Characterizing the Electroencephalogram Signature of Fentanyl During Induction of General Anesthesia

NCT number: NCT03866278

Version Date: 12/5/2019

Characterizing the Electroencephalogram Signature of Fentanyl During Induction of General Anesthesia

PRINCIPAL INVESTIGATORS: Patrick L. Purdon, Ph.D.

CO-INVESTIGATORS: Emery Brown, M.D., Ph.D., Eric T. Pierce, M.D., Ph.D., Andrew C. Mullen, S.Bc.

VERSION DATE: 12/5/2019

BACKGROUND AND SIGNIFICANCE

Each day in the United States, more than 50,000 patients receive general anesthesia for surgical procedures (Barash, 2013). The state of general anesthesia has four characteristics: hypnosis, amnesia, analgesia, and lack of movement (Barash, 2013). While historically anesthesiologists rely on pharmacokinetics to track the loss of consciousness, new research in anesthesiology has identified the salient features of the electroencephalogram (EEG) that correlate to states of sedation and unconsciousness induced by different anesthetic drugs (Purdon et al., 2015). While the EEG features of many sedative-hypnotic anesthetics have been well-characterized, the opioid analgesic drugs have not been analyzed in detail in this way. A characterization of the EEG signatures of opioid analgesic drugs could be useful in monitoring and titrating the effects of these drugs.

Fentanyl is one of the most commonly used opioid analgesic drugs. Prior to induction of general anesthesia, fentanyl is frequently administered to blunt the nociceptive response to intubation. A typical scenario is to administer 2 to 4 mcg/kg of fentanyl first, followed by a sedative hypnotic drug such as propofol to induce general anesthesia. In this study, we propose to administer a total of either 4 or 6 mcg/kg, followed by a sedative hypnotic drug. The higher total dose of fentanyl, 6 mcg/kg, will be administered if the patient is still responsive to somatosensory stimulation after receiving 4 mcg/kg of fentanyl. We will be using a patient's ideal body weight (IBW) scalar (Devine 1974) to calculate the appropriate dosage of drug. At this dose, fentanyl will serve to blunt nociception during intubation, but will also contribute to intraoperative pain management. During this time, we will record the EEG using standard EEG-based anesthetic monitors that are routinely used in the operating room. We will assess the patient's level of responsiveness using an auditory task and ulnar nerve stimulation. These measurements will allow us to identify the EEG signatures of fentanyl for future use in EEG-based anesthetic monitoring.

SPECIFIC AIMS

The specific aims of this study are:

Specific Aim 1: Identify and analyze electroencephalogram (EEG) signals correlated with administration of fentanyl.

Specific Aim 2: Characterize the relationship between fentanyl-induced EEG signals and autonomic signals such as respiration, heart rate, and blood pressure.

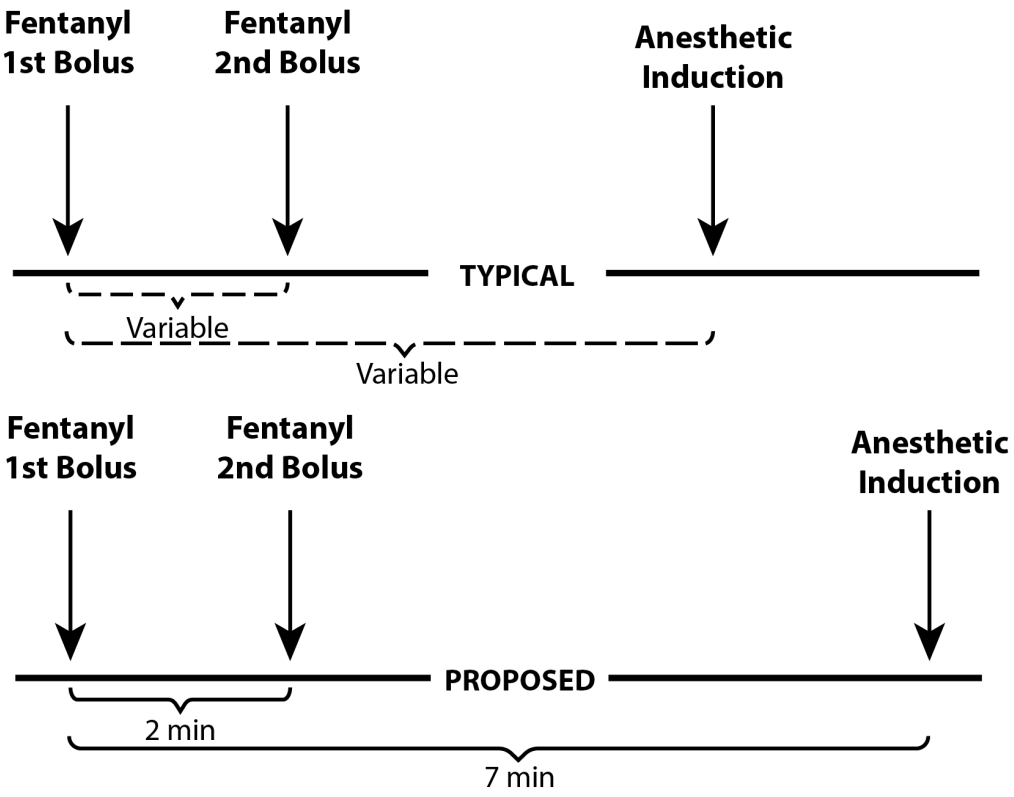
Specific Aim 3: Compare the fentanyl-induced EEG signals with those observed after induction of general anesthesia.

