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I653 and Isoflurane Produce Similar Dose-related Changes in the Electroencephalogram of Pigs

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I653 is a new volatile anesthetic structurally similar to enflurane and isoflurane. Since enflurane can induce convulsions, whereas isoflurane progressively depresses cortical electrical activity, the authors believed it important to assess the effect of I653 on the EEG (in both the "time" and "frequency" domain). The EEG was assessed visually and quantitatively, and a new EEG parameter was introduced. The burst-suppression ratio (percentage of time the EEG was isoelectric) quantified the extent of burst suppression phenomena. Eight swine were anesthetized with I653 or isoflurane in oxygen and in random sequence, exposed to approximately 0.8, 1.2, or 1.6 MAC with normocapnea and to 1.2 MAC with hypocapnea ($P_{ET}CO_2$ of 25 mmHg). Four animals were also anesthetized with 3.2% (1.2 MAC) enflurane in oxygen. Both I653 and isoflurane produced a dose-related depression of cortical electrical activity. At 0.8 and 1.2 MAC of either agent, occasional sharp waves occurred singly, were apparently not related to external (auditory) stimuli, and probably represented normal variation in the EEG. No electrographic or gross motor seizures occurred with either I653 or isoflurane. In contrast, all pigs given enflurane developed seizures during hypocapnea. At equipotent concentrations, I653 and isoflurane had the same effect on EEG parameters. Increasing doses of either I653 or isoflurane caused decreasing amplitude and frequency and increasing suppression. Hypocapnea during either agent slightly increased high-frequency activity, and slightly decreased burst suppression. (Key words: Anesthetics, volatile: enflurane; isoflurane; I653. Brain: electroencephalogram. Monitoring: electroencephalography. Potency: anesthetic; MAC.)

SPIKING OR FRANK convulsions may appear in the electroencephalograms of humans and animals given various inhaled anesthetics. Such abnormalities can occur with enflurane (and also with cyclopropane, diethyl ether, and fluroxene[1]). The increased cerebral metabolic rate[2] and possible increase in intracranial pressure associated with this epileptiform activity is considered undesirable. In contrast, isoflurane progressively depresses cortical electrical activity, and does so at relatively low, clinically relevant concentrations.[3,4]

I653 (difluoromethyl 1-fluoro 2,2,2-trifluoroethyl ether) is a new volatile anesthetic that differs from isoflurane in the substitution of a fluorine for the chlorine atom on the α-carbon of the ethyl group. This anesthetic's low solubility (blood:gas partition coefficient = 0.42)[5] makes it a potentially useful agent where rapid awakening is needed. However, the value of this new agent would be diminished if I653 resembled enflurane more than isoflurane in its effect on the electroencephalogram (EEG). Accordingly, we report here a comparison of EEG activity during anesthesia with I653, isoflurane, or enflurane in swine.

Materials and Methods

Eight young, female, domestic swine (*sus scrofa*) were studied following approval of the experimental protocol by the University of California Committee on Animal Research. The average weight (mean ± SE) of the animals was 17.0 ± 2.4 kg. We chose animals of this size and age (about 8–10 weeks) because, by 1 month of age, the EEG of a young swine resembles that of a mature swine.[6] The domestic pig has extensive frontal sinuses which extend caudally beyond the posterior aspect of the orbits. Posteriorly, the skull becomes massive, the bone often becoming 2–3 cm thick at the occiput.[7] These anatomical features substantially distort electrical conduction through the skull, making detailed localization of electrical activity impossible. Accordingly, we used only two EEG channels to detect anomalous electrical activity.

