Published in final edited form as:

Methods Enzymol. 2018 ; 602: 289–298. doi:10.1016/bs.mie.2018.01.011.

Xenon Anesthesia and CT: Noninvasive Measures of Brain Anesthetic Concentration

Andrew McKinstry-Wu¹, Charles W. Carspecken, Alex Proekt, and Max B. Kelz

University of Pennsylvania, Philadelphia, PA, United States

Abstract

The existence of a barrier between anesthetic behavioral state transitions has been observed across phyla, but demonstrating that such a barrier exists and is not a pharmacokinetic artifact has not yet been possible in humans. Such an investigation requires temporally precise information regarding the brain concentration of anesthetic in order to demonstrate the specific pharmacokinetic–pharmacodynamic mismatch that is hysteresis. We propose a method to noninvasively determine brain tissue anesthetic concentration using computerized tomography and the radiopaque gaseous anesthetic xenon. Such a technique can be used to investigate pharmacokinetic–pharmacodynamic mismatches in humans.

1. INTRODUCTION

Any study of pharmacodynamics in vivo requires an exact knowledge of drug concentration in relevant tissue. This is of particular importance in the study of anesthetic effects as (1) not all of the relevant molecular targets are necessarily known and (2) one of the primary effects of the class, hypnosis, appears to be a system-level phenomenon that requires a behavioral endpoint to assess. Detailed models of pharmacokinetics have been critical to the study of anesthetic effects in order to be able to tightly correlate drug concentration with anesthetic action. Validation of these pharmacokinetic models, or study of pharmacodynamic effects that can occur semiindependently of pharmacokinetics (pharmacokinetic–pharmacodynamic mismatches) require temporally precise and accurate measures of drug concentration in relevant tissues. In animal models, this is typically achieved through tissue biopsy or harvest—which is exactly how the first pharmacokinetic models for volatile anesthetics were validated. Alternate approaches, such as microdialysis, are slightly less invasive ways to determine tissue concentration of a drug, though these approaches can be limited in their spatial or temporal resolution, and still require the implantation of a device (Kennedy, 2013). Both direct tissue sampling or a semiinvasive approach such as microdialysis prove inadequate when such approaches are not possible (as in human subject research). These categories of studies require a noninvasive method of determining tissue drug levels with temporal precision.

Theoretically, noninvasive determination of tissue drug levels could be achieved by modifying the drug under investigation. One such modification would be creating a version

¹Corresponding author: andrew.mckinstry-wu@uphs.upenn.edu.

of the compound with an attached or associated fluorescent marker. This approach will not necessarily work with investigations of small molecules, however, as the tag itself possibly alters the physicochemical properties of the compound—thus making the modified compound an inexact model of the original compound under investigation (Etrych et al., 2016). An alternative approach leaving the chemical composition of the drug unchanged would be incorporation of radioisotopes in the synthesis of the drug. This solution is imperfect, as it would not resolve issues of precision of spatial localization and safety (in the case of human subject research).

We propose a general method of studying the in vivo effects of a general anesthetic, xenon gas, in human volunteers, that allows for temporally and spatially precise noninvasive measurement of drug tissue concentration using computerized tomography (CT). This method allows simultaneous monitoring of behavior, electroencephalography, and brain xenon concentration and could determine whether hysteretic pharmacokinetic–pharmacodynamic mismatch occurs. For example, this approach would allow for investigation of whether the barrier impeding transitions between hypnotic and awake states previously described in multiple animal models, known as neural inertia, also exists in humans (Friedman et al., 2010; Joiner et al., 2013).

