The Role of Clinical Pharmacology in the Trial of Conrad Murray for the Death of Michael Jackson

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Michael Jackson died at approximately noon on June 25, 2009. Dr. Conrad Murray, a cardiologist, was attending to Michael Jackson at the time of his death. The following facts are not in dispute.

1. Conrad Murray had been administering propofol every night for more than 2 months to help Jackson sleep.

2. Murray had no monitoring, no infusion pump, no resuscitation equipment, and kept no records.

3. Murray left Jackson to make phone calls. His phone records document 45 minutes of calls.

4. The last call apparently ended when Murray found that Jackson had arrested.

5. Murray delayed calling 911 for 20 minutes.

6. Murray told paramedics, and physicians at UCLA, that he gave Jackson just 4 mg of lorazepam. He never mentioned propofol.

7. On autopsy Michael Jackson had anesthetic levels of propofol in his blood, as well as lorazepam and lidocaine.

Murray was found guilty of manslaughter on November 7th. The clinical pharmacology of propofol and lorazepam figured prominently in the trial. Going into the trial, Paul White and I submitted our expert reviews of the pharmacology of propofol. Our written opinions, which were submitted to the court months in advance of the trial, appear on the following pages.

The lecture will review how the clinical pharmacology unfolded during the course of the trial.

March 8, 2011

J. Michael Flanagan
Flanagan, Unger, Grover & McCool
1156 North Brand Blvd.
Glendale, CA 91202-2582

Re: Michael Jackson Case

Dear Mr. Flanagan:

Thank you for asking me to review the expert reports and autopsy materials related to the unfortunate death of Mr. Michael Jackson on June 25, 2009. In considering the possible causes of Mr. Jackson's untimely death, it is my opinion that the most likely cause of death was the self-administration of a lethal combination propofol and lidocaine.

Mr. Jackson apparently became dependent on propofol [Diprivan], a popular intravenous sedative-hypnotic, for the treatment of his chronic insomnia while on concert tours in the past. As reported by Zacny et. al. (Anesth Analg. 1993;77:544-52), subanesthetic dosages of propofol appear to have a high abuse potential. Mr. Jackson was frequently administered propofol by a continuous infusion and even reportedly self-administered the drug for inducing sleep on occasion. In addition to his dependency on propofol, Mr. Jackson was also receiving parenteral meperidine (Demerol) and midazolam (Versed) on a frequent basis from Dr. Arnold Klein, and had apparently developed a dependence on this highly-addictive narcotic compound. The primary metabolite of meperidine, normeperidine has a longer half-life and therefore, accumulates faster than the parent compound. More importantly, normeperidine can produce excitatory neurotoxic effects which are manifest as central nervous system stimulation and seizure-like activity following administration of multiple doses of meperidine (Ruffmann et. al. Epileptogenic drugs: a systematic review. Expert Rev Neurother 2006;6:575-89; and Jiraki K.

Lethal effects of normeperidine. Am J Forensic Med Pathol. 1992;13:42-3). Normeperidine blood concentrations are maximum within 2 to 4 hr and remain elevated for 12 hr before declining by 24 hr (Verbeeck et. al. Clin Pharmacol Ther 1981;30:619-28). It is my opinion that the regular use of meperidine and resultant levels of normeperidine likely contributed to Mr. Jackson's inability to sleep. Of note, the amount of meperidine which was being administered to Mr. Jackson was unknowingly tapered in the days leading up to his death. The withdrawal symptoms associated with the discontinuation of meperidine after a prolonged period of regular use would be expected to result in withdrawal symptoms which would have further exacerbated Mr. Jackson's symptoms of insomnia and likely increased his desire to receive propofol to facilitate sleep.

Dr. Conrad Murray, a board certified cardiologist with experience in the use of propofol for conscious sedation, was caring for Mr. Jackson and his family. Dr. Murray (and apparently others) administered propofol infusions to Mr. Jackson to facilitate his ability to sleep. In the days leading up to Mr. Jackson's death, Dr. Murray was attempting to wean Mr. Jackson off propofol by using a combination of oral and parenteral benzodiazepines to produce a sleep-like state. Dr. Murray was unaware of the fact that Mr. Jackson had been receiving a combination of meperidine and midazolam on a regular basis from Dr. Klein, and that the dose of the narcotic analgesic had recently been reduced. Despite receiving a large amount of the long-acting benzodiazepine, lorazepam (Ativan), as well as diazepam and midazolam (Versed), in the early morning of June 25th, Mr. Jackson was unable to sleep. It is my opinion that the failure of this combination of benzodiazepines to induce sleep was probably related to the central tolerance that had developed to the benzodiazepine's hypnotic effect as a result of Mr. Jackson's frequent use of midazolam as an adjuvant to meperidine.

At the insistence of Mr. Jackson, Dr. Murray slowly administered a small bolus ("sedative") dose of propofol (25 mg IV) in combination with lidocaine (25 mg IV) around 10:45-10:50 AM on the morning of his death. According to Dr. Murray, Mr. Jackson appeared to drift off into a 'light' sleep over the next 10-15 min. Dr. Murray subsequently left the room to place a phone call.

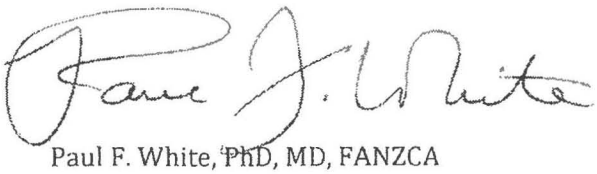
This small amount of propofol (25 mg) would not be expected to produce significant respiratory depressant effects even in the presence of the benzodiazepines. Furthermore, a 25 mg IV bolus dose of propofol would result in a 'peak' propofol blood level < 1 ug/ml. The fact that Mr. Jackson had propofol blood levels of 2.6-4.1 ug/ml in his circulatory system and a propofol concentration > 6 ug/g in his liver after death, suggests that he self-administered a much large dose of propofol after Dr. Murray left his room. Given the presence of a high concentration of propofol in his blood, as well as both propofol (130 ug) and lidocaine (1.6 mg) in his post-mortem gastric contents, it is my opinion that Mr. Jackson self-administered these drugs intravenously and/or orally after Dr. Murray stepped out of the room to make a series of telephone calls. The presence of a second 10 ml syringe and needle containing residual amounts of propofol and lidocaine on the floor next to Mr. Jackson bed (in addition to the one use by Dr. Murray to administer the 5 ml bolus of propofol [25 mg] and lidocaine (25 mg] IV), an empty 20 ml bottle of propofol and two empty 20 ml bottles of lidocaine found at the bedside, are consistent with the coroner's toxicological findings and the presumed cause of death (i.e., cardiorespiratory arrest due to oral and/or IV ingestion of a toxic combination of lidocaine and propofol). In order to mask the unpleasant taste of the oral lidocaine-propofol combination, it is speculated that Mr. Jackson added a portion of the lidocaine-propofol mixture to one of the fruit drink bottles found at his bedside.

