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No EEG Evidence of Acute Tolerance to Desflurane in Swine

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Desflurane is a potent inhaled anesthetic associated with a dose-dependent depression of cortical electrical activity. Recently, it has been suggested that the burst suppression pattern seen in dogs given moderately high doses (2.0 MAC) of desflurane may spontaneously subside. This observation suggests the development of acute tolerance to at least some of the anesthetic effects of this drug. No other volatile anesthetic has been found to produce acute tolerance. We attempted to replicate these findings in domestic swine. Five juvenile swine (25–30 kg) were anesthetized with desflurane in oxygen and during normocapnia were exposed to two doses of desflurane sufficient to induce burst suppression (1.5 and 1.7 MAC) for 35 min at each dose, with a period of EEG recovery (0.6 MAC) before, between (in 3 of 5 animals), and after the high doses. Frontoparietal EEG was continuously recorded and the burst suppression ratio continuously calculated. Suppression was more complete at 1.7 MAC than at 1.5 MAC (98.24 ± 1.75 *vs.* 90.80 ± 3.05%, respectively, mean ± standard deviation). The degree of burst suppression activity did not change over time at either 1.5 ($P > 0.33$) or 1.7 MAC desflurane ($P > 0.41$). There was no EEG evidence of tolerance to desflurane anesthesia in swine. (Key words: Anesthetics, volatile: desflurane. Monitoring, brain: electroencephalogram. Tolerance, acute.)

DESFLURANE is a volatile anesthetic that depresses cerebrocortical electrical activity in a dose-dependent fashion in swine,[1] humans,[2] and dogs.[3] However, Lutz *et al.* suggested that this depression may subside spontaneously in dogs,[3] indicating the development of acute tolerance. Lutz *et al.* observed that the burst suppression initially found in the EEG during steady-state 2.0 MAC (14.0%) desflurane reverted over approximately 30 min to the pattern of continuous EEG activity associated with lower doses of desflurane. No other inhaled anesthetic has been found to produce acute tolerance. If this tolerance goes involves more than a change in EEG activity, it might have significant implications in the clinical management of desflurane anesthesia. Accordingly, we attempted to replicate the results of Lutz *et al.*[3]

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Materials and Methods

With the approval of the University of California Committee on Animal Research, in five juvenile, unpremedicated, domestic swine (25–30 kg), anesthesia was induced by inhalation of desflurane in oxygen *via* face mask. After induction, intravenous access was established *via* an ear vein. Laryngoscopy was performed and the trachea intubated. Succinylcholine was used to facilitate laryngoscopy in two of the pigs. Mechanical ventilation was instituted to maintain normocapnia (end-tidal carbon dioxide tension [$P_{ET_{CO_2}}$] ≈ 35 mmHg). Tracheal gas concentrations were continuously measured with a multichannel infrared analyzer (PB-254, Datex). Normothermia was maintained with an electric heating blanket and infrared lamps. Arterial blood pressure was monitored either from a femoral arterial catheter connected to a pressure transducer or by frequent (every 1–2 min) noninvasive oscillometric measurements with an appropriate-size cuff on a forelimb. Phenylephrine was infused as needed to maintain mean arterial blood pressure greater than 60 mmHg. Two channels of EEG signal were obtained using platinum subdermal needle electrodes (E-2, Grass, Quincy, MA) placed in a bilateral frontal–parietal configuration. The contact impedances were always less than 5 kohm and balanced within 2 kohm. The EEG was amplified and analyzed on-line by a Neurotrac monitor (Interspec, Ambler, PA). The amplified EEG was continuously written on a strip-chart recorder (ES-2000, Gould Instruments, Cleveland, OH) for the duration of each study. Further analysis was performed in real time with Mac-n-Trac software (Moberg Medical, Ambler, PA) and using a "virtual" instrument written with LabView software (National Instruments, Austin, TX). The burst suppression ratio[1] (BSR) was continuously measured during the experimental procedure. This EEG parameter reflects the relative duration of electrocortical suppression between bursts of activity and is sensitive to the level of end-tidal concentration of desflurane[1,2] or isoflurane.[1] The BSR is defined as the percentage time that the EEG signal reflects significant (<5 μv peak-to-peak), contiguous (>500 ms per suppression) electrocortical suppression.

