THE PHARMACOKINETICS AND PHARMACODYNAMICS OF THIOPENTAL AS USED IN LETHAL INJECTION

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Thiopental (sometimes called, although inaccurately, Sodium Pentothal) was the most commonly used intravenous anesthetic agent for about fifty years, beginning in the mid-1940s.[1] As states began to discuss and develop protocols for lethal injection in the 1970s, thiopental was the logical choice as the medication to render the inmate unconscious prior to the administration of subsequent medications, most commonly pancuronium (a medication that paralyzes skeletal muscle and results in cessation of breathing) followed by potassium chloride (a salt that is a necessary component of the diet but when given intravenously in large doses results in the cessation of electrical activity in the heart).

It is virtually unanimously accepted by physicians, particularly anesthesiologists, that the administration of lethal doses of pancuronium and/or potassium chloride to a conscious person would result in extreme suffering. For this reason, all of the protocols for lethal injection that we have reviewed precede the administration of pancuronium and potassium chloride with a dose of thiopental intended to render the inmate unconscious for a period of time far in excess of that necessary to complete the execution.[2] When implemented as written, meaning the correct doses of the correct medications are administered in the correct order into a properly functioning intravenous delivery system and with sufficient time for thiopental to produce its effect, all of the protocols we have reviewed are intended to result in the rapid death of the inmate without undue pain or suffering.

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1. *See* A.S. Evers et al., *General Anesthetics*, *in* GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 341, 342 (Laurence L. Brunton et al. eds., McGraw-Hill, 11th ed. 2006).

2. One or both of the authors has reviewed the protocols used by Alabama, Arkansas, California, Delaware, Florida, Georgia, Kentucky, Maryland, Missouri, Montana, North Carolina, Ohio, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and the federal government.

This paper will concentrate on the pharmacokinetics and pharmacodynamics of thiopental. As applied here, pharmacokinetics is the study of the concentration of thiopental as a function of time in tissues (particularly brain), while pharmacodynamics is the study of the effects of thiopental (particularly the production of unconsciousness and impairment of the heart's ability to circulate blood).[3] By using generally accepted computer modeling techniques, and considering the wealth of published studies on the pharmacology of thiopental, we can prepare predictions of such relevant parameters as the onset (how long it takes for the inmate to become unconscious) and duration (how long the inmate would remain unconscious) of the pharmacological effects of thiopental.[4]

Thiopental is usually described as an "ultra-short acting" sedative/hypnotic agent in pharmacology and anesthesiology texts.[5] This description is semantically correct, but only when thiopental is compared to other barbiturates. Indeed, when thiopental was used to induce (i.e., begin) a general anesthetic, the typical adult dose was about 300 mg and the typical patient would remain unconscious for 5 to 10 minutes.[6] The usual anesthetic regimen would involve the subsequent administration of anesthetic gases that would keep the patient unconscious for the duration of the surgical procedure. The protocols for lethal injection mandate doses of thiopental ranging from 2000 to 5000 mg, i.e., about seven to sixteen times higher than those used to begin a typical anesthetic.[7] However, the relationship between the dose of thiopental and its duration of action is *not* linear. For example, as the dose of thio-

3. K.B. Johnson & Talmage D. Egan, *Principles of Pharmacokinetics and Pharmacodynamics: Applied Clinical Pharmacology for the Practitioner*, *in* ANESTHESIOLOGY 821, 821 (D.E. Longnecker et al. eds., McGraw-Hill 3d ed. 2008).

4. *See generally* Colin A. Shanks et al., *A Pharmacokinetic-Pharmacodynamic Model for Quantal Responses with Thiopental*, 21 J. PHARMACOKINETICS & BIOPHARMACODYNAMICS 309, 309-21 (1993) (providing the pharmacokinetic model for thiopental and the pharmacodynamic model for burst suppression); *see also* Robert J. Telford et al., *Fentanyl does not Alter the "Sleep" Plasma Concentration of Thiopental*, 75 ANESTHESIA & ANALGESIA 523, 523-29 (1993) (providing the pharmacodynamic model for unconsciousness).

5. Thiopental is "ultra-short acting" only in comparison to the barbiturates that are classified as "short-acting," "intermediate-acting," and "long-acting." This differentiation is primarily of historical interest. *See, e.g.*, LOUIS S. GOODMAN & ALFRED GILMAN, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 138 (Macmillan Co., 2d ed. 1955).