The combination of large doses of propofol and lidocaine in the presence of the long-acting benzodiazepine lorazepam, likely have resulted in an acute cardiopulmonary arrest. The central nervous system depressant effects of this combination of medications can produce significant ventilatory depressant effects, as well as upper airway obstruction (due to relaxation of the pharyngeal musculature). It is my professional opinion that the misguided effort of Mr. Jackson to relieve his persistent insomnia by self-administering a lethal combination of lidocaine and propofol resulted in his untimely death.

A copy of my curriculum vitae is attached. As you can see, I have studied the clinical effects of propofol, parenteral benzodiapines and narcotic analgesics for over 25 years, and I have more

than 400 peer-reviewed publications. My clinical research group at Stanford University developed many of the techniques for administering boluses and/or infusions of propofol for sedation and hypnosis which are currently in widespread clinical use throughout the world. I have also studied the acute cardiopulmonary depressant effects of these centrally-active drugs in both volunteers and patients. Please let me know if you have any questions or concerns regarding my comments regarding the documents that I have been asked to review in this case.

Respectfully submitted,



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April 15, 2011

David Walgren
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Re: Analysis of the death of Michael Jackson.

Dear Mr. Walgren:

I have reviewed the materials that you have provided to me. These include reports of the interviews with the paramedics who responded to the 911 call, the interviews with Jackson employees involved with housekeeping and security, and the interviews with doctors at UCLA. It also includes the deposition of Conrad Murray, various photographs, Murray's curriculum vitae, the summary of calls from Murray's cell phone, and the preliminary hearing testimony. I have also reviewed the autopsy report and the laboratory toxicology report.

To quickly review my qualifications, I am a Professor of Anesthesiology at Columbia University, an Adjunct Professor of Anesthesia at Stanford University, and an Adjunct Professor of Bioengineering and Therapeutic Sciences at the University of California at San Francisco. I was at Stanford University from 1986-1987 for a fellowship in Clinical Pharmacology in Anesthesia, and was a member of the Stanford Faculty from 1987-2007. My work at Stanford University included 10 years studying the pharmacokinetics and pharmacodynamics of propofol, including propofol administration for sedation. This work included my performing the modeling and simulation that is basis of the current FDA package insert on the use of propofol for sedation. I have studied the pharmacokinetics and pharmacodynamics of lorazepam and midazolam for ICU sedation. I have studied the pharmacokinetics and pharmacodynamics of lidocaine for use in chronic pain management. Thus, based on my research at Stanford University and my publications in the peer reviewed medical literature I am comfortable asserting my expertise in the clinical pharmacology of propofol, midazolam, lorazepam, and lidocaine.

I am a practicing board-certified anesthesiologist with 25 years of experience. Additionally, I am the Editor-in-Chief of *Anesthesia & Analgesia*, the oldest and largest journal in the field of perioperative medicine, including sedation. The journal receives more than 2000 submissions yearly. As a result, I see a broad spectrum of anesthesia practices from around the world. Thus, I

believe I am well qualified to assert whether or not the care provided to Mr. Jackson is consistent with contemporary standards.

I have divided my analysis into four sections. The first describes the standard of care of for safe sedation. The second enumerates Murray's deviations from the standard of care. The third is my analysis of the toxicology results, and an assessment of the role of propofol, lorazepam, midazolam, and lidocaine in Michael Jackson's death. The fourth is a summary of my conclusions.

Standard of Care for Safe Sedation

Pre procedure setup

Before each procedure it is necessary to prepare the room and check the equipment. The following steps are required:

1. Emergency Airway Equipment. This includes having *instantly available* an oral airway, a nasal airway, and the ability to administer oxygen under pressure. "Instantly available" oral airway and nasal airways means that they are physically located next to the patient, so that an airway can be grabbed within a second in an emergency. "Administering oxygen under pressure" means that I can place a mask over the patient's face and force oxygen into the lungs. In the operating room I do this with an anesthesia circuit, which I always test prior to every case to verify that I can "squeeze the bag" to administer pure oxygen to the patient. When an anesthesia machine is not available, as is often the case when providing sedation for remote locations such as the endoscopy suite, I make certain that I have a bag and mask circuit, often called a "resuscitation bag" or an "Ambu bag." Depending on the patient, the expected dose of sedative, and the procedure I may also have a laryngoscope, endotracheal tube, and laryngeal mask airway readily available. "Readily available" means that I could access these within 1-2 minutes.

2. Suction apparatus. Patients undergoing sedation are at risk of aspiration. Aspiration occurs when the contents of the stomach are regurgitated, and go down the trachea ("windpipe") of a patient. Aspiration of stomach contents into the trachea and lungs is one of the most feared complications of sedation and anesthesia. Aspiration can be fatal, depending on the volume and exact contents of what is aspirated. To avoid aspiration elective procedures are always done on fasted patients, meaning patients who have not had anything to eat or drink for several hours prior to anesthesia. Certain kinds of medical conditions increase the risk of aspiration. In some of these conditions, fasting alone is not enough to ensure that the patient does not aspirate, and those patients cannot be safely sedated. Instead, these patients must receive general anesthesia, with the trachea protected with an endotracheal tube."

   If a patient regurgitates during sedation and anesthesia there are several procedures that must be performed instantly to protect the patient. First, the head must be turned to the

side, so that vomitus in the mouth is expelled, decreasing the chance that it goes down the trachea. Second, the mouth must be *instantly* suctioned. As before, "instantly" means within one second, because once vomitus appears in the mouth if it is not suctioned out it may be inhaled in the next breath. Thus, part of the pre-procedure preparation is verifying that I have a working suction apparatus. In a hospital setting this is typically the suction that is provided through a connector on the wall. In an office setting this may be provided by a portable suction pump. However, under no circumstances would I ever provide sedation without working suction.

3. Infusion pump. Propofol is not well suited for sedation using a syringe, because the onset and offset of the drug is too fast. Instead, anesthesia professionals virtually always administer propofol for sedation by continuous infusion. The infusion rate is controlled by a programmed infusion pump. Performing safe sedation requires setting up the propofol infusion line and the infusion pump. I typically run propofol through the infusion line, and then mount the infusion line in my infusion pump. The pump is programmed with the weight of the patient, and with the desire dose of propofol. If I do not know the weight of the patient then the programming is delayed until the patient is brought into the procedure room.