2. RELEVANT PROPERTIES AND USES OF XENON

Xenon, a group 18 (noble gas) element, has anesthetic, physicochemical, and radiographic properties making it an ideal agent for the study of anesthetic pharmacokinetic–pharmacodynamic mismatch. Xenon is a naturally occurring, minimally reactive, rare element present in the atmosphere (0.0000087%). Purified xenon is obtained through fractional distillation of liquid air—a process requiring large amounts of energy to produce small quantities of pure gas. Despite being extremely chemically nonreactive, xenon acts as a general anesthetic at concentrations that allow for a nonhypoxic inhaled gas mixture at normal temperature and pressure. The minimum alveolar concentration necessary to produce immobility to a surgical stimulus for xenon in humans has variously been found to be as low as 63% to as high as 71%, while the concentration at which 50% of human subjects regain responsiveness is 33% (Goto et al., 2000; Hecker, Baumert, Horn, & Rossaint, 2004). Xenon is minimally soluble in blood (having a very low blood–gas partition coefficient) and is readily and rapidly diffusing, resulting in extremely fast, predictable kinetics. Unlike other inhaled general anesthetics, it has very little effect on cardiac output as it does not cause vaso-dilation, nor does it cause significant decrease in renal blood flow compared to other anesthetics (Hecker et al., 2004). Therefore, xenon has little effect on its own kinetics. Xenon is radiodense, having an X-ray mass attenuation coefficient roughly equivalent to iodine ($3.633\text{cm}^2/\text{g}$ at 80keV for xenon vs $3.510\text{cm}^2/\text{g}$ for iodine) (Hubbell & Seltzer, 2004). Thus, increases in xenon concentration will increase radiopacity linearly in a dose-dependent fashion.

Research studies have previously employed xenon's radiographic, physicochemical, or anesthetic properties separately to answer questions unrelated to pharmacokinetic–pharmacodynamic mismatch. Extensive clinical research and overseas use in clinical practice have shown xenon to be an extremely safe and reliable anesthetic (Law, Lo, & Gan,

2016), although studies of xenon as a sole anesthetic are not numerous (due to the high cost of distillation) with other agents frequently used for induction. Many of the anesthetic clinical studies involving xenon administration examined xenon's neuroprotective properties in the face of ischemic injury. A subset of imaging studies employ lower concentration inhalation of a radioactive isotope of xenon, ^{133}Xe , for ventilation/perfusion scans of the lungs, and perfusion imaging of the heart or liver, while both inhaled ^{133}Xe and stable xenon isotopes have been used for studies calculating cerebral blood flow (Coin & Coin, 1980; Drayer et al., 1978; Korhola, Valle, Frick, Wiljasalo, & Riihimäki, 1977; Strieder, Barnes, Aronow, Russell, & Kazemi, 1967; Winkler et al., 1977).

3. XENON DELIVERY

The high cost of xenon gas presents a practical limitation for its use as an inhaled agent. In order to maximally conserve the valuable gas, xenon must be used sparingly and, if possible, scavenged for reuse. Solutions for clinical practice in Europe rely on limiting xenon waste through the use of closed-circuit delivery methods that can also be used for nonclinical applications. Anesthesia workstations with dedicated closed-circuit xenon delivery modes are available commercially from vendors in Europe and are the current best option for xenon delivery (Stephan, Germany; Heinen and Lowenstein, Germany; Air Liquide, France). These workstations have the added benefit of integrated gas analyzers capable of independently verifying delivered xenon concentration. Other xenon delivery systems designed for delivery of xenon during imaging studies or for neuroprotection could also potentially be used for this investigation, but these may not be capable of delivering sufficient concentrations of xenon to produce general anesthesia (often as a safety measure).

Closed-loop delivery systems were designed with endotracheally intubated subjects in mind, but also can be used to deliver the slow, noninvasive, inhaled anesthetic dose-ramp required for studying pharmacokinetic–pharmacodynamic mismatch. Invasive airways, such as endotracheal tubes or laryngeal masks, produce excellent seals that limit gas leakage in an otherwise closed breathing circuit. Unfortunately, these invasive airways are also noxious stimuli that may consequently impede assessments of hypnotic potency. When properly fitted and adjusted, an anesthetic mask with attached head harness can provide an adequate noninvasive seal that allows for xenon administration in a closed circuit. Facial hair can impede the mask's seal, so subjects should shave any facial hair prior to mask fitting. For persistent small leaks, petroleum jelly applied to the portions of the mask in contact with the subject's face can help to minimize gas leaks. The tightly sealed mask also ensures that the subject is inhaling the intended concentration of xenon. The other requirement to control the concentration of inhaled xenon is verifying delivered xenon concentration via gas analysis. While mass spectrometry is the gold standard, it is not a viable solution for obtaining real-time gas measurements due to cost and availability of mass spectrometry devices. To address this, commercial xenon delivery systems use thermal conductivity sensors to analyze xenon concentration. Thermal conductivity allows for measurement of inhaled and end-tidal concentrations of xenon with short latency permitting estimation of equilibrium in blood with stabilization of end-tidal xenon. Thermal conductivity works on the principle that in a mixture of two known gases with different and known thermal conductivities, analyzing the thermal conductivity allows estimation of the relative concentrations of the two gases (King,

Bretland, Wilkes, & Dingley, 2005). This functions well for xenon, which is delivered along with a balance of oxygen. When compared to the gold standard of mass spectrometry, thermal conductivity has been shown to be accurate to within 1%–2.5% (Luginbühl, Lauber, Feigenwinter, & Zbinden, 2002). While this level of accuracy limits the value of thermal conductivity as an absolute measure of end-tidal xenon concentration, it is sufficient for the purpose of this study type, as the ultimate measure against which we will compare our various endpoints is tissue xenon concentration as determined by CT.