The animals were surgically prepared with chronically indwelling pulmonary arterial and aortic catheters[8] and allowed to recover for at least 3 days. Fasted, unmedicated animals (water was allowed *ad libitum*) were restrained in a padded sling (Charles River Laboratories, Wilmington, MA). EEG signals were obtained from five subcutaneous 30-g platinum needle electrodes (model E-2, Grass® Instrument, Quincy, MA). A ground electrode was placed at the vertex, and signals recorded from a frontal channel whose electrodes were

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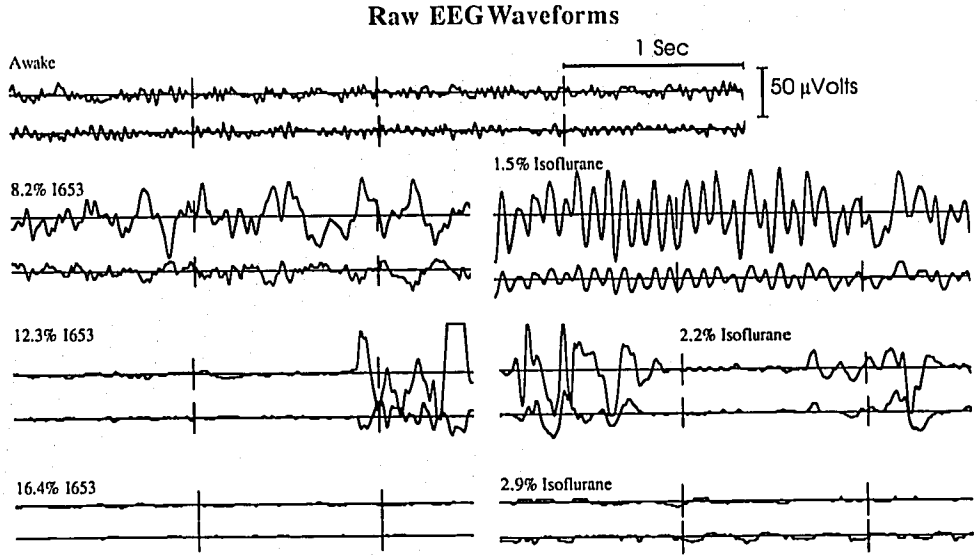

FIG. 1. Examples of raw EEG waveforms during the awake, resting state and at 0.8, 1.2, and 1.6 MAC of I653 and 0.7, 1.1, and 1.4 MAC of isoflurane. Note the (paroxysmal) alpha activity with 1.5% isoflurane; this pattern was frequently seen with either I653 or isoflurane. There is extensive burst suppression at the high concentration with either agent. All waveforms taken from a single animal.

placed 2 cm medial to, and 1 cm caudal to, the lateral canthus of the orbit bilaterally, and from an occipital channel whose electrodes were placed at the occipital ridge, each about 1.5 cm lateral to the median line. Placement of these electrodes was usually well tolerated in conscious, unmedicated animals, and within 10 min the swine usually appeared relaxed (eyes closed, stable blood pressure and heart rate, slowing of EEG), and baseline EEG recordings were made.

Anesthesia was induced with either I653 or isoflurane (in random sequence) in oxygen. All animals received both agents. Endotracheal intubation followed succinylcholine (2 mg/kg iv). Mechanical ventilation was adjusted to maintain normocapnea ($P_{ET}CO_2 \approx$ 35–40 mmHg). An external heating blanket was used to maintain body temperature (measured by the pulmonary artery catheter thermistor) within 0.5° C of its initial value. The initial study protocol specified measurements at 1.0, 1.5, and 2.0 MAC for each agent. We used a previously reported value of MAC[9] of isoflurane (1.45%) and the mean MAC of the first two animals in this study for I653 (7.9%). Each animal was therefore given 8.2, 12.3, and 16.4% I653 or 1.5, 2.2, and 2.9% isoflurane in random sequence. Subsequently we determined MAC for I653 to be 10%, and MAC for isoflurane to be 2.0%.‡‡ Therefore, the actual concentrations of agent corresponded to approximately 0.8, 1.2, and 1.6 MAC for I653 and 0.7, 1.1, and 1.4 MAC for isoflurane. I653 was measured with a Beckman® LB-2 infrared halothane analyzer. Since the output of the analyzer was not linearly related to the concentration of I653, a calibration curve was constructed using known concentrations of I653. Isoflurane concentration was measured with a Puritan Bennett® PB-222 (Wilmington, MA), calibrated with known concentrations of isoflurane. After the end-tidal concentration of agent was stable for 15 min, 4–5 min of EEG were digitized. The EEG response, if any, to 50 loud hand claps at approximately 1-s intervals was also recorded. At 12.3% I653 or 2.2% isoflurane, the effect of hypocapnea on central nervous system activity was assessed by increasing the ventilatory rate to decrease the $P_{ET}CO_2$ to 20–25 mmHg. The agents were tested in random order. The response to the second anesthetic agent was studied 3–7 days after the first agent. Three animals of this cohort, and one other, were later anesthetized with 3.2% enflurane (our estimate of 1.2 MAC in this group of animals) and their EEG response to the auditory stimuli during normocapnea and hypocapnea tested.