   An infusion pump is absolutely required to control the rate of propofol infusion. Without an infusion pump, the rate of propofol delivery is controlled by means of a very crude roller clamp on the propofol infusion line. Roller clamps are not accurate. Additionally, when using any system that depends on gravity alone to control the propofol infusion rate, the rate may change with any pressure differential between the propofol infusion tubing and the saline infusion tubing, or with changes in the height of the patient or the propofol vial. Additionally, roller clamps are prone to failure as a "wide open" infusion. I would never consider administering a propofol infusion without an infusion pump.

4. Intravenous infusion line. The propofol infusion line is not attached directly to the patient. Instead, an intravenous infusion line containing saline is attached through an intravenous catheter placed in an accessible vein in the patient. The line is prepared in advance, and checked to see that it does not contain air.

5. Oxygen delivery. Anesthesia professionals virtually always administer oxygen to patients undergoing sedation. I set up my oxygen delivery in advance of the case, making certain that I have an adequate supply of oxygen. I also have nasal prongs or facemask ready for the patient. The patient wears the nasal prongs or facemask during the procedure, increasing the safety margin.

6. Monitors. Every patient undergoing sedation must be monitoring using pulse oximetry. This is absolutely mandatory. The pulse oximeter must show the pulse, the percent oxygen saturation, and have an audible alarm. Under no circumstances would I provide sedation without a proper pulse oximeter.

Every patient undergoing sedation should also have a blood pressure cuff and an electrocardiogram in place, so that the basic vital signs are monitored at regular intervals (at least once every 15 minutes, although most anesthesiologists monitor every 2-3 minutes). Typically this is an automated blood pressure cuff. It is possible to provide adequate monitoring with a manual blood pressure cuff if the individual is highly compulsive about checking blood pressure at regular intervals.

I nearly always have access to capnometry – continuous monitoring of exhaled carbon dioxide. This is very useful to see exactly how quickly the patient is breathing. Capnometry is often the first monitor to detect apnea, which is when the patient stops breathing. There are some remote locations where capnometry is not available. If capnometry is not available, I make certain that I am physically positioned so that I can continuously watch the patient's breathing. Under no circumstances would I ever provide sedation if I could not continuously assess the patient's breathing.

Emergency Drugs. Depending on the nature of the planned sedation I typically prepare resuscitation drugs. If there is a chance that the patient may become hypotensive (dangerously low blood pressure) I prepare ephedrine and phenylephrine. These are drugs that raise blood pressure. Patients who are dehydrated are most likely to have a low blood pressure during propofol sedation and anesthesia. If the patient requires deep sedation, a large dose of drug, or I have any reason to believe that I may need to place an endotracheal tube, then I always prepare succinylcholine. This is a drug that paralyzes the muscles, allowing me to place an endotracheal tube in the windpipe to protect the patient.

7. Patient warming. Because of changes in the distribution of blood flow during sedation and anesthesia it is common that patients lose body heat. The resulting hypothermia increases the risk of complications. Therefore, it is necessary to have a means to reduce heat loss during sedation. Often this is done with forced air warming blankets. However, in remote locations this may be done with blankets. The critical aspect is to see that some measure is available to prevent hypothermia during sedation and anesthesia.

8. Chart. It is mandatory to record the delivery of care during sedation. Proper charting is fundamental to anesthesia care. Prior to every case I make certain that I have the materials available (at a minimum, a preprinted anesthesia record and a pen). Without a chart it is easy to miss trends in the patient's vital signs, forget exactly how much drug has been given, or even forget to check your monitors at all. Charting forces continuous scanning of the monitors of the patient's vital signs, visual assessment of the patient, and verification that the anesthetic infusion is uninterrupted. Under no circumstances would I provide sedation to a patient without proper charting.

Initiation of Sedation

Once the procedure room has been prepared for sedation, the following steps are required before sedation is started:

1. I review the patient's medical chart. That includes a review of all studies, notes by other doctors, and previous anesthesia records. I look for anything that might flag a special concern regarding anesthesia.

2. I interview the patient. Important questions include when the patient last had anything to eat or drink, and the current status of the patient's health. It is also important to establish whether the patient may be dehydrated, as dehydration increases the risk of low blood pressure.

3. I establish a doctor-patient relationship. The doctor-patient relationship is fundamental to good patient care. In this relationship, I advise the patient on reasonable medical choices. If there are several options, I present them to the patient, and the relative risks and benefits of the choices. However, medicine is not a smorgasbord, where patients can chose anything they like. Sometimes patients make unreasonable requests. It is my responsibility as the patient's doctor to decline any request that is medically unreasonable or irresponsible.

4. I examine the patient. This always includes, at a minimum, an examination of the airway and an initial set of vital signs, prior to the administration of any drug. Depending on the circumstances I may also listen to the patient's lungs and heart, perform a neurologic examination, or proceed with any other relevant aspects of a routine physical examination.

5. Written informed consent is obtained. Informed consent is a process by which the risks of the procedure are communicated to the patient, and the patient consents to the risks of the procedure. Informed consent is fundamental to the ethical practice of medicine. Informed consent should always be documented with the patient's signature. There are specific procedures covering medical emergencies when informed consent cannot be obtained. However, for elective procedures with mentally competent patients failure to obtain informed consent is considered an egregious breach of the standard of care and an unethical violation of patient rights.

6. The patient is brought into the procedure room and positioned appropriately. The monitors are attached (at a minimum a pulse oximeter, blood pressure cuff, electrocardiogram). The intravenous is started, and it is verified to be running well. The propofol infusion line is connected to the intravenous catheter.

7. The patient is placed on oxygen, either through nasal prongs or a mask.

8. I check the pump, to be certain that it is set to give the correct amount of drug.

9. I scan to verify that I have access to my airway equipment, suction, oxygen under pressure, emergency drugs, a means of keeping the patient warm, and my chart.

10. Once I have verified that everything is in place, I adjust the rate of the saline infusion (which is controlled with a roller clamp) so that I can readily see drops in the drip chamber. This verifies that the intravenous is open to the vein.

11. I then start the propofol infusion, and carefully observe the patient's response.

Maintenance of sedation

Once sedation is started, the patient is at risk for complications. The most serious complication is the decrease in breathing, leading to inadequate delivery of oxygen to the lungs and decreased oxygen delivery to vital organs. If this is not immediately addressed serious injury or death may result. Only slightly less dire is the possibility of regurgitation of stomach contents. The following steps are critical in the maintenance of sedation.