STUDY PROCEDURES

Overview

During this study we will measure EEG and responses to auditory and ulnar nerve stimuli during induction of general anesthesia in surgical patients. The anesthetic will be administered according to a typical sequence in which fentanyl is first administered, followed by a sedative hypnotic drug for induction of general anesthesia. The primary difference is that, in this study, we will record the EEG and response data for a short period of time after initial administration of fentanyl and prior to administration of a sedative hypnotic drug to induce general anesthesia (**Figure 1**). The choice of anesthetics and anesthetic doses will be at the discretion of the anesthesiologist caring for the patient.

The protocol has been reviewed and approved by the Clinical Operations Committee in the MGH Department of Anesthesia, Critical Care and Pain Management, who confirm that the anesthetic protocol is consistent with routine clinical care (see attached letter from the Clinical Operations Committee).



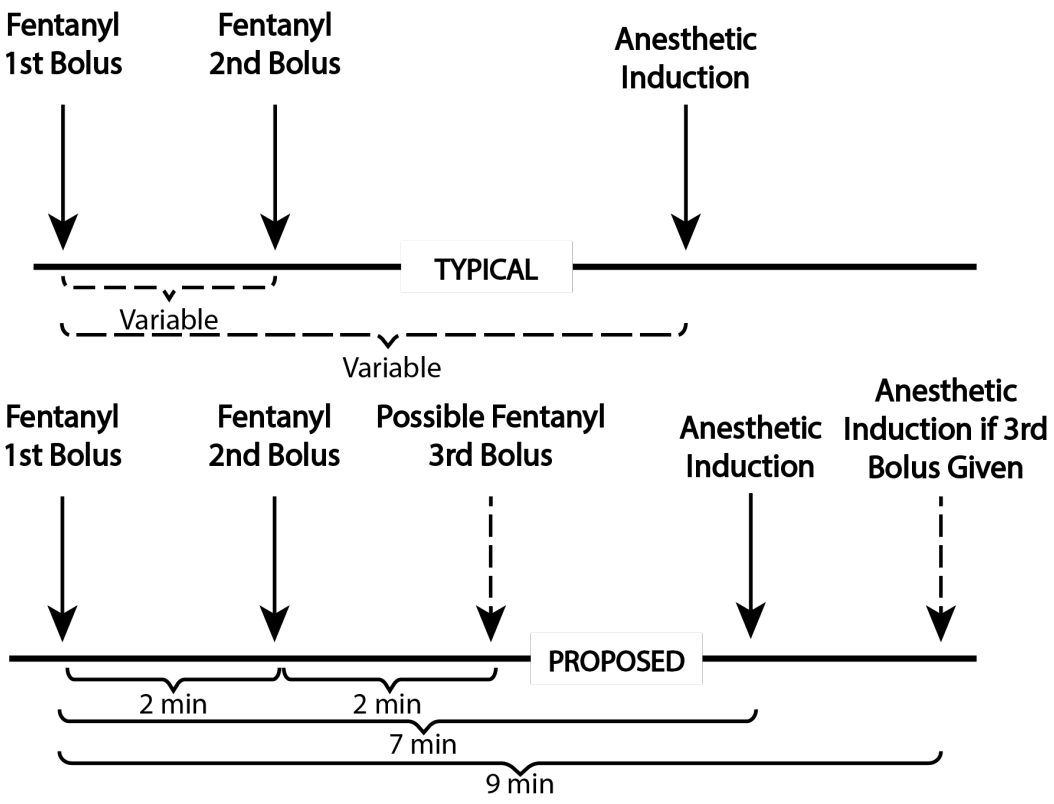


Figure 1 Proposed recording period and anesthetic sequence versus typical clinical practice during which fentanyl will be the sole anesthetic agent used. The third bolus is only administered in the event that the patient is responding to somatosensory stimulation two minutes after the second bolus of fentanyl.