The EEG was processed by a Cerebrotrac™ (Shorashim R & D, Israel) which amplified and bandpass-filtered (3 dB approximately 1.5 and 32 Hz). Both channels of amplified EEG waveform were continuously recorded on a strip chart recorder and observed by an experienced observer (IJR). The Cerebrotrac digitized the data at 128 Hz per channel with 0.390 μV resolution and performed real time spectral analysis and display. The digitized EEG waveforms were transmitted to a Macintosh Plus™ computer (Apple Computer, Cupertino, CA) for additional analysis and display. Using custom-written software, the Macintosh™ performed both time series and spectral analysis. A new parameter, known as the burst-suppression ratio (BSR), was intro-

‡‡ Eger EI II, Weiskopf RB, Rampil IJ: Unpublished data, 1987.

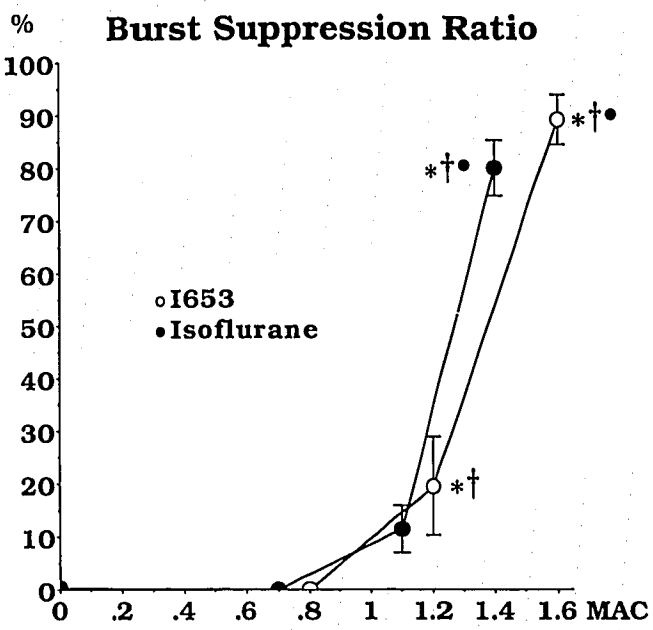

FIG. 2. Burst Suppression ratio (mean ± SE) increased monotonically with increases in anesthetic concentrations. Values for each of eight animals were calculated from 15 sequential noise-free epoches (60 s) and averaged together for each drug at each concentration. These data are from frontal leads. Statistical differences ($P < 0.05$) where present are noted as follows: compared with awake (*), 0.7/0.8 MAC of same agent (†), and 1.1/1.2 MAC of same agent (•). There were no inter-agent differences at any dose level.

duced to quantify the burst-suppression phenomena. The algorithm defined intervals of suppression as periods longer than 240 ms during which time the EEG voltage did not exceed 5.0 μV, then calculated the percentage of time in each 4-s epoch that met the criteria for suppression.

At each study condition outlined in the protocol, EEG data were averaged for the first 15 sequential, noise-free epoches (60 s total). Data for the awake state and different depths of anesthesia were then compared with Analysis of Variance using Repeated Measures and, when indicated, differences between groups were examined using the Tukey test for multiple comparisons. The EEG data obtained during hypocapnea at 1.2 MAC were compared with those during normocapnea (same anesthetic) by paired, two-tailed t test. Differences were considered significant if $P < 0.05$.

Results

Rare sharp waves were apparent in the EEG tracings obtained during 0.8 and 1.2 MAC of I653 and the 0.7 and 1.1 MAC of isoflurane. These isolated sharp waves were not related to external stimuli and probably represented normal variation in the EEG. No EEG or gross motor evidence of seizures were noted during administration of either agent.