1. Constant observation of mental status. During sedation it is important to assess exactly how much drug (propofol) is required. The goal is to deliver exactly enough drug to achieve the desired level of sedation, without giving too much drug which increases the risk of complications. I typically assess drug effect by asking the patient questions while the sedative is taking effect. This way I can determine how much propofol will be required. As the sedation is maintained, I will intentionally reduce the amount of propofol to get the patient "light", so that I can affirm that the patient is getting no more drug than necessary.

2. Constant observation of vital signs. Every two or three minutes I scan the patient's vital signs. Every five minutes I record the vital signs in the patient's anesthesia record. The vital signs include.
    a. Breathing: I make certain that I am physically positioned so that I can watch the patient's chest move. Ideally I would like to have immediate access to the airway as well, although some surgical procedures can make this difficult. Typically those are procedures by ear/nose/throat surgeons, and they are competent to open the airway. Observing the movement of the chest, and the airway, also provides a means to immediately observe regurgitation.
    b. Oxygen saturation: Pulse oximeters used for monitoring must have an audible tone triggered by the heartbeat. That tone goes down in pitch as the patient's oxygen saturation decreases. Like most anesthesiologists, I am acutely attuned to this tone. I assess the oxygen level in the blood with literally every heartbeat.
    c. Blood pressure: The blood pressure cuff is cycled at least every 5 minutes to record a blood pressure. Because frequent recordings are mandatory, it is much

more convenient to use an automated blood pressure cuff. I have never used a manual blood pressure cuff during propofol sedation.

d. Heart rate: The heart rate is assessed using the electrocardiogram. The electrocardiogram also shows the shape of the electrical signal, which contains important information about the patient's heart rhythm, and the status of the heart.

3. Constant observation of the infusions. The patient has two infusions, an infusion of saline, sometimes called the "carrier" infusion, and the infusion of propofol. These have to be constantly scanned to verify that they are running well, and that the saline bag (usually 1 liter) and the propofol bottle are not about to run empty.

4. Constant documentation. I am constantly writing my observations on the anesthesia record. This provides an account of exactly what I have done, and how the patient has responded. It is often through the anesthesia record that I identify trends (breathing rate slowing, blood pressure dropping) that require intervention. It is also by examining the record created in real time that I can best understand the dose vs. response relationship.

5. Manage emergence from sedation. Typically this is unremarkable with propofol. After the infusion is turned off the patient simply awakens, opens his or her eyes, and talks. However, there can be emergence delirium, which includes fearful yelling and screaming, flailing of arms and legs, attempts to hit anyone within arms' distance.

6. Competency to handle adverse events. If everything goes fine, the above steps are all that is required to provide safe sedation. However, adverse events can and do happen. Some events are common, such as hypotension (low blood pressure), airway obstruction (the tongue falls back and blocks the throat), hypoventilation (slowed breathing), and hypoxia (decreased oxygen saturation in the blood). I must be competent at recognizing and treating these common complications. Other events are uncommon. The list is enormous, and includes regurgitation / aspiration, cardiac arrest, pulmonary embolus, and seizures. Even though these are uncommon, I must be competent to diagnose and treat these conditions.

Resuscitation

1. The requirements of cardiopulmonary resuscitation have been codified by the American Heart Association. The three basic components are
    a. chest compression to circulate blood,
    b. opening the airway to allow air to flow into the patient, and
    c. provision of air through a bag-mask device or mouth-to-mouth resuscitation.

2. CPR is unlikely to bring a patient who has suffered a cardiac arrest back to life. It is only a temporary intervention, intended to keep the patient alive until advanced medical help arrives. Thus, the FIRST intervention once a patient is discovered to have arrested is to

call for help.

3. In any medical emergency it is absolutely essential that all relevant information be communicated quickly and effectively to those providing medical care.

Conrad Murray's deviations from the standard of care

In the following assessment, *egregious* violations of the standard of care are individual failures that would be expected to cause a catastrophic outcome, and would almost never be committed by a skilled physician. *Serious* violations would contribute to a catastrophic outcome, but usually in combination with other errors. *Minor* violations would contribute to injury, but unlikely to play a significant role in catastrophic outcomes. *Unconscionable* violations are fundamentally unethical.

Pre procedure setup

1. Emergency Airway Equipment. An oral airway, a nasal airway, and the ability to administer oxygen under pressure was not *instantly available*. This is an **egregious** violation of the standard of care for sedation. Additionally, given the large doses of propofol being used every night to sedate Jackson, it is mandatory to have a laryngoscope, an endotracheal tube, and a laryngeal mask airway readily available. Failure to have these available, with anticipated propofol doses of approximately 100 milliliters is a **serious** violation of the standard of care.

2. Suction apparatus. Patients undergoing sedation are at risk of aspiration. There is no evidence that suction was available to Murray. This is an **egregious** violation of the standard of care.

3. Infusion pump. There is no evidence that an infusion pump was used to administer propofol. This is an **egregious** violation of the standard of care.

4. Intravenous infusion line. The intravenous infusion line appears to have been prepared competently.

5. Oxygen delivery. There is no evidence that Jackson was routinely given supplemental oxygen when propofol was delivered. Given the large doses of propofol employed, this represents a **serious** violation of the standard of care.

6. Monitors. Murray states that he used pulse oximetry. A Nonin Onyx 9500 pulse oximeter was found at the scene. This pulse oximeter has no audible pulse, no alarm, and a small display that cannot be read at a distance. It is utterly inadequate for sedation. Failure to have a proper pulse oximeter represents an **egregious** violation of the standard of care.

   There was no evidence that the blood pressure cuff found in Jackson's home was used.

Murray's checking the femoral pulse rather than the blood pressure suggests the blood pressure cuff was not on Jackson at the time of his arrest. This represents an **egregious** violation of the standard of care, particularly given the large dose of propofol and Murray's testimony that Jackson was dehydrated.

There was no electrocardiogram equipment available. This represents an **egregious** violation of the standard of care, particularly given the large dose of propofol and Murray's testimony that Jackson was dehydrated.

There was no capnometry. While capnometry is standard for sedation by anesthesia providers, it is not considered a standard for all sedation providers. Thus, the lack of capnometry is within the standard of care.

7. Emergency Drugs. There is no evidence that ephedrine, phenylephrine, or succinylcholine were drawn up in advance of the procedure, or even available in Jackson's house. Given the large anticipated dose of propofol, this represents a **serious** violation of the standard of care.

8. Patient warming. There is no evidence that Murray attempted to assess Jackson's temperature, or prevent the heat loss that accompanies sedation and anesthesia. This represents a **minor** violation of the standard of care.

9. Chart. Murray did not keep any records of the sedation. This represents an **egregious** violation of the standard of care.