.

EEG recordings

EEG data will be recorded from the EEG-based anesthesia monitors that are currently being used in all operating rooms at Massachusetts General Hospital (Sedline, Masimo Corporation, Irvine, CA).

Anesthetic Procedures

The anesthetic will be administered according to a typical sequence in which fentanyl is first administered, followed by a sedative hypnotic drug for induction of general anesthesia. The fentanyl will be administered in two boluses of 2 mcg/kg, spaced 2 minutes apart, for a total amount of 4 mcg/kg of fentanyl. Weight will be calculated using the ideal body weight (IBW) scalar.

If the subject is conscious after receiving 4 mcg/kg fentanyl, they will receive an additional 2 mcg/kg bolus of fentanyl after 2 minutes of observation. Consciousness will be determined by the subject's continued participation in the behavioral test, as described below. If the subject has stopped responding to the auditory stimuli, a study team member will attempt to rouse the subject, in the following order: (1) verbally, (2) physically by tapping the subject on the

shoulder, and finally, (3) physically with electrical stimulation through the ulnar nerve electrodes. If the subject responds to any of these stimuli, they will be given the third 2 mcg/kg bolus of fentanyl and monitored for 5 minutes. If the subject does not respond to these stimuli, the subject will not be given any additional fentanyl.

We will then record 5 minutes of EEG and behavioral responses, prior to administration of the sedative-hypnotic drug for general anesthesia. During this time, the patient will be ventilated, as needed, by bag mask ventilation. After this 5-minute period, general anesthesia will be induced according to the clinical anesthesiologist's discretion. Again, as stated above, the primary difference between this protocol and a typical anesthetic induction is the few minutes added between fentanyl administration and induction of general anesthesia. Ventilation will be closely monitored and assisted with anesthesia mask ventilation as needed during the experimental period. If the ventilation becomes difficult, the protocol will be abandoned and induction will be initiated as per the anesthesia team's judgment.

No pre-medication prior to induction will be given, but if needed, midazolam will be administered as clinically indicated. At all times, the patient's clinical anesthesiologist will have full control in managing the anesthetic, and may choose to intervene at any time before, during, or after the 5-minute recording period if deemed clinically necessary. As part of this, prior to the start of the study, the patient's clinical anesthesiologist may decide that the protocol is inappropriate for the patient, in which case the clinical anesthesiologist will carry out the induction of general anesthesia as they deem most appropriate.

Auditory and Somatosensory stimuli

The subject will be asked to listen to a series of sounds played through headphones, and to respond via button press to identify the sound as either a train of clicks, or verbal stimuli. The auditory stimulus will begin prior to administration of fentanyl and will continue through the end of the induction period. If a patient has stopped responding to the auditory stimuli within the 5-minute period between administration of fentanyl and induction of general anesthesia, 250msec ulnar nerve stimuli at 60mA will be performed to assess whether the subject can be aroused to consciousness. Responses to this ulnar nerve stimuli, including movement, grimacing, eye opening, or verbal responses, will be noted. A member of the study team will attempt to rouse the subject with verbal stimuli or tapping the subject's shoulder before using ulnar nerve stimulation.

Data from the electronic medical record for general anesthesia and sedation

We will gather data from the electronic medical record on the drugs given, their dosage, and the times when they are administered, as well as physiological parameters such as heart rate, respiration rate, and blood pressure. The fidelity of the $EtCO_2$ waveform depends on how well the ventilation mask fits and seals against the patient's face. Therefore, to provide redundancy, we will use a chest belt as an additional measure of respiration.

Data Analysis

Spectral analyses on the EEG will be performed in off-line analysis. The EEG power in different frequency bands will be analyzed as a function of auditory task behavior, the predicted drug plasma concentrations, and the physiological recordings of respiration rate, end-tidal CO2, heart rate, blood pressure, and oxygen saturation.

Sample Size Calculation

We are observing frontal EEG to detect changes from baseline spectral features when fentanyl is administered and desire detecting an effect size of approximately 10%. Using standard sample size and power calculations based on normally-distributed effects and errors, with an equal value standard deviation (SNR=0.1), type 1 error of 0.05, and desired power of 0.8, we arrive at a sample size of 80.

SUBJECT RECRUITMENT, SELECTION, AND ENROLLMENT

These studies will take place at Massachusetts General Hospital. Patients scheduled to undergo surgery lasting 2 hours or greater, in the age range of 18 to 65, will be eligible for this study.

