Effect of suxamethonium on the auditory evoked response in humans


Summary
We have studied the arousal effect of suxamethonium on the auditory evoked response (AER) of the electroencephalogram (EEG) in 40 ASA I and II patients during isoflurane anaesthesia. After induction of anaesthesia, the patient's lungs were ventilated for 20 min with 0.6 MAC end-expiratory isoflurane (0.59–0.77 % depending on the age of the patient), and 50 % nitrous oxide in oxygen. The patients were then allocated randomly to one of two groups: 21 received suxamethonium 1 mg kg⁻¹, while 19 were given saline. The AER before and after administration of suxamethonium or saline was compared to determine the changes in Pa and Nb amplitudes and latencies. Pa amplitude after suxamethonium increased by 53 % (95 % confidence interval (CI) 15, 104 %) compared with a reduction in Pa amplitude in the saline group of 11 % (95 % CI, 110 %) and decreased in the saline group by 11 % (95 % CI, 15–41, 12 %) (P = 0.004) suggesting an arousal effect. Similarly, Nb amplitude increased in the suxamethonium group by 47 % (95 % CI, 3, 110 %) and decreased in the saline group by 11 % (95 % CI, −33, 19 %) (P = 0.03). We conclude that suxamethonium caused arousal according to the AER and postulate that this may have been caused by increased muscle afferent activity after stimulation of muscle spindles, although further studies are required to confirm this. (Br. J. Anaesth. 1996; 76: 34–37)

Key words

The auditory evoked response (AER) has been shown to reflect levels of anaesthesia [1]. The Pa and Nb waves are early cortical components of the AER which originate in the primary auditory cortex in response to an auditory stimulus. The early cortical responses show graded changes with increasing anaesthetic concentrations for a wide range of anaesthetic drugs [2−5]. In particular, the amplitude of Pa decreases and the latency of Nb increases with increasing depth of anaesthesia, while Pa amplitude increases and Nb latency decreases during emergence from anaesthesia. When a stimulus is applied to a patient during steady state anaesthesia, for example skin incision [6] or tracheal intubation [7], Pa and Nb amplitudes increase, suggesting arousal, although no significant change has been demonstrated in Nb latency. The AER therefore reflects both level of anaesthesia and the balance between anaesthesia and stimulation. During the course of other studies in which suxamethonium was used, we observed that suxamethonium caused an arousal effect on the AER. We therefore designed a study to investigate the effects of suxamethonium on the AER.

Patients and methods
This study was approved by the Harrow Research Ethics Committee. We studied 40 ASA I and II unpremedicated patients, aged 18–65 yr. All patients gave written informed consent. Patients were excluded if they were pregnant or if ventilation of their lungs using a laryngeal mask airway (LMA) was contraindicated (hiatus hernia, oesophageal reflux).

Anaesthesia was induced with propofol 1–2 mg kg⁻¹ and an LMA was inserted. The patients’ lungs were ventilated with a Manley MP3 ventilator to normocapnia, measured by a Datex Capnomac Ultima. Anaesthesia was maintained with isoflurane and 50 % nitrous oxide in oxygen. The end-expiratory isoflurane concentration was measured using a calibrated Datex Capnomac Ultima and was kept at 0.6 MAC, age-adjusted [8] (0.59–0.77 % depending on the age of the patient), for 20 min to allow alveolar and brain concentrations of isoflurane to reach equilibrium [9]. Patients were then allocated randomly to receive either suxamethonium 1 mg kg⁻¹ or saline control.

The AER was recorded from mastoid to forehead silver-silver chloride electrodes in response to a rarefaction click stimulus at 6 s⁻¹. This auditory stimulus was delivered to each ear simultaneously through close fitting ear pieces at 75 dB above the average hearing threshold. The EEG signal was analogue filtered on input with bandwidths of 25–
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500 Hz to produce the AER recording which was displayed and stored continuously throughout the study on a portable computer. The AER recording continued for 2 min and 40 s after suxamethonium or saline to allow collection of 1024 sweeps of AER data. During this period, patients were left unstimulated to allow any change in AER to reflect the effect of suxamethonium or saline alone.