Initiation of Sedation

1. Medical records. Murray knew that Jackson was seeing other doctors. He also knew that Jackson had multiple skin lesions reflecting multiple injections. However he did not contact any of Jackson's doctors to inquire about the nature of Jackson's medical care. This is a **serious** violation of the standard of care.

2. Patient interview. Murray did interview Jackson prior to the procedure. He identified one risk factor, dehydration. However, there is no evidence that he made any effort to identify if Jackson had anything to eat or drink prior to giving him intravenous sedatives. There is also no evidence that Murray took any precautions against aspiration. This is a **serious** violation of the standard of care.

3. Doctor-patient relationship. Murray did not establish a doctor-patient relationship. Judging by his actions, his relationship with Jackson was an employee-employer relationship. Jackson wanted propofol sedation. Had Murray established a doctor-patient relationship, he might have refused. However, in an employee-employer relationship, Murray complied. This is an **egregious** violation of the standard of care.

4. Patient examination. There is no evidence that Murray examined Jackson, or measured his heart rate, blood pressure, and oxygen saturation prior to the start of sedation. This is a **serious** violation of the standard of care.

5. Informed Consent. There is no evidence that Murray provide Jackson with informed consent of any kind. This represents an **unconscionable** violation of Michael Jackson's patient rights. It is also an **egregious** violation of the standard of care.

6. Placing of monitors. There is no evidence that a blood pressure cuff and electrocardiogram were attached to Jackson prior to starting the propofol infusion. This is a **serious** violation of the standard of care.

7. There is no evidence that Jackson received oxygen prior to the initiation of sedation. This is a **serious** violation of the standard of care.

Maintenance of sedation

1. Constant observation of mental status. The phone records show that Murray was talking on the phone for 47 minutes immediately prior to or concurrent with Jackson's arrest. It is not possible to talk on a cell phone and simultaneously pay second-by-second attention to mental status. It is not possible to adjust the propofol infusion to provide just the right amount of drug without constant observation of mental status. Had Murray constantly observed mental status, and known how to assess it, he would have recognized the overdose before Jackson suffered a respiratory arrest. Had Murray adjusted the infusion to provide just enough propofol for Jackson to sleep, Jackson would not have had a respiratory arrest. Murray has admitted to physically leaving the room to use the bathroom. This is completely unacceptable. If it is necessary to leave the patient, then an absolutely minimal requirement is that another individual be left in attendance. Failure to constantly observe mental status and adjust the infusion is an **egregious** violation of the standard of care.

2. Constant observation of vital signs. This was not done.
    a. Breathing: Had Murray paid vigilant attention to Jackson's breathing, he would have recognized the slowed breathing before the eventual respiratory arrest. Had that been done, he could have turned off the propofol infusion, and Jackson would not have had a respiratory arrest. Murray has admitted to physically leaving the room to use the bathroom. It is completely unacceptable to leave Jackson alone. It is analogous to the driver of a motor home saying that he walked into the bathroom while the motor home cruised down the freeway on autopilot. Failure to constantly observe breathing is an **egregious** violation of the standard of care.
    b. Oxygen saturation: I have already discussed the lack of an appropriate pulse oximeter as an egregious violation of the standard of care, so I will not elaborate further.

c. Blood pressure: I have already discussed the failure to monitor blood pressure as an egregious violation of the standard of care, so I will not elaborate further.
d. Heart rate: I have already discussed the lack of an electrocardiogram as an egregious violation of the standard of care, so I will not elaborate further.

3. Constant observation of the infusions. There was no infusion pump, and so Murray only had a very crude instrument to assess infusion rate: counting the visible drips of propofol in the drip chamber. This is inadequate to assess the rate of infusion. Additionally, the use of a roller clamp leaves open the possibility that Murray, or perhaps even Jackson, opened up the clamp and all of the propofol quickly infused into the patient. Control of the propofol infusion, and constantly monitoring of the infusion rate, is Murray's responsibility. His failure to use an infusion pump, and failure to monitor the infusion rate, is an **egregious** violation of the standard of care.

4. Constant documentation. Murray's failure to keep any records of any kind regarding the administration of propofol is an **egregious** violation of the standard of care.

5. Competency to handle adverse events. Murray was manifestly incompetent in performing CPR, attempting one handed CPR with Jackson on a bed. There is no evidence that he attempted to use an oral or nasal airway. A bag-mask device was visible in some of the photographs, but there is no description of Murray using it. Murray did not have any emergency drugs drawn up, which also suggests incompetence to handle emergencies. Murray's incompetence in preparing for adverse events is an **egregious** violation of the standard of care.

Resuscitation

1. a) Murray's chest compressions were inadequate. Michael Jackson was not moved to the floor, and Murray provided compressions with just one hand. There is no reason to believe that one handed chest compressions on a bed would be effective. This is a **serious** violation in the standard of care,

   b) Murray describes giving mouth to mouth resuscitation. This meets the standard for opening an airway expected of a lay person. However, the standard of care for a physician performing sedation is that an oral or nasal airway device be used to keep the airway open. Failure to place an oral or nasal airway represents a **serious** violation of the standard of care.

   c) Murray describes mouth to mouth resuscitation. However, photographs from the scene show a bag-mask device. If this device was indeed used by Murray, then that is consistent with the standard of care. However, he did not mention the bag-mask device in his deposition. Failure to use the bag-mask device would be considered a serious deviation from the standard of care. The available evidence does not permit a conclusion as to whether or not the bag-mask device was used.

Lastly, in his deposition Murray describes raising Michael Jackson's legs. That has no role in CPR, unless the person has suffered a traumatic injury and is bleeding. It is unclear why Murray performed this maneuver. Raising Jackson's legs reflects a lack of training and experience with CPR. It is a **minor** violation of the standard of care.

2. The first intervention in an arrest is to call for help. In an out-of-hospital arrest this would typically be a direction to another person to call 911. If another person is not available, then the responder should call 911. In his deposition Murray states that he did not call for help immediately. He did call Michael Williams, a member of Jackson's security detail. He did not instruct Williams to call 911 for assistance. That is an **egregious** violation of the standard of care.

   The first person to arrive at the scene was Alberto Alvarez. Instead of instructing Alvarez to call 911, Murray instructed Alvarez to place the bottles of sedatives into bags, and to remove the propofol infusion vial from the intravenous pole. By directing Alvarez to place the vials of sedatives into the canvass-type bags, and remove the propofol infusion from the IV pole, Murray further delayed Alvarez's call to 911. This is an **egregious** violation of the standard of care.