After induction, the minimum concentration of desflurane (range 6.0–8.0%; 0.6–0.8 MAC) preventing spontaneous movement in each animal was administered for 15 min. This provided a stable baseline of continuous EEG activity. The inspired concentration was then increased in a prospectively randomized fashion to produce an end-tidal concentration of either 1.5 or 1.7 MAC. This

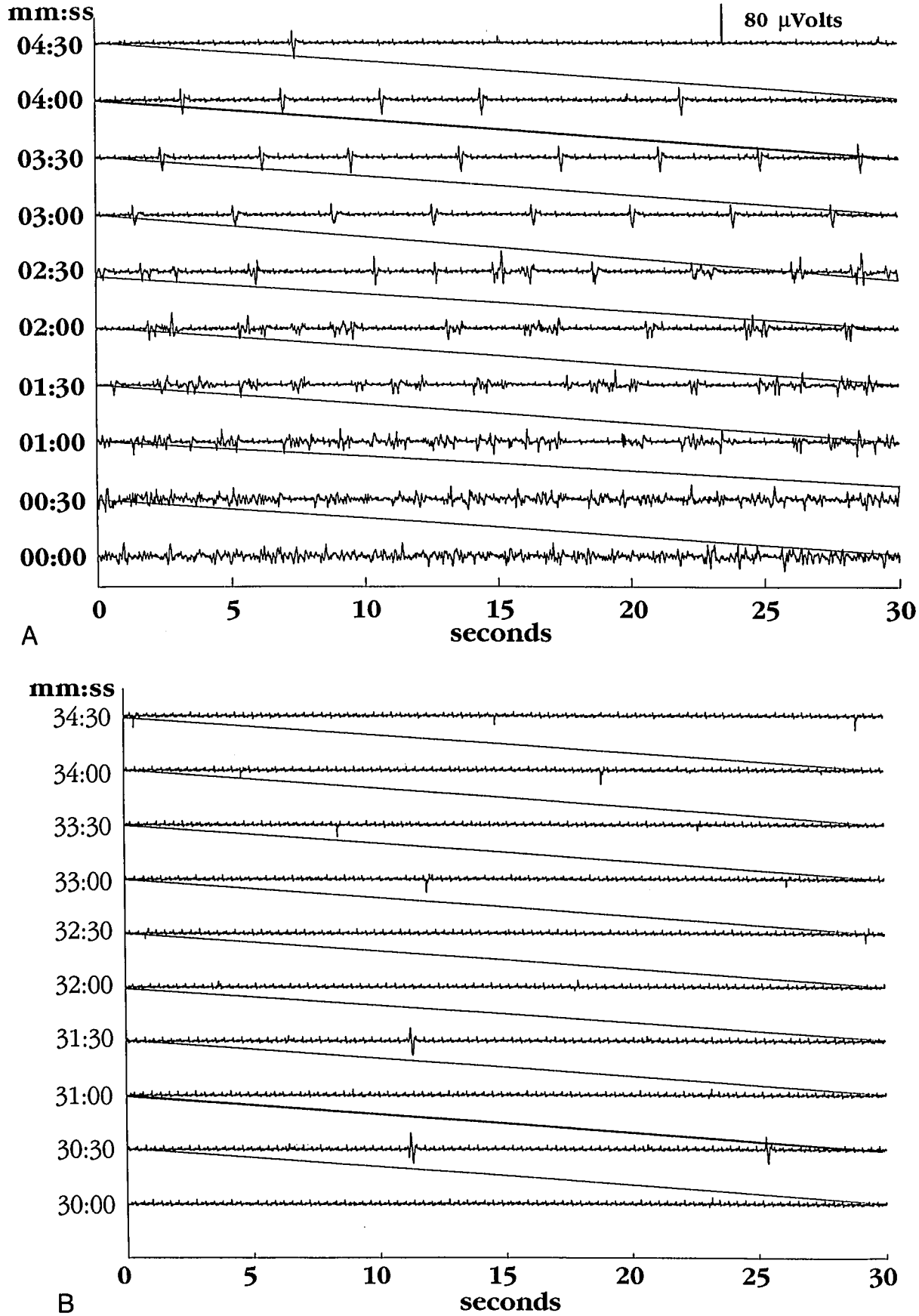

FIG. 1. See legend on following page.

FIG. 1. *A:* A representative sample of porcine EEG during the transition from an inspired concentration of 0.6 to 1.7 MAC. Each horizontal trace is 30 s and is temporally contiguous with the traces above and below it for a total duration of 5 min. The EEG initially displays continuous activity (*bottom of chart*) with a predominance of alpha and beta activity. Polyspiking becomes evident at 00:23, and the first episode of suppression occurs at 00:25. Sharp waves become more prevalent over the next 30 s, and the background activity diminishes. The EEG becomes progressively suppressed as the end-tidal concentration increases, with the BSR exceeding 50% by 02:00 and 90% by 04:00. *B:* A plot of the EEG activity from the same animal at the end of a steady-state exposure of 1.7 MAC. The signal plotted was acquired in the interval 30–35 min after establishing a steady state end-tidal desflurane concentration. The format and voltage gain is the same as in *A*.

end-tidal concentration was sustained at the desired level for at least 35 min after approximately 10 min were allowed for equilibration. In three animals, the end-tidal anesthetic concentration was then decreased and maintained at the earlier 0.6–0.8 MAC level for 15–20 min. The end-tidal anesthetic concentration was then altered in all animals to equilibrate for 10 min to the remaining high level of desflurane (either 1.5 or 1.7 MAC) and held constant at that concentration for at least 35 min. Finally, the end-tidal desflurane concentration was again reduced to the 0.6–0.8 MAC level for 15 min.