6. Mark Dershwitz & C.E. Rosow, *Intravenous Anesthetics*, *in* ANESTHESIOLOGY, *supra* note 3, at 849, 856. R

7. *See supra* note 2 for the list of states whose protocols the authors have reviewed. R

pental is increased sevenfold to 2000 mg, the duration of unconsciousness is *not* also increased sevenfold but actually much more, as described later. The pharmacological term "sedative/hypnotic" means that at low doses (e.g. 25 - 100 mg), thiopental causes sedation (i.e., sleepiness), while at higher doses it produces hypnosis (i.e., unconsciousness).[8] At sedative doses, it produces no analgesia (pain relief) and in fact probably increases the perception of painful stimuli. When a person is rendered unconscious by thiopental, the conscious perception of pain is abolished. The body may, however, react in a reflex manner to pain and exhibit such phenomena as movement, a fast heart rate, sweating, or tearing. Additionally, the state of consciousness produced by a drug is also affected by the strength of applied stimuli. Thus, at the threshold of unconsciousness pain may reverse the state and produce consciousness, making it difficult to distinguish between reflex responses to pain and conscious response. Therefore, it has been argued by some that deep unconsciousness, as defined by burst suppression on the electroencephalogram ("EEG"), be the level of unconsciousness produced in lethal injection.[9]

We will present models to describe the onset and duration of unconsciousness as a function of the dose of thiopental. For example, with the administration of 2000 mg of thiopental to an 80-kg person, loss of consciousness will occur within approximately 1.0 to 1.5 minutes, while duration of unconsciousness will last approximately two hours. The time for onset of burst suppression in the same individual would be approximately 1.5 to 2.5 minutes and would reliably last only seven minutes. Larger doses of thiopental will be shown to result in further prolongation of the duration of unconsciousness and burst suppression.

There is an enormous body of anesthesiology literature supporting the use of mathematical modeling of the pharmacokinetic and pharmacodynamic behavior of intravenous anesthetic agents like thiopental.[10] Such modeling underlies the commonly utilized tech-

8. Dershwitz & Rosow, *Intravenous Anesthetics*, *supra* note 6, at 850. R

9. *See* Testimony of Thomas K. Henthorn, Taylor vs. Crawford et al., No. 05-4173-CV-S-FJG, 2006 WL 1779035, slip op at *7 (W.D. Mo. June 26, 2006).

10. *See, e.g.*, such comprehensive review articles and book chapters as: Dershwitz & Rosow, *supra* note 6, at 849-68; J. Sear, *Total Intravenous Anesthesia*, *in* ANESTHESIOLOGY, *supra* note 3, at 897, 897-917; Thomas K. Henthorn, *The Effect of Altered Physiological States on Intravenous Anesthetics*, 182 HANDB. EXP. PHARMACOL. 363, 363-77 (2008); Thomas K. Henthorn, *Recirculatory Pharmacokinetics: Which Covariates Affect the Pharmacokinetics of Intravenous Agents?*, 523 ADV. EXP. MED. BIOL. 27, 27-33 (2003); Harmut Derendorf et al., *Pharmacokinetic/Pharmacodynamic Modeling in Drug research and Development*, 40 J. CLIN. PHARMACOL. 1399, 1399- R R R

nique of target-controlled intravenous drug infusions. Mathematical modeling of intravenous anesthetics has been extensively studied and has been validated in the real world practice of target-controlled infusions ("TCI").[11] TCI couples a small computer with an infusion pump so that multi-compartment models are used to predict and adjust anesthetic drug infusion rates on a second-by-second basis to reach and maintain plasma concentrations determined by the practitioner.[12] TCI devices are in common use in anesthetic practice worldwide. Median absolute performance errors for TCI of predicted versus actual drug concentrations are in the range of ±30% when literature values for pharmacokinetic parameters are used to drive the TCI device.[13] Therefore, similar errors can be expected when applying the simulations presented here to any given individual. Thus the methodology employed in performing the pharmacological simulations employed herein has undergone peer review and its application to the actual practice of anesthesia is well studied.