3. Murray withheld information about the propofol infusion administration from the paramedics and the physicians at UCLA attempting to save Jackson's life. This is an **egregious** violation of the standard of care. Additionally, withholding information represents an **unconscionable** violation of the Hippocratic Oath ("I will apply, for the benefit of the sick, all measures that are required") and the Declaration of Geneva ("The health and life of my patient will be my first consideration"). [verbatim quotations taken from Wikipedia]

The role of propofol, lorazepam, midazolam, and lidocaine in Michael Jackson's death

I will rely on several research articles in this analysis. All of these derive from my research at Stanford University, and I am the principle investigator for each of these studies.

Propofol

1. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology. 1998;88:1170-82
2. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ. The influence of age on propofol pharmacodynamics. Anesthesiology. 1999;90:1502-16
3. Barr J, Egan TD, Sandoval NF, Zomorodi K, Cohane C, Gambus PL, Shafer SL. Propofol dosing regimens for ICU sedation based upon an integrated pharmacokinetic-pharmacodynamic model. Anesthesiology. 2001;95:324-33

Lorazepam / Midazolam

1. Barr J, Zomorodi K, Bertaccini EJ, Shafer SL, Geller E. A double-blind, randomized comparison of i.v. lorazepam versus midazolam for sedation of ICU patients via a pharmacologic model. Anesthesiology. 2001;95:286-98.

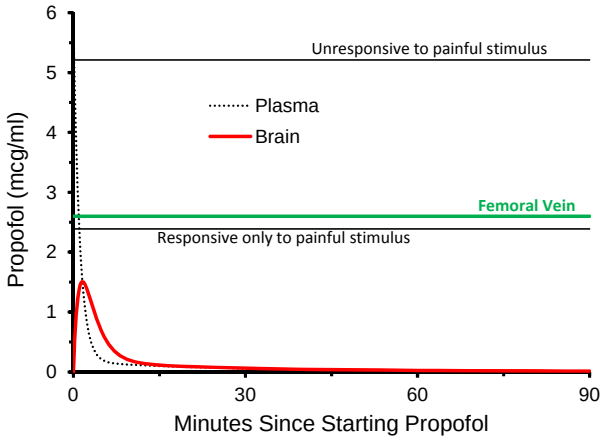
Lidocaine

1. Schnider TW, Gaeta R, Brose W, Minto CF, Gregg KM, Shafer SL. Derivation and cross-validation of pharmacokinetic parameters for computer-controlled infusion of lidocaine in pain therapy. Anesthesiology. 1996;84:1043-50

Propofol Simulations

The following propofol simulations are based on the pharmacokinetics and pharmacodynamic model of propofol reported by Schnider (propofol references 1 and 2 above). The drug levels associated with different levels of sedation are based on the report of propofol sedation by Barr (propofol reference 3 above).

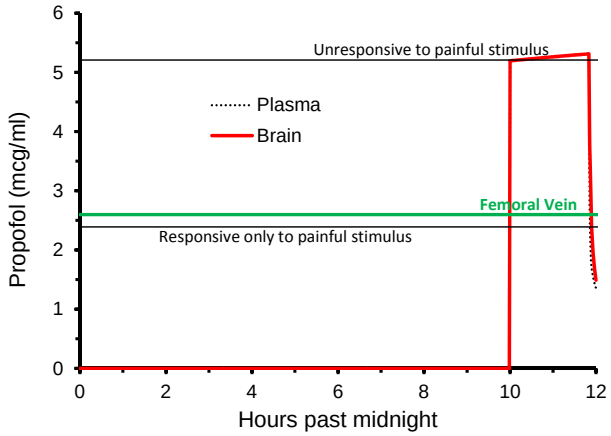
The distinction between plasma concentration (the dotted black curve) and brain concentration ("effect site," the solid red) is important. Without making this distinction it is not clear why the initial bolus must be supplemented by a continuous infusion to maintain drug effect.



Murray asserts that Jackson only received 25 mg of propofol. The simulation to the right shows the plasma and brain concentrations expected from a 25 mg

bolus of propofol. The initial plasma propofol concentration, shown as a dotted black line, is approximately 4 mcg/ml. However, the decline in concentration is very fast, and within 10 minutes the plasma concentration is approximately 0.1 mcg/ml. The green line shows the measurement in the femoral vein. Just 10 minutes after the infusion ends the plasma propofol concentrations are approximately 25 times less than the concentration measured in the femoral vein. Based on the measured propofol concentrations, Jackson received far more than 25 mg of propofol as stated by Murray in his deposition.

The red line shows the expected concentrations of propofol in the brain ("effect site"). They are modest, and never exceed the concentration associated with deep sedation (non-response to noxious stimulation). Thus, the brain levels are too low to be toxic. Murray's claim to have administered only 25 mg of propofol is inconsistent with the blood levels at autopsy and the profound effect (death) on Jackson.



An empty 100 ml vial of propofol was found in the blue bag, where it was placed by Alvarez, who removed it from the IV pole. There is a tear in the rubber stopper that clearly shows it was "spiked" with an infusion line. To understand what *might* have happened, I have simulated an infusion of 100 mls of propofol, starting at 10 am, and ending at 11:50 am.

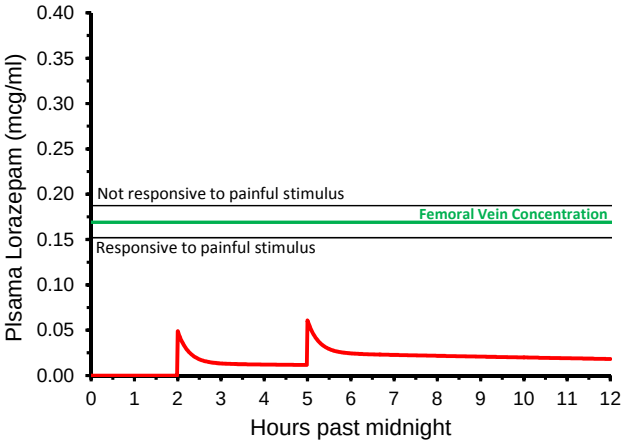
The rate of 100 mls of propofol given over 110 minutes is 9.1 mg/min. The rapid onset and offset of propofol drug effect is observed. One hundred mls of propofol, given over 1 hour and 50 minutes, would produce concentrations of propofol consistent with general anesthesia ("unresponsive to painful stimulus"). The bottle was empty, so the data are consistent with the infusion abruptly stopping simply because the bottle ran out of propofol. The rapid drop seen at 11:50 shows the rapid decline in propofol concentration expected at the end of an infusion.

The rapid decline in concentration means that at the time of Jackson's arrest there was no steady-state equilibration of propofol. In this setting the amount of propofol in any blood sample depends on the composition of individual body tissues and the blood flow to those tissues. It is expected that venous samples from different sites will give different concentrations of propofol.