The burst suppression data were analyzed by computing the average suppression for the first and last 5 min of steady-state high-dose desflurane in each animal. The mean values for all animals at the start and end of each dose were compared with a paired two-tailed t test. $P < 0.05$ was considered significant.

Results

The administration of high-dose desflurane produced partial (1.5 MAC) or complete (1.7 MAC) suppression of background EEG activity in all pigs (fig. 1). As noted previously,[1] the bursts of EEG activity remaining during high-dose desflurane administration contained a large fraction of high-frequency activity, resembling sharp waves or polyspikes. Suppression was more complete at 1.7 than at 1.5 MAC (BSR 98.24 ± 1.75 *vs.* 90.80 ± 3.05%, respectively, mean ± standard deviation). The degree of burst suppression activity did not change over time at either 1.5 MAC ($P > 0.33$) or 1.7 MAC desflurane ($P > 0.41$) (fig. 2). There was no evidence of tolerance to desflurane anesthesia in the continuously observed raw waveform or processed quantitative EEG.

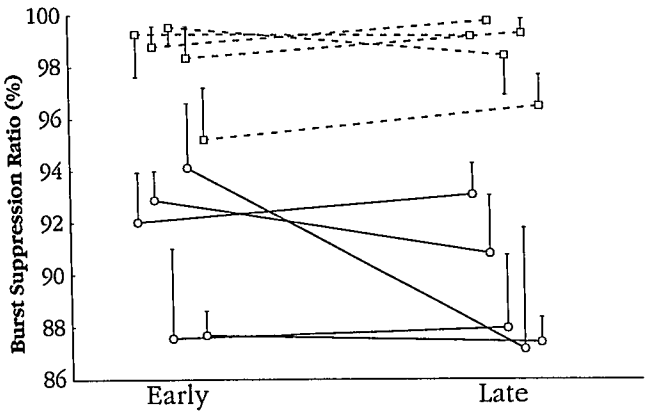

FIG. 2. The 5-min averaged burst suppression ratios (as defined in the text) and associated standard deviations are plotted for each animal at the beginning (Early) and end (Late) of each high-dose state. The average degree of suppression is greater at 1.7 MAC (squares) than at 1.5 MAC (circles). The only animal to have a statistically significant decrease in suppression had only a 7% increase in activity over the 35-min monitoring interval.