Subject Recruitment and Enrollment

Potential subjects will be identified by anesthesiologists, who are not the patient's anesthesiologist, on our study staff. Potential subjects will be approached in the preoperative period by an anesthesiologist or a preoperative nurse to assess their interest in research participation. Interested patients will then be approached by anesthesiologist co-investigators on our study staff. A research assistant or coordinator may query EPIC for potential subjects and will confirm on EPIC that a potential subject identified by the physician investigator meets eligibility requirements. A research assistant or coordinator may query EPIC for potential patients and will confirm that potential subjects identified by the physician investigator meet eligibility requirements. Patients undergoing surgeries anticipated to take longer than 2 hours, and that typically require intravenous opioids for post-operative management, will be selected, since in these patients use of fentanyl during the induction period would be appropriate clinically. Permission for patient participation will be obtained from the patient's surgeon prior to enrollment. Subjects will be approached during the pre-operative period to describe the study and obtain consent. Every effort will be made to avoid protocol related delays in starting surgery.

Consent will be obtained by a study clinician in the pre-anesthesia or perioperative ward prior to anesthesia and surgery. Prior to the study, each subject will sign witnessed, informed consent for this study. There will be no randomization or treatment assignment as there is no therapy being studied.

Subject Selection

Only those patients capable of giving their own consent will be considered for this study. All study subjects will be American Society of Anesthesiologists (ASA) physical status classification P1 to P3. That is, all study subjects will have at most mild to moderate systemic

disease. A subject's medical history will be reviewed to rule out active and chronic medical problems.

***Conditions that will exclude subjects from the study entirely*:**

Craniofacial abnormalities

Allergies to fentanyl, bisulfite, eggs or egg products, latex, soybeans, soybean oil

BMI $\leq$ 35 (kg/m^2)

Known or suspected difficult intubation

Known or suspected need for rapid sequence induction and intubation

History of obstructive sleep apnea requiring CPAP

History of uncontrolled gastroesophageal reflux disease (GERD)

Opiate use within 24 hours

History of opiate abuse within 3 years

RISKS AND POTENTIAL BENEFITS

Risk and Discomfort

There is risk of bradycardia, hypotension requiring pressors, as well as transient muscle rigidity and difficulty ventilating; however, these are not added risks as they are existing side-effects of general anesthesia. Through rare, it is possible for patients to develop muscle rigidity after administration of fentanyl. When such cases occur during routine clinical care, anesthesiologists administer a fast-acting muscle relaxant such as succinylcholine to counteract this side effect. The standard anesthesia drug tray is stocked with succinylcholine syringes for this and other reasons. In our study, in the rare event of muscle rigidity, the anesthesiologist will administer succinylcholine as they would do in routine clinical care. If muscle rigidity occurs, no additional fentanyl will be administered. Subjects may experience slight transient discomfort from the stick-on Masimo EEG sensor as well as from the respiration band. If the patient can be roused to consciousness during the 250-millisecond ulnar nerve stimulation, they may experience transient discomfort. In this case, the patient will have already received boluses of fentanyl reducing this discomfort

Potential Benefits

There are no direct benefits for subjects. However, the knowledge gained from this study may help to improve anesthesia monitoring, which may benefit future patients.

MONITORING AND QUALITY ASSURANCE

Monitoring the validity and integrity of the data and adherence to the IRB-approved protocol will be the primary responsibility of the Principal Investigator, Patrick L. Purdon, Ph.D. For each case, they will confirm that all informed consent has been properly obtained, and that all data is appropriately recorded and maintained. This study involves no more than minimal risk, thus no formal DSMB is planned. In accordance with the PHRC guidelines, adverse events and unanticipated problems involving risks to subjects or others will be reviewed by the clinical co-investigator, Dr. Eric Pierce, who will judge whether event(s) were expected or not, or related or not to the study. Individual reports of adverse events will be submitted to the PHRC/IRB promptly. Adverse events and unanticipated problems involving risks to subjects or others will be reported to the PHRC in accordance with PHRC adverse event and unanticipated problems reporting guidelines. In addition, the investigator will also determine the best course of action to ensure subject safety.

Privacy of data will be ensured by de-identifying data. Data will be stored on password-protected and encrypted MGH Partners computers. Each subject will be assigned an alphanumeric code (with the key kept in a password protected file accessible only to study staff). Any data that may require physical transfer from one place to another will be performed using removable data storage devices encrypted under the 256-bit Advanced Encryption Standard (AES), as per Partners recommendations.

REFERENCES

Barash, Paul G. Handbook of Clinical Anesthesia. Lippincott Williams & Wilkins/Wolters Kluwer, 2013

Devine, B. J. Gentamicin therapy. Drug Intell Clin Pharm, 1974;8:650-5

Purdon, Patrick L., et al. "Clinical Electroencephalography for Anesthesiologists." Anesthesiology, vol. 123, no. 4, 2015, pp. 937–960., doi:10.1097/aln.0000000000000841.