acid from the oesophagus was a sequence of oesophageal peristaltic waves that occurred only rarely during stable sleep. The present results (which also showed a prolongation of gastro-oesophageal reflux during sleep) suggest that similar factors may operate in infants and children.

In the present study it was striking that not only did gastro-oesophageal reflux during sleep commonly start during active or indeterminate sleep, but it also often ended during the same type of sleep phase. To our knowledge this has not previously been reported. This observation was true not only for spikes and short episodes ending within the same epoch, but was also true for more prolonged episodes of gastro-oesophageal reflux lasting for more than one epoch and, on occasions, for more than one sleep cycle. The high proportion of episodes ending in the indeterminate sleep phase suggests that movement may have a role in bringing about the clearance of gastric contents from the oesophagus by reflex.

The confirmation that gastro-oesophageal reflux during sleep occurs often during active sleep is important. Protective pulmonary reflexes are usually depressed during the active sleep phase. For example, during active sleep in dogs, cough is absent and arousal delayed when fluid is injected into the trachea,7 and there is a failure to augment ventilation and delayed arousal during hypercapnoea.8 In calves there is failure to augment ventilation and delayed arousal during rapidly progressing hypoxia.9 In active sleep in infants the oxygen stores of the lungs are reduced,10 there is more rapid onset of hypoxaemia during apnoea, and failure to augment intercostal activity during obstructed inspiration.11 Active sleep is therefore a time of depressed protective reflexes and increased vulnerability. That gastro-oesophageal reflux during sleep is most common during active sleep is therefore somewhat disconcerting, and may partly explain why reflux during sleep is a risk factor for pulmonary disease.

The occurrence of gastro-oesophageal reflux during indeterminate and active sleep phases is also important in the pathogenesis of reflux. Werlin et al18 studied the mechanisms of gastro-oesophageal reflux in infants and young children and concluded that episodes of reflux are associated with intervals of normal basal pressure at the lower oesophageal sphincter accompanied either by transient inappropriate relaxations of the sphincter, or by transient increases in intra-abdominal pressure, or both. In indeterminate sleep the increased incidence of drops in pH that begin in epochs with movements may be due to contraction of the diaphragm that splints and stabilises the chest during gross body movements. The increase in abdominal pressure that results may temporarily overwhelm the pressure barrier at the lower oesophageal sphincter. The mechanisms whereby gastro-oesophageal reflux is initiated in active sleep are not clear. Perhaps modulation of neural activity during active sleep also influences the pressure at the lower oesophageal sphincter, making brief inappropriate relaxations more likely during this time.

In conclusion, gastro-oesophageal reflux in infants during the night occurred most commonly during periods of wakefulness either before they went to sleep or—less commonly—during brief awakenings during sleep. There was a significant change from shorter less acid drops in pH during wakefulness to longer more acid reflux during sleep. While the infants were asleep gastro-oesophageal reflux was most common during periods of indeterminate sleep, particularly associated with brief gross body movements, and in active sleep. Drops in pH usually started and ended during these sleep phases.
Sleep phase and gastro-oesophageal reflux in infants at possible risk of SIDS 269

It was uncommon for an episode of gastro-oesophageal reflux to start or end in quiet sleep. As the infants studied all presented with symptoms that were possibly attributable to gastro-oesophageal reflux, the conclusions reached are not necessarily applicable to normal healthy symptom free infants with presumed physiological reflux during sleep.

This work was supported by a generous grant (36 HS) from the Foundation for the Study of Infant Deaths. We thank the parents of the infants studied for their cooperation and support throughout, Dr Peter Swift who referred cases for study, and the staff of the radioisotope unit at Leicester Royal Infirmary for their cooperation.

References

Correspondence to Professor H Simpson, Department of Child Health, University of Leicester, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX.

Accepted 1 September 1988

Archives of Disease in Childhood

You are invited to meet the editors on Tuesday 11 April 1989 at 9-15 pm at the Annual Meeting of the British Paediatric Association. The speakers will be Malcolm Chiswick on how papers are assessed and Bernard Valman on how the final decision is made.