4. SYNCHRONOUS ELECTROENCEPHALOGRAPHIC (EEG), BEHAVIORAL, AND TISSUE CONCENTRATION MEASURES

The relative speed of obtaining a head CT to determine brain tissue concentration of xenon allows for significant temporal resolution. When coupled with other endpoints that have equal or better temporal resolution, such as behavioral and EEG measures, CT can produce a tight association among brain tissue concentration and those other endpoints. The ideal test would timelock a stimulus with both an EEG and behavioral responses. We recommend an auditory stimulus for ease of administration, nonnoxious nature of the stimulus, and potential for evaluation of response while subject is either conscious or unconscious. Auditory tasks can further be subdivided into active and passive tasks, in order to potentially gain additional information when the subject is unable to provide an active response. For the active task we recommend a go/no go task, where, for example, the presented stimulus could be a recorded “go” or a phase-scrambled version of the same recording (distribution within the frequency domain was identical between the two recordings). This type of task has previously been shown to be sensitive to effects of sedation from both benzodiazepines and ethanol, with increases in latency to response and decreases in response accuracy (Deakin, Aitken, Dowson, Robbins, & Sahakian, 2004; Fillmore & Weafer, 2004). As this task can be mentally demanding after a time, this active task should be limited to a 5-min period where a stimulus is presented once a second. Between these 5 min of active task, it is possible to present a 5-min passive stimulus of a tone at random intervals from 2 to 7 s to provoke an auditory evoked potential on EEG. Response to an auditory stimulus allows time-locking for both the stimulus and response to the subject’s EEG, as well as obtain both a discrete (present or absent, correct or incorrect) and continuous (time to response) evaluation of the response for the active task.

5. GENERAL METHOD FOR EVALUATING ANESTHETIC PHARMACOKINETIC–PHARMACODYNAMIC MISMATCH IN HUMANS WITH EEG AND BEHAVIORAL TESTING

Preparation and Baseline Testing

- Subject comes in having refrained from eating for the past 8h, from most liquids for the past 4h, and clear liquids for the previous 2h.
- Given the high emetic potential of xenon, multiple forms of antinausea prophylaxis are recommended. A minimum of two agents with different pharmacologic targets is ideal. In order to minimize agents with psycho-active

effects, a 5-HT₃ antagonist (such as ondansetron) and NK1 antagonist (such as aprepitant) are recommended.

- After an intravenous line is placed and EEG headcap is affixed, ear buds should be inserted and mask fitted with harness attached, with the subject breathing room air.
- It is important to check the mask for air leaks, followed by connecting subject to basic vital sign monitoring (EKG, pulse oximeter, and blood pressure) prior to beginning continuous monitoring.
- After the subject lies on the CT table, assess the comfort of the subject and add any necessary padding placed to minimize any potential noxious stimuli. If the subject feels subjective increased work of breathing, pressure support ventilation can alleviate this sensation. If pressure support is given, the subject's mask should be rechecked for gas leaks.
- Begin EEG acquisition and record at least 5 min of baseline eyes closed EEG prior to the start of testing.
- Subject should perform baseline passive and active attention tasks— performing multiple rounds of baseline tasks will be useful for later analyses comparing tasks at a given xenon concentration to baseline.
- Acquire baseline CT full head image, choose a plane with minimal to no artifact from EEG cap for all further CT images.

Xenon Administration

- We suggest administering xenon in ascending and descending steps with sufficient time at each step to reach equilibrium prior to testing. It will also be helpful to have increased resolution at concentrations near to predicted loss and reestablishment of consciousness, which generally fall in the range of 30%–45% in healthy subjects. In order to capture the full range of responses, we recommend starting at a dose of 20%, where there is mild impairment with no loss of consciousness and climbing as high as 60% to ensure capturing outliers. Given that we have generally seen equilibration around 10 min, 20 min steps allow for 10 min of testing at each step.
- Xenon concentration is increased or decreased based on the step and subject breathes the new concentration. Serial single slice head CTs should be obtained at regular intervals to establish brain concentration and certify when steady-state concentration is reached. For instance, in a 20-min step, single slice CTs might be taken at minute, 5, 10, 15, and 19 with the expectation that steady state will occur in the vicinity of minute 10.
- The subject should perform the serial tasks, passive and active.