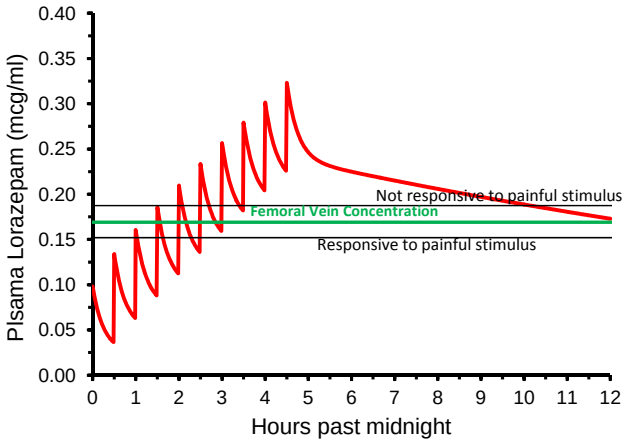
The measured propofol blood levels, the empty 100 ml vial of propofol, and the ensuing death of Jackson all support the conclusion that Jackson received a lethal dose of propofol from Murray. There is no possibility that Jackson received just 25 mg of propofol, as Murray stated in his deposition.

Lorazepam simulations

Murray's deposition states that he gave Jackson 2 intravenous doses of 2 mg of lorazepam: one at approximately 2 am, and the second at approximately 5 am. The red line in the figure to the right shows the expected plasma lorazepam concentrations based on these doses and the pharmacokinetic model reported by Barr et al (lorazepam / midazolam reference 1). The thresholds for deep sedation (response only to painful stimulus) and general anesthesia (no response to painful stimulus) are also from Barr. The expected lorazepam concentrations are well below those observed at autopsy (green line).



Two open vials of lorazepam were found in Jackson's home. A vial of lorazepam contains 10 mls of lorazepam, at a concentration of 4 mg/ml. The figure to the right shows the expected concentrations if Jackson received a bolus of 1 ml (4 mg) of lorazepam every 30 minutes until 40 mg had been given. The lorazepam levels rise over time, eventually reaching the level of general anesthesia.

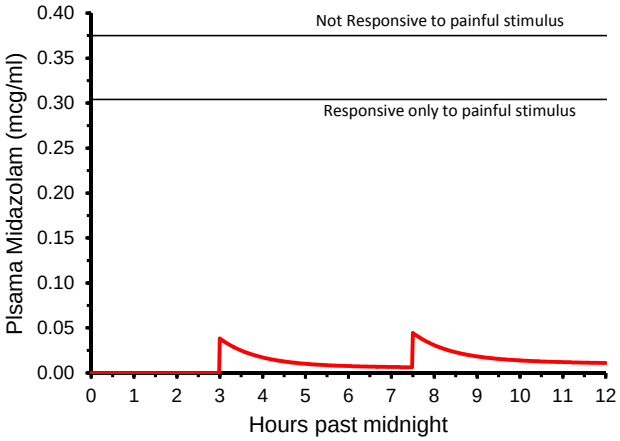


Once lorazepam is no longer given, the plasma lorazepam concentrations steadily decrease, reaching the level observed at autopsy at noon. At the time of Jackson's death (approximately noon) the lorazepam concentrations were falling slowly, and in approximate equilibration among body tissues. As a result, lorazepam concentrations sampled in blood at different sites at autopsy will be less variable than propofol concentrations, since propofol was not in equilibrium. This is consistent with the toxicology report.

Murray did not give Jackson 4 mg of lorazepam. The data suggest a far higher dose, possibly an entire 40 mg vial of lorazepam. Lorazepam contributed to death of Jackson.

Midazolam simulations

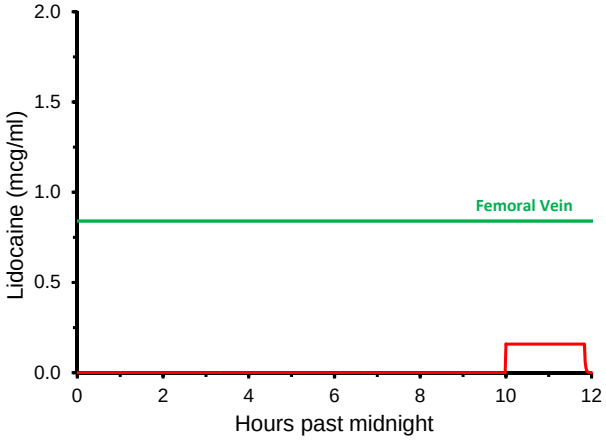
Murray's deposition states that he gave Jackson 4 mg of midazolam, 2 mg at 3 am and 2 mg at 7:30 am. The simulation below shows the expected midazolam concentrations, again based on the pharmacokinetics reported by Barr. The simulation shows that the midazolam levels should be almost undetectable at autopsy. This was the case. The data support Murray's statement that he gave just 4 mg of midazolam. Midazolam did not play a significant role in the death of Jackson.



Lidocaine Simulations

Lidocaine was not given separately, but rather drawn up with propofol to decrease propofol pain on injection. A typical dose would be 1 ml (10 mg) of lidocaine for every 9 mls of propofol. It is clear from Murray's deposition that he routinely mixed lidocaine with propofol, but there are no data on the ratio that he used.

If we assume the more or less standard mixture of 10 mg of lidocaine with 9 mls of propofol, and that Jackson received 110 mls of this mixture (100 mls of propofol + 10 mls of lidocaine), then we can simulate the expected lidocaine concentrations, using the pharmacokinetics reported by Schnider (lidocaine reference 1 above). The resulting lidocaine levels are approximately 1/5th of the measured concentration in the femoral vein. The most likely explanation is that Murray did not use the more or less standard dilution, but rather diluted lidocaine with propofol 1:1, i.e., mixed 5 mls of lidocaine with 5 mls of propofol. That would have produced almost exactly the lidocaine concentration measured in femoral blood at autopsy.



Mild lidocaine toxicity (ringing in the ears, perioral numbness) is expected at lidocaine concentrations of 5-10 mcg/ml. The lidocaine concentration associated with seizures is approximately 40 mcg/ml (see Rutten et al, Hemodynamic and Central Nervous System Effects of Intravenous Bolus Doses of Lidocaine, Bupivacaine, and Ropivacaine in Sheep, Anesth Analg 1989;69:291-9.) Jackson's lidocaine levels on autopsy were about 1/10th the concentration associated with mild toxicity, and 1/50th the concentration associated with serious toxicity.

