NITROUS OXIDE AND ISOFLURANE ARE SYNERGISTIC WITH RESPECT TO AMPLITUDE AND LATENCY EFFECTS ON SENSORY EVOKED POTENTIALS

Tod Sloan, MD, MBA, PhD1, H. Sloan, MD2 and J. Rogers, MD2

ABSTRACT.

Objective. Combinations of anesthetic agents are frequently employed to produce the desired clinical effect. No systematic study has been conducted on the effect of the combination of nitrous oxide with a potent inhalational agent such as isoflurane on sensory evoked responses. Methods. Median nerve somatosensory evoked responses from the cervical and cortical regions (SSEP), auditory brainstem responses (ABR) and flash visual evoked responses (VEP) were tested in baboons. The latency and amplitude of the major response peaks were recorded at five proportionate mixtures of isoflurane (I) and nitrous oxide (N₂O) (0.8% I only, 0.6% I/20% N₂O, 0.4% I/40% N₂O, 0.2% I/60% N₂O, and 79% N₂O only). A similar set of experiments were also conducted with 0.8% isoflurane and 0.6% halothane. All data were normalized to 0.8% isoflurane only and Dunnett’s method of analysis used to determine which mixtures deviated from the reference values with 0.8% isoflurane. Results. Several combinations of isoflurane with nitrous oxide produced increases in latency (ABR: wave V, VEP, cortical SSEP) and decreases in amplitude (ABR: amplitude ratio V/I, VEP, cortical SSEP) from that expected if the effects were additive. No deviations were observed with combinations of isoflurane and halothane. Conclusions. These studies are consistent with drug synergy when isoflurane is mixed with nitrous oxide. This suggests that if these agents are considered for anesthesia when sensory evoked responses are to be monitored that the combination of these agents may produce more amplitude and latency changes than expected from a proportionate mixture of the individual agents.

KEY WORDS. halothane, isoflurane, nitrous oxide, evoked potential, baboon.

INTRODUCTION

In many respects, anesthesiology is the art of mixing different medications to take advantage of their combination to accomplish the needed pharmacologic and physiologic state for surgery [1]. The choice of anesthesia medications is extremely important when intraoperative monitoring of neurophysiological function is used [2–4]. The use of inhalational agents in this circumstance is of substantial importance due to the significant depressant effects they have on sensory and motor evoked potentials (MEP). Accordingly the choice and dosage of these agents is paramount to the success of monitoring as well as the clinical state of anesthesia.
The current potent inhalational agents (isoflurane, desflurane, sevoflurane) and nitrous oxide have been used for anesthesia, with a combination of a potent agent commonly mixed with nitrous oxide. Observations of the effects of the latter combination on clinical endpoints has shown variable results compared to the pure agents depending on the specific neurological endpoint and the species studied. Since systematic studies with sensory evoked responses have not been conducted, we evaluated the effects of isoflurane with nitrous oxide on visual, auditory and somatosensory evoked responses in a primate model to determine the implications for intraoperative neurophysiological monitoring.

**METHODS AND MATERIALS**

In a study approved by the institutional animal care and use committee, we examined the effect of combinations of isoflurane with nitrous oxide and combinations of isoflurane with halothane in five male and female baboons (17–24 kg) (Papio hamadryas anubis). After an overnight fast the animals were given ketamine (15 mg/kg) with atropine (0.02 mg/kg) intramuscularly. An intravenous line was then placed in a leg vein and balanced salt solution was infused continuously. Lidocaine (approximately 1 mg/kg of a 4% solution) was sprayed on the vocal cords during direct laryngoscopy, and the trachea was intubated approximately 2 min later using a 5.0 mm (inside diameter) cuffed endotracheal tube. The lungs were ventilated mechanically (Harvard Respirator 665, South Natick, MA) with 40% oxygen and a tidal volume of 12 ml/kg at a rate sufficient to produce an end-tidal carbon dioxide tension of 38–42 mm Hg.

The animal was placed in the right lateral decubitus position on a padded table with the head elevated on a soft pad and the left arm resting in a padded support. Blankets and hot water warming pads (Aquamatic K module, Ruleville, OH) were used to maintain an esophageal temperature of 36–37°C (Monotherm 6500, Precision Biomedical, Piano, TX). The electrocardiogram (Grass Instrument Co., Model 7D Polygraph, Quincy, MA), blood pressure (Omega 1400 NIBP, Tulsa, OK), hemoglobin oxygen saturation (Ohmeda Biox 3700, Boulder, CO), and end-tidal carbon dioxide (Instrumentation Laboratories IL 200, Lexington, MA) were monitored continuously during the study. End-tidal concentrations of anesthetic agents (halothane, isoflurane, nitrous oxide) were measured using an Ohmeda 5250 RGM gas analyzer (Soma Technology, Inc. Bloomfield, CT).

In the first set of experiments to explore the effect of combining nitrous oxide with isoflurane, isoflurane was mixed with nitrous oxide in varying proportions. In these studies the anesthesia started with 0.8% isoflurane (0.6 MAC [5, 6]) in an air/oxygen mixture from an anesthesia machine using a non-rebreathing circuit and an inspired oxygen concentration of 21%. Approximately 1 h later triplicate sensory evoked responses (as below) were recorded in random order. Then the flow from a second anesthesia machine delivering 80% nitrous oxide (MAC is approximately 200% [7]) was mixed with the output of the anesthesia machine delivering the isoflurane. The proportions of flow from these two machines allowed proportionate anesthetic mixtures of 0.8–0% isoflurane with 0–80% nitrous oxide. When pure nitrous oxide was delivered the concentration was adjusted to 79%. Five anesthetic mixtures were tested: 0.8% ISO (no N2O), 0.6% ISO/20% N2O, 0.4% ISO/40% N2O, 0.2% ISO/60% N2O, and 79% N2O (no ISO). All five animals were tested at these mixtures after equilibration at each mixture for 1 h. Each animal was also tested using the reverse paradigm (i.e., starting with 79% nitrous oxide) after 1 month’s rest. After each testing the animals were returned to their housing for recovery.

In a second set of studies similar to the first study, more than 1 month later, the mixture of isoflurane and halothane was studied. Initially, isoflurane at 0.8% was delivered by an anesthesia machine to produce general anesthesia and testing conducted 1 h later. The anesthetic concentration was then changed by adding flow from a second anesthesia machine delivering 0.6% halothane (0.6 MAC [5, 7]) to produce proportionate mixtures of the two anesthetics. Five anesthetic mixtures were tested: 0.8% ISO (no HAL), 0.6% ISO/0.15% HAL, 0.4% ISO/0.3% HAL, 0.2% ISO/0.45% HAL, and 0.6% HAL (no ISO). After equilibration at each new anesthetic mixture for 1 h, triplicate recordings of the sensory responses were made. Each of the five animals were tested in this paradigm were also tested more than 1 month later using a paradigm that started at 0.6% halothane (the reverse order of above).

Sensory evoked potentials were recorded in triplicate using a Biologic Navigator (Mundelein, IL). Median nerve somatosensory evoked potentials (SSEP) were produced using subdermal needle electrodes placed at the wrist using 300 μs square wave pulses at 5.7 Hertz (Hz) and a constant current twice that necessary to produce a motor response. Cortical responses were recorded from a subdermal needle placed at C3’ (0.5 cm behind C3 in the international 10–20 system) and cervical responses recorded on the skin posterior to the second cervical vertebrae. These responses were referenced to a subdermal needle over Fz and a ground placed at the shoulder. 500 averages were recorded using a recording window of 60 ms, filtration of 10–500 Hz (no notch filter), and