Recovery

- Vital signs continue to be monitored during the recovery period, though subjects return quite rapidly to baseline.
- Once the subject feels fully recovered and vital signs are stable, headcap and intravenous line are removed, and the subject is discharged. Note that due to the possibility of continued fatigue after anesthetic exposure, the subject should not drive themselves.

6. DATA ANALYSIS

The primary focus of the investigation is the detection of possible differences in brain state during periods of identical brain xenon concentration. In order to establish identical concentrations of xenon in the brain, we compare the baseline CT slice to the same slice during the exposure and calculate the difference in Hounsfield units at an identical region of interest in the two slices (Fig. 1). That difference corresponds linearly to the xenon concentration in tissue and timepoints with an identical difference of Hounsfield units have the same concentration of xenon. We have found that approximately 5 min of inhalation of xenon is sufficient to reach equilibrium in the brain.

Having established identical brain concentrations of xenon, performance at those identical concentrations can be compared, different only in whether the subject was previously awake or anesthetized. Depending on the exact nature of the active task, analysis endpoints can include presence or absence of response, response accuracy, and latency to response. For the suggested passive task, EEG can be used to analyze the auditory evoked potential looking at response amplitude of the evoked peaks and latency to those peaks. Gross and regional spectral differences in the EEG during periods of identical xenon concentration can be compared. Previously described spectral characteristics of xenon hypnosis include frontal–parietal and temporal–occipital increases in relative and total delta power, frontal–parietal and temporal–occipital increases in total theta power, and frontal–parietal and temporal–occipital decrease in relative and total beta power (Laitio et al., 2008). These previous results were recorded with four-channel EEG, however, which lacks resolution for examining any real regional differences in band power. Higher channel count allows for more complex connectivity analyses, including transfer entropy, phase–lag index, and coherence.

7. CHALLENGES AND POTENTIAL PITFALLS

A study of this complexity presents numerous potential challenges. While higher-energy CT scans produce increased image quality and resolution, limiting the overall radiation dose for healthy volunteers is critical. Such a study can require many CT images, so limiting the image to a single level, and using a lower power CT, at 70keV, with a larger region of interest to calculate Hounsfield unit change can help to limit radiation dose at the expense of noise and resolution. If the study was focusing on the xenon concentration at a smaller region, a higher energy CT for increased resolution may be necessary. The EEG headcap can additionally cause artifacts in the CT image. In order to minimize those artifacts, a full head CT at baseline can help to choose a level with minimal artifact from the EEG cap for all

subsequent scans. Finally, with a subject near the border of consciousness and disinhibited, there is a risk of movement artifact. Acclimatizing the subject to the scanner, mask, and headcap while they are fully awake can minimize provoked anxiety and subsequent movement.

Aside from radiologic issues, the administration of xenon, while extremely safe when compared with most other inhaled anesthetics, does carry some risks. These include not only the disinhibition previously mentioned, but also significant risk of nausea and vomiting. We found that pretreatment with two separate anti-nausea agents, aprepitant and ondansetron, can prevent nausea and vomiting. Finally, as xenon is more dense than air, there is potential for greater work of breathing at higher inhaled concentrations. Providing mild pressure support during xenon administration proved sufficient to alleviate any subjective increase in work of breathing.

ACKNOWLEDGMENTS

Development and implementation of the described techniques were possible through the generous support of the James S. McDonnell Foundation and the National Institutes of Health, via K08 GM123317. These protocols were developed collaboratively with John Woo at the University of Pennsylvania. Additional thanks to Mathias Bresner for providing neurocognitive testing, W. Andrew Kofke for his expertise in xenon delivery, to George Mashour and Michael Avidan for their support, and for the generous support of the Department of Anesthesiology and Critical Care at the University of Pennsylvania.