Rejected hypotheses

I have reviewed and rejected following hypotheses:

Oral self-administration of propofol

There is zero possibility that the propofol was orally ingested. It is biologically impossible that a person could orally absorb a lethal dose of propofol from the stomach and intestines. All blood from the stomach and intestines flows directly to the liver, where it is subjected to first pass metabolism. The liver has enormous capacity to metabolize propofol. The clearance of propofol exceeds total hepatic blood flow. As a result, the hepatic extraction ratio is nearly 1. That means that nearly 100% of all propofol absorbed through the stomach and intestines would be metabolized by the liver, and none of it would get past the liver into the systemic circulation. Based on fundamental pharmacokinetic principles that govern oral drug bioavailability, almost no propofol should reach the systemic circulation.

This has been studied in pigs (Cozanitiks DA, Levonenm K, Marvola PH. Rosenberg PH, Sandholm M. A comparative study of intravenous and rectal administration of propofol in piglets. Acta Anaesthesiol Scand. 1991;35:575-577). In this study, intravenous administration of **5 mg/kg** of propofol gave peak levels of ~3500 ng/ml. Rectal administration of **55 mg/kg** gave peak levels of ~40 ng/ml, nearly 1/100th of the concentration seen with IV dosage, despite receiving 10 fold more drug. These authors estimated that the oral bioavailability of propofol is less than 1%.

Putting these numbers in context, if Michael Jackson drank 20 mls of propofol (200 mg), that would have had the same systemic delivery equivalent to 2 mg iv, which is $1/5^{th}$ of a cc of drug.

There is no mystery about the propofol content in the stomach on autopsy. The stomach has a blood supply, just like every other organ. Propofol and lidocaine diffused from the blood into the stomach tissue, and from there into the gastric contents.

The propofol concentrations in the stomach at autopsy were 1.9 mcg / ml (130 mcg/70 mls). That is lower than the propofol concentration in the systemic circulation (2.6 mcg/ml). That's expected, because propofol is just diffusing down a concentration gradient.

The lidocaine levels in the stomach at autopsy were 22.9 mcg/ml (1600 mcg/70 mls). These are substantially higher than the femoral blood concentration (0.84 mcg/ml). This is also expected. Lidocaine is an uncharged lipophilic molecule at systemic pH. The uncharged form equilibrates across tissues. However, in the acidic environment of the stomach lidocaine will become protonated (charged). The charged form is trapped in the stomach, because it does not cross back into the systemic circulation and is not in equilibration with blood. This is called "ion trapping" and it is well known for lidocaine. Ion trapping is the reason anesthesiologists intentionally add bicarbonate to lidocaine. That temporarily increases the unionized fraction to increase delivery to the cell. Once in the cell, the lidocaine is again protonated, and it becomes trapped in the cell.

Thus, the contents of the stomach are entirely consistent with intravenous delivery.

Self-administration of intravenous propofol

No vials of propofol were found without their rubber stoppers. All propofol had to be either infused or administered by hand-held syringe. It is not easy for a novice to draw up drugs into a syringe, because the syringe must start out with enough air to replace the volume of the withdrawn drug. Adding lidocaine to the propofol requires a second withdrawal step. It takes a little coordination to properly orient the vials and syringes so that the propofol remains in the syringe while the lidocaine is drawn up. No syringe larger than a "10 ml" (actually a 12 ml) syringe was found at the site. Twelve mls of propofol would produce at least 5 minutes of unconsciousness. For Jackson to have self-administered 100 mls of propofol would thus have required 8 separate draws into the syringe, and he would have needed at least 40 minutes of unobserved time for each injection, loss of consciousness, and recovery. It is not believable.

The only rate-control system present was the simple roller clamp on the intravenous tubing. Jackson could have opened up the propofol infusion. This would have only been possible because of the **egregious** failure to control the rate of propofol infusion with a proper infusion pump, and the **egregious** lack of vigilance by Murray during the procedure. In the presence of appropriate vigilance, any attempt by Jackson to manipulate the infusion rate would have been noticed and prevented. Additionally, the **egregious** lack of vigilance to the infusion itself would be responsible for failure to notice the "wide open" infusion of propofol, preventing appropriate intervention. Thus, it is entirely possible that Jackson opened up the roller clamp while Murray was absent from the room. However, this represents an **egregious** failure in care by Murray.

Contribution of lidocaine

Lidocaine played no role in the death of Jackson. The concentrations were too low to be of any clinical significance.

Contribution of meperidine

The records of Dr. Klein show that Jackson liked meperidine. The records document that Jackson was able to tolerate many days without meperidine. That is typical of a person who likes opioids, but is not physically addicted to them. Addicts cannot go for days without opioids without developing signs of opioid withdrawal. There was no meperidine, and no normeperidine, the active metabolite, in Jackson's body at the time of his death. It did not contribute to his death.

Differing ratios of lidocaine and propofol in different samples

During washout, the concentrations of propofol and lidocaine in blood will depend on the capacity of individual tissues to bind these molecules and the blood flow to the tissues. Propofol and lidocaine bind to tissues in very different ways, with propofol being highly bound by fat.

They would be expected to wash out of different tissues with very different time frames. One cannot infer anything from the relative concentration of propofol and lidocaine in different samples.

Summary and Conclusion

My assessment of Murray's conduct of sedation identified 17 egregious violations of the standard of care, 10 serious violations of the standard of care, and 2 minor violations of the standard of care. Additionally, Murray's failure to obtain informed consent, and his failure to properly inform the paramedics and physicians of the propofol administration are unconscionable violations. They are fundamentally unethical.

There is almost nothing in Murray's care of Michael Jackson that reflected the actions of a trained physician. Murray's medical training and licensure yielded two contributions to the care of Jackson: 1) he was able to place an intravenous line in Jackson, and 2) he appears to have purchased a bag-mask device for resuscitation. Every other aspect of Murray's delivery of sedation to Jackson, as well as his efforts to resuscitate Jackson, was that of an unskilled non-medically trained person.

Jackson died following a lethal dose of propofol. Jackson also received a potentially toxic dose of lorazepam, which added to the effects of the propofol. There was no significant contribution of midazolam in Jackson's death. Lidocaine played no role in the death of Jackson.

Murray's primary use of his medical training and licensure was to give Jackson access to unlimited supplies of propofol. He administered propofol with complete disregard for Jackson's safety, and did not even follow the basic rules of cardiopulmonary resuscitation following Jackson's arrest.

Dr. Conrad Murray is responsible for the death of Michael Jackson through an **extreme** violation of the standard of care including two profoundly **unconscionable** ethical violations.

Sincerely,

Steven L. Shafer, MD
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Professor of Anesthesiology, Columbia University
Adjunct Professor of Anesthesia, Stanford University
Adjunct Professor of Bioengineering and Therapeutic Sciences, UCSF