I. The Onset Times for Thiopental Administered at Various Rates

No drug, including thiopental, has an effect the moment it is injected. It must first be transported by circulating blood to the site of action, i.e., the brain in the case of thiopental. The drug must then cross the blood-brain barrier to reach drug receptors in the neural cells of the brain. The drug-receptor interaction then triggers a cellular response resulting in the drug effect. As thiopental concentrations at the site of action continue to rise, more intense drug responses are seen. The interval between injecting the drug, and seeing an effect, i.e. the process of accumulating adequate drug concentrations in the blood and subsequently the brain, is called hysteresis.[14] A good way to think about hysteresis is to compare it to using a stove. Turning the flame on is akin to injecting the drug; transporting the heat to the surface of the pan is analogous to the

1418 (2000); D.R. Stanski, *Pharmacodynamic Modeling of Anesthetic EEG Drug Effects*, 32 Annu. Rev. Pharmacol. Toxicol. 423, 423-47 (1992).

11. *See* Talmage D. Egan, *Target-Controlled Drug Delivery: Progress Toward an Intravenous "Vaporizer" and Automated Anesthetic Administration*, 99 Anesthesiology 1214, 1215 (2003).

12. *Id.*

13. *See id.* at 1216-17; *see also* Robert A.Veselis et al., *Performance of Computer-Assisted Continuous Infusion at Low Concentrations of Intravenous Sedatives*, 84 Anesthesia & Analgesia 1049, 1053-57 (1997).

14. Johnson & Egan, *supra* note 3, at 825. R

circulation delivering the drug to the site of action; and cooking the food in the pan is akin to producing the drug effect. Your dinner can range from undercooked to well done, depending on how long it's exposed to the flame "dose" the stove is delivering. Similarly the heating effect continues for some time even after the flame is turned off. Therefore, with hysteresis it is possible to have the same effect at two different plasma drug concentrations just as it is possible for a pan to be at the same temperature at two different flame settings, once during heating and again during cooling. Pharmacokinetic-pharmacodynamic modeling is able to mathematically describe this hysteresis and fully explain how the same blood drug concentration can produce variable effects.[15]

In a lethal injection setting, once an injection of thiopental has begun, the drug must pass through the IV tubing from the "injection room" to the "death chamber" before reaching the vein of the condemned inmate. For instance, if the tubing is ten feet long with a typical tubing volume of 1.8 mL/foot, then the total volume is 18 mL. Assuming fluid traveling in a tube as a perfect cylinder and an injection speed of 2 mL/sec, it would take a full 9 seconds for the drug to reach the vein.

After entering the bloodstream the drug must circulate with the blood to reach the brain before concentrations at the site of effect can begin to rise. Depending on where the intravenous catheter is placed in the inmate, it could take up to 15 seconds for the drug to reach the right-sided chambers of the heart and thus be considered within the central circulation where the flow of blood is at its greatest. From the right side of the heart, the blood flows through the pulmonary arteries to the capillaries of lungs, recollects in the pulmonary veins and flows back to the left side of the heart. The powerful left ventricle of the heart then pumps the blood out through the aortic arch into all of the arteries of the body, including the carotid and vertebral arteries leading to the brain.

The principles governing the time required for an injected drug to pass through IV tubing to reach the vein also apply to the drug within the bloodstream. That is, the time elapsed is directly related to the volume of the system and the flow rate of the fluid in the system. The volume of the central circulation as a percentage of the body's total blood volume is near maximum when lying flat, approximately one third of the total blood volume or 1.7 L for the typical male inmate. It would be higher tilted head down and

15. *See generally id.* at 825.

lower when standing. In a sedated adult it would be reasonable to assume a total blood flow (or cardiac output) of 5 L/min. Thus the time required for drug just arriving in the right side of the heart to pass through the central circulation to reach the brain would be 1.7 L divided by 5 L/min, which is approximately 20 seconds.

Adding the 15 seconds for venous transit (times vary greatly with the distance from the heart and the flow in the particular vein selected for the intravenous catheter) to the 20 seconds for central circulation transit, one can appreciate the concept of arm-brain circulation time, which is empirically spoken of among anesthesiologists as being approximately one-half minute. Again, there will be an additional 9 seconds or so added to time required to see the initial thiopental response due to the very long length of intravenous tubing leading from the "injection room" to the "death chamber."

In the fluid medium of the body, drug diffuses from areas of high concentration to adjacent areas where the concentration is lower. During the onset of effect, thiopental diffuses from the blood where the concentrations become quite high, after the initial 35 seconds required for transit, into the brain where the thiopental concentration starts at zero. Without continued thiopental administration, diffusion continues in this direction for approximately 2.5 minutes, at which time blood and brain concentrations are momentarily equal. Then diffusion reverses direction and the drug begins to move from the brain back into the blood. Brain concentrations will continue to fall at a rate governed by the decrease in blood concentrations since brain concentrations will never fall below those of the blood during this phase. Figure 1 depicts the probability of unconsciousness or burst suppression as a function of the brain concentration of thiopental.

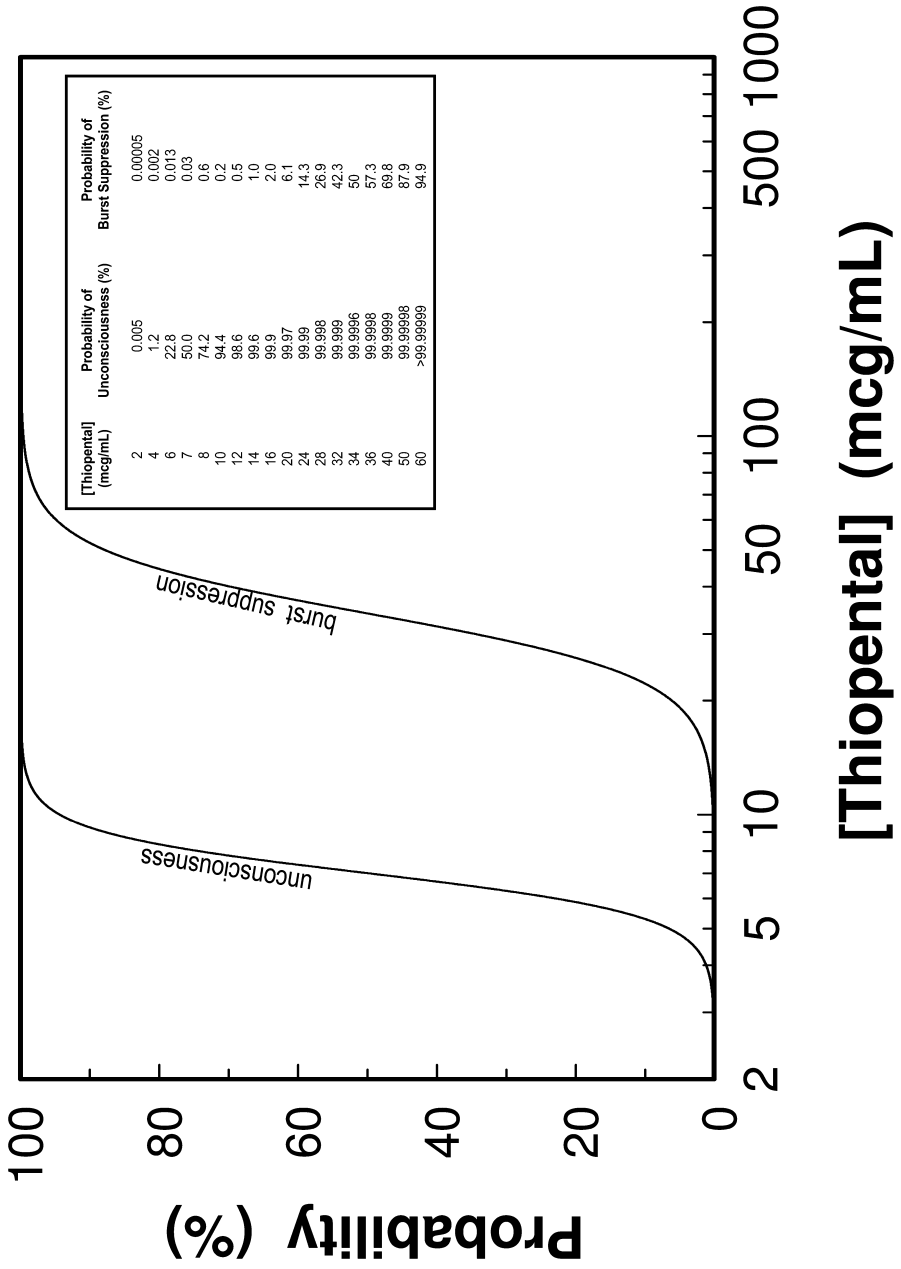


Figure 1: The probability that a person will experience unconsciousness or burst suppression on the EEG as a function of the brain concentration of thiopental. Note that the x-axis is shown as a logarithmic scale for clarity.[16]

16. *See, e.g.*, *supra* note 4 and accompanying text. **R**