I653 and isoflurane produced EEG waveforms and quantitative EEG values statistically indistinguishable from each other at equipotent concentrations (fig. 1). At the lowest concentration tested of either agent, all animals exhibited occasional paroxysmal rhythmic activity in the alpha or beta range. Burst-suppression began at anesthetic concentrations below 1 MAC with both agents, and isoelectricity was nearly complete at 1.6 MAC (fig. 2). There was no frontal-occipital difference in the BSR. The root mean square (RMS), or "average" EEG amplitude, peaked below 1 MAC and declined with increasing concentrations of both agents (fig. 3). As predicted by the anatomy of the porcine skull, the occipital RMS values were smaller than those from the frontal lead. The zero crossing frequency (ZXF), a simple measure of "average" frequency, declined with increasing concentrations of either agent from an awake baseline of 11.4 ± 0.8 (SEM) Hz to values of 3.3 ± .49 with isoflurane (1.4 MAC) and 2.4 ± 0.60 Hz with I653 (1.6 MAC) (fig. 4). The burst-suppression activity declined slightly and the ZXF increased slightly with hypocapnea. These changes did not reach statistical significance or clinical significance

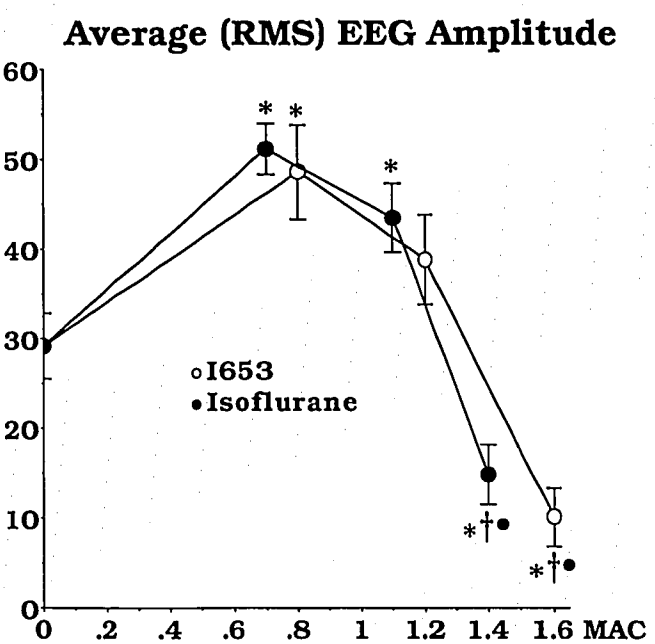

FIG. 3. Root mean square or average amplitude of raw EEG (mean ± SE) peaked at 0.8 MAC. This dose response curve is compatible with the classic curve described by Faulconer and Bickford.[1] Statistical differences ($P < 0.05$) where present are noted as follows: compared with awake (*), 0.7/0.8 MAC of same agent (†), and 1.1/1.2 MAC of same agent (•).

(a change large enough to detect during intraoperative monitoring). There was no increase in sharp wave activity during hypocapnea with either agent.

EEG responses evoked by auditory stimuli were most apparent at the highest concentrations of either agent, perhaps because, at this level of anesthesia, spontaneous activity was minimal. During either hypocapnea at approximately 1.2 MAC or normocapnea at any anesthetic concentration, auditory stimuli never induced either electrographic epileptiform activity or gross motor seizures. This is not because swine do not display seizure activity. Gross electrographic and motor seizures occurred during hypocapnea with, or without, rhythmic auditory stimuli in all four animals given 3.2% enflurane (fig. 5).

Discussion

Our determination of MAC for isoflurane differs from that (1.45%) previously reported.[9] We chose to use the value of 2.0% as established in our laboratory.

Rudo and Krantz[10] observed that increased fluorination of anesthetic ethers correlated with a propensity to cause convulsive activity. Clark and Rosner[11] also suggested that increasing acidity of the ether oxygen by increasing fluorination of adjacent carbons increases the potential for cerebral irritability and seizures.

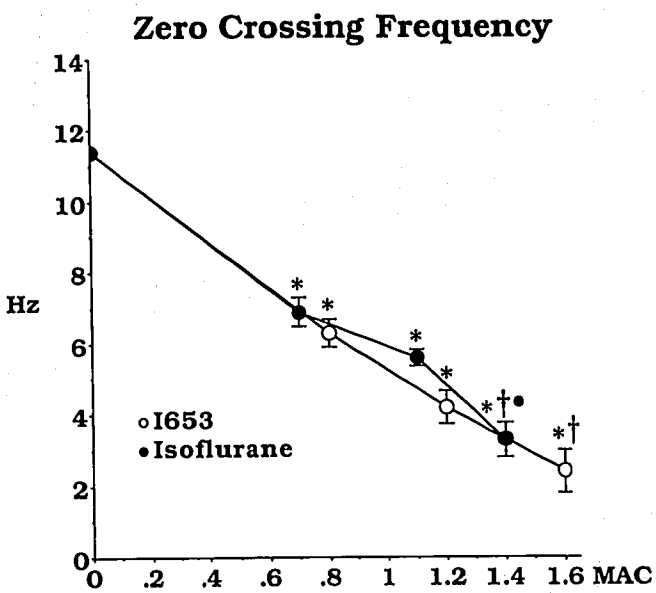

FIG. 4. Zero crossing frequency (mean ± SE) determines the "average" frequency in an epoch by measuring the average time interval between the point where the EEG voltage crosses the zero axis, then computing the reciprocal, which is frequency. Statistical differences ($P < 0.05$) where present are noted as follows: compared with awake (*), 0/7/0.8 MAC of same agent (†), and 1.1/1.2 MAC of same agent (●).

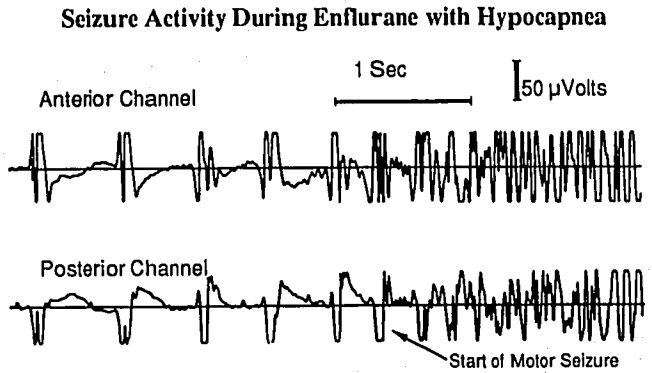

FIG. 5. The raw EEG waveforms illustrate auditory stimulus related "spike and wave" potentials that progress to a grand mal seizure with continued stimulation. This animal had been at a steady-state concentration of enflurane (3.2%) and an end-tidal P_{CO_2} of 25 mmHg for 15 min prior to auditory stimulation. The seizure spikes were clipped by the EEG amplifier because of their high voltage.

Stockard[1] disputed the applicability of this observation, pointing to several counter-examples. A close relative of the convulsant flurothyl (Indoklon) is perfluorodiethyl ether, which has an even more acidic ether oxygen but lacks convulsive properties.[1] I653 is another counter-example, because it is even more fluorinated than enflurane, yet does not have significant epileptogenic potential.

Our results indicate that the EEG effects of I653 closely parallel those of isoflurane and not those of enflurane. If the other cerebral effects of I653 match those of isoflurane, that would add to the desirable properties of I653. The suppression of EEG activity produced by isoflurane is associated with a substantial decrease in cerebral metabolic requirements.[12] The degree of inhibition of cerebrovascular autoregulation remains to be determined for I653.

The EEG "signature" of I653 is readily discerned, and a moderate level of anesthesia is easily defined by the appearance of 10–30% burst-suppression. This signature may be useful in a closed-loop system of automated anesthetic delivery. Although an identical opportunity exists with isoflurane, I653 has the advantage of a far lower solubility, and hence the system using I653 would have a more robust control over the level of anesthesia. In addition, because of the lower solubility of I653, there would be less concern that recovery would be prolonged if anesthesia were controlled at a moderate or deep level for a prolonged period of time.

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