Discussion

Acute tolerance to some effects of nitrous oxide may occur in both animals and humans.[4–6] Recently, Avramov *et al.* demonstrated a sequential change in EEG patterns associated with the introduction of nitrous oxide to a baseline halothane anesthetic[7] that suggested the development of acute tolerance. However, acute tolerance to any potent** inhaled anesthetic remains to be verified. Earlier, Eger *et al.* demonstrated that after sufficient time (1–2 h) for brain concentration to equilibrate with alveolar concentration, the MAC is constant for halothane, fluroxene, and cyclopropane over at least 10 h in dogs.[8,9] Gregory††, testing MAC at each skin incision in patients undergoing sequential bilateral inguinal herniorrhaphy in which the incisions were separated by approximately 30 min, found no difference in MAC over that time span. In human volunteers exposed to desflurane for 6–8 h (in several concentration steps), the EEG, both qualitatively and quantitatively, appears stable when measured at equipotent concentration steps several hours apart.[2] These data probably rule out the existence of tolerance to potent inhaled anesthetics occurring with a time course of most clinical interest, namely a few hours.

Acute changes in brain sensitivity to volatile anesthetics may occur, but these would be difficult to appreciate if the time course for the change in sensitivity is faster than the pharmacokinetically dictated uptake and distribution of the agent. It is in the "middle range" of time constants (15 min to 1 h) that the current controversy exists. Lutz

** "Potent" is defined in this context as producing surgical anesthesia at a low enough concentration to permit concomitant administration of high concentrations of oxygen (fractional inspired oxygen concentration [$F_{I_{O_2}}$] > 70%).

†† Gregory GA: Unpublished observations, cited in reference 9.

et al.[3] anesthetized their animals for several hours with halothane before switching to desflurane. In the current study, we used only desflurane and began monitoring as soon as anesthesia had been induced and a relatively stable end-tidal concentration had been achieved (range 15–25 min after the start of induction).

Lutz *et al.*[3] did not measure the changes in EEG in their dogs quantitatively, such that subtle changes over time at less than the 1.5 MAC dose may not have been revealed. The time course of the tolerance phenomena was not described, although highly suppressed EEG was apparently restored to continuous activity by 30 min at 2.0 MAC. In the current study, we could not use 2.0 MAC because, for swine, that concentration (20%) lies outside the linear range of our gas analyzers. The doses we chose to examine, however, straddled the dose that provided essentially complete suppression, and thus should have been maximally sensitive in detecting reduction in degree of suppression.

There remain several possible explanations for the different results obtained by Lutz *et al.*[3] and the current study. The study in dogs may have been confounded by a period of halothane anesthesia preceding desflurane and/or by alterations in cortical function resulting from intracranial surgery prior to exposure to desflurane. If, in a study not confounded by these variables, tolerance is verified in dogs, then the tolerance phenomenon must be factored into the current theories regarding mechanisms of general anesthesia, and evidence for tolerance should be sought in other species. Preliminary observations of raw EEG waveforms in 12 human volunteers during 20-min periods of steady state at several concentrations of desflurane did not indicate the occurrence of tolerance,‡‡ and repeated exposures to set concentrations after 6 h of desflurane anesthesia produced an EEG that was quantitatively indistinguishable from initial exposures.[2]

In summary, continuous EEG monitoring did not produce evidence of acute tolerance to desflurane anesthesia in swine given concentrations of desflurane that produced near isoelectricity. These concentrations were similar to those reported to be associated with acute tolerance in dogs.

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