REFERENCES

- Coin CG, & Coin JT (1980). Contact enhancement by xenon gas in computed tomography of the spinal cord and brain: Preliminary observations. *Journal of Computer Assisted Tomography*, 4(2), 217–221. [PubMed: 7365019]
- Deakin JB, Aitken MR, Dowson JH, Robbins TW, & Sahakian BJ (2004). Diazepam produces disinhibitory cognitive effects in male volunteers. *Psychopharmacology*, 173(1–2), 88–97. [PubMed: 14689162]
- Drayer BP, Wolfson SK, Reinmuth OM, Dujovny M, Boehnke M, & Cook EE (1978). Xenon enhanced CT for analysis of cerebral integrity, perfusion, and blood flow. *Stroke*, 9(2), 123–130. [PubMed: 417427]
- Etrych T, Lucas H, Janoušková O, Chytil P, Mueller T, & Mäder K (2016). Fluorescence optical imaging in anticancer drug delivery. *Journal of Controlled Release: Official Journal of the Controlled Release Society*, 226, 168–181.
- Fillmore MT, & Weafer J (2004). Alcohol impairment of behavior in men and women. *Addiction*, 99(10), 1237–1246. [PubMed: 15369556]
- Friedman EB, Sun Y, Moore JT, Hung HT, Meng QC, Perera P, et al. (2010). A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: Evidence for neural inertia. *PLoS One*, 5(7), e11903. [PubMed: 20689589]
- Goto T, Nakata Y, Ishiguro Y, Niimi Y, Suwa K, & Morita S (2000). Minimum alveolar concentration—awake of xenon alone and in combination with isoflurane or sevoflurane. *Anesthesiology*, 93(5), 1188–1193. [PubMed: 11046204]
- Hecker K, Baumert JH, Horn N, & Rossaint R (2004). Xenon, a modern anaesthesia gas. *Minerva Anestesiologica*, 70(5), 255–260. [PubMed: 15181400]
- Hubbell JH, & Seltzer SM (2004). Tables of X-ray mass attenuation coefficients and mass energy-absorption coefficients (version 1.4). National Institute of Standards and Technology. <https://www.nist.gov/pml/x-ray-mass-attenuation-coefficients>.
- Joiner WJ, Friedman EB, Hung HT, Koh K, Sowcik M, Sehgal A, et al. (2013). Genetic and anatomical basis of the barrier separating wakefulness and anesthetic-induced unresponsiveness. *PLoS Genetics*, 9(9), e1003605. [PubMed: 24039590]

- Kennedy RT (2013). Emerging trends in in vivo neurochemical monitoring by micro-dialysis. *Current Opinion in Chemical Biology*, 17, 860–867. [PubMed: 23856056]
- King R, Bretland M, Wilkes A, & Dingley J (2005). Xenon measurement in breathing systems: A comparison of ultrasonic and thermal conductivity methods. *Anaesthesia*, 60(12), 1226–1230. [PubMed: 16288621]
- Korhola O, Valle M, Frick MH, Wiljasalo M, & Riihimäki E (1977). Regional myocardial perfusion abnormalities on xenon-133 imaging in patients with angina pectoris and normal coronary arteries. *The American Journal of Cardiology*, 39(3), 355–359. [PubMed: 842456]
- Laitio RM, et al. (2008). Bispectral index, entropy, and quantitative electroencephalogram during single-agent xenon anesthesia. *Anesthesiology*, 108(1), 63–70. [PubMed: 18156883]
- Law L, Lo E, & Gan T (2016). Xenon anesthesia: A systematic review and meta-analysis of randomized controlled trials. *Anesthesia and Analgesia*, 122(3), 678–697. [PubMed: 26273750]
- Luginbühl M, Lauber R, Feigenwinter P, & Zbinden AM (2002). Monitoring xenon in the breathing circuit with a thermal conductivity sensor. Comparison with a mass spectrometer and implications on monitoring other gases. *Journal of Clinical Monitoring and Computing*, 17(1), 23–30. [PubMed: 12102245]
- Strieder DJ, Barnes BA, Aronow S, Russell PS, & Kazemi H (1967). Xenon 133 study of ventilation and perfusion in normal and transplanted dog lungs. *Journal of Applied Physiology*, 23(3), 359–366. [PubMed: 4860349]
- Winkler, et al. (1977). Xenon inhalation as an adjunct to computerized tomography of the brain: Preliminary study. *Investigative Radiology*, 12(1), 15–18. [PubMed: 402332]

Fig. 1.

Increased brain tissue concentration of xenon results in increased radiopacity. These serial images show the same section of brain with increasing and decreasing inhaled xenon concentration.