After each study the average of 1024 sweeps, representing 2 min and 40 s of AER data, before and after administration of suxamethonium or saline were filtered further using a high pass filter of 25 Hz and three-point smoothing. The waveforms were then printed out and analysed. Pa and Nb amplitudes and latencies were determined, and values before and after suxamethonium or saline were compared. The difference between values before (baseline) and after drug administration were calculated to show the effect of suxamethonium and saline on these AER variables.

For statistical analysis, all AER values were log_{10} transformed in order to produce homogeneity of variance and normality of residuals. A two sample t test was used to compare the mean change from baseline in the two groups. The difference between two logarithms is the logarithm of their ratios. When converted back to the original scale of measurement, a 95% confidence interval for the change from baseline on the logarithmic scale corresponds to a 95% confidence interval for the percentage change from baseline. The SD in the two groups for latencies were significantly different, and therefore a t test which does not assume equal variance was used for these values. The 95% confidence intervals for the geometric means of each group were also determined.

Results

We enrolled 44 patients into the study. Muscle artefact appears on the AER waveform in both unparalysed patients and during fasciculation in patients who have received suxamethonium. Data were included only when the underlying AER waveforms were unambiguously identifiable. On this basis data from four patients, two from each group, were excluded. Thus the results of 40 patients are presented (mean age 35.5 (range 18–63) yr; 22 females and 18 males). Twenty-one patients received suxamethonium and 19 were given saline as a control.

Typical changes in the AER waveform after suxamethonium were an increase in Pa and Nb amplitudes (fig. 1). Pa amplitude increased in 18 of 21 patients after suxamethonium and in only nine of 19 patients after saline (fig. 2). Similarly, Nb amplitude increased in 14 of 21 patients who received suxamethonium compared with eight of 19 in the saline group (fig. 3).

The percentage changes in Pa and Nb amplitudes and Pa and Nb latencies for both groups after suxamethonium or saline are shown in table 1. The mean percentage increase in Pa amplitude from baseline in the suxamethonium group was 53% (95% confidence interval (CI) 15, 104%) while in the saline group it decreased by 19% (CI −41, 12%) (P = 0.004) (fig. 4). Nb amplitude also increased significantly after suxamethonium compared with saline control. There were no significant differences for either Pa or Nb latencies between the two groups.

Discussion

The aim of this study was to assess the effects of suxamethonium on the AER during steady state isoflurane anaesthesia. We have shown that suxamethonium caused a significant increase in Pa and Nb amplitudes of the AER, similar to those after other stimuli, for example surgical stimulation and tracheal intubation [6, 7]. We conclude, therefore, that according to the AER suxamethonium caused arousal.
Previous studies have shown that suxamethonium produces an arousal pattern on the electroencephalogram (EEG) in anaesthetized humans. Mori, Iwabuchi and Fujita [10] demonstrated a change from 50–200- Hz fast wave activity of 14–18 Hz. These changes occurred 60–90 s after administration of suxamethonium at a time when muscle fasciculation occurred. Oshima, Shingu and Mori [11] showed that activation of the EEG by suxamethonium was similar to that after surgical incision. This supports our findings that surgical incision and suxamethonium have similar arousal effects on the Pa and Nb amplitudes of the AER.

There are several possible causes for the arousal effects of suxamethonium. As this drug does not cross the blood–brain barrier [12] and has no effect on the EEG when injected directly into carotid arteries [13], its arousal effect on the EEG is thought to arise from its peripheral action. Muscle fasciculation caused by suxamethonium has been shown to cause arousal of the raw EEG in both humans [10, 11] and animals [13, 14]. Lanier, Milde and Michenfelder [14] showed that when dogs anaesthetized with halothane developed fasciculations after suxamethonium, there was an increase in electromyographic (EMG) activity leading to an increase in muscle spindle afferent activity, an arousal effect on the EEG and an increase in cerebral blood flow. All of these changes coincided with the duration of action of suxamethonium.

EEG arousal caused by suxamethonium, however, also occurs in the absence of fasciculation. In a later study by Lanier, Iaizzo and Milde [15], dogs anaesthetized with halothane were given a “de-fasciculating” dose of pancuronium (0.01 mg kg\(^{-1}\)) before administration of suxamethonium. Although this dose was insufficient to cause muscle paralysis to allow intubation, it did prevent fasciculation after suxamethonium. In these dogs, therefore, there was no change in EMG activity after suxamethonium. However, muscle spindle afferent activity increased, followed by EEG arousal and an increase in cerebral blood flow.

The arousal effect of suxamethonium on the EEG therefore, is not dependent on muscle fasciculation per se, but is caused by increased neuronal transmission to areas of the cortex which receive input from muscle spindles [16]. These are stimulated either indirectly as a result of extrafusal muscle fibre fasciculation, or directly by stimulation of muscle spindles themselves by suxamethonium. Suxamethonium has been shown to cause sustained contraction of intrafusal muscle fibres (muscle spindles) [17] resulting in increased muscle afferent activity [18]. This effect can be reproduced by repeated injections of suxamethonium [19] and blocked by complete neuromuscular block [20]. Indeed, a “paralysing” dose of non-depolarizing neuromuscular blocker before administration of suxamethonium has been shown to block EEG arousal after suxamethonium in humans [10] and dogs [14] anaesthetized with halothane. Increasing the depth of anaesthesia also obviates the arousal effect of suxamethonium on the EEG [14], indicating the balance which exists between anaesthesia and stimulation. The mechanism by which suxamethonium causes arousal on the AER may be similar to that postulated for its arousal effects on the EEG. However, further studies on the effect of suxamethonium on the AER after pretreatment with a defasciculating or paralysing dose of a non-depolarizing neuromuscular blocker are needed to define the mechanism by which suxamethonium causes AER arousal.

Anecdotal evidence suggests that reports of awareness or arousal in anaesthetized patients are more common at, or around the time of tracheal intubation. This may be explained by the fact that two stimuli, administration of suxamethonium and tracheal intubation, both of which cause arousal according to the AER, occur almost simultaneously. The arousal effect of suxamethonium has been demonstrated in the clinical setting by Hobbs, Bush

Table 1 Mean (95% confidence intervals) percentage changes in Pa and Nb amplitudes and Pa and Nb latencies from their geometric means in patients after administration of suxamethonium (Sux) (n = 21) or saline (n = 19). P values relate to the comparison of the percentage change from baseline in patients receiving suxamethonium or saline

<table>
<thead>
<tr>
<th>AER variable</th>
<th>Treatment</th>
<th>Baseline geometric mean</th>
<th>% Change from baseline</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pa amplitude (μV)</td>
<td>Sux</td>
<td>0.19 (0.15, 0.23)</td>
<td>53 (15, 104)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>0.24 (0.17, 0.33)</td>
<td>−19 (−41, 12)</td>
<td></td>
</tr>
<tr>
<td>Nb amplitude (μV)</td>
<td>Sux</td>
<td>0.19 (0.14, 0.26)</td>
<td>47 (3, 110)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>0.23 (0.18, 0.30)</td>
<td>−11 (−33, 19)</td>
<td></td>
</tr>
<tr>
<td>Pa latency (ms)</td>
<td>Sux</td>
<td>42.4 (39.8, 45.2)</td>
<td>−12 (−16, −7)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>42.3 (38.9, 45.9)</td>
<td>−9 (−17, 1)</td>
<td></td>
</tr>
<tr>
<td>Nb latency (ms)</td>
<td>Sux</td>
<td>60.8 (57.1, 64.9)</td>
<td>−14 (−19, −8)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>62.6 (58.7, 66.7)</td>
<td>−10 (−19, 1)</td>
<td></td>
</tr>
</tbody>
</table>
and Downham [21], in a study on paediatric patients anaesthetized with a nitrous oxide–oxygen–neuromuscular blocker technique. This study showed that the incidence of dreaming was increased (P < 0.05) if intermittent suxamethonium was chosen as the neuromuscular blocker (24 %) compared with atracurium (9 %). Minton and colleagues [22] showed, in a within-patient study, that intracranial pressure (ICP) in patients with brain tumours increased after suxamethonium, whereas this increase was blocked if suxamethonium was given after a paralysing dose of vecuronium. The authors concluded that the increase in ICP in their patients after suxamethonium alone resulted from an increase in cerebral blood flow produced by EEG arousal caused by stimulation of muscle spindles.

We postulate, therefore, that the increases in Pa and Nb amplitudes which we have described after suxamethonium, may result from cerebral arousal caused by increased muscle spindle afferent activity. The role of extrafusal muscle fasciculation in this phenomenon cannot be determined because our study was not designed to distinguish between the direct and indirect effects of suxamethonium on muscle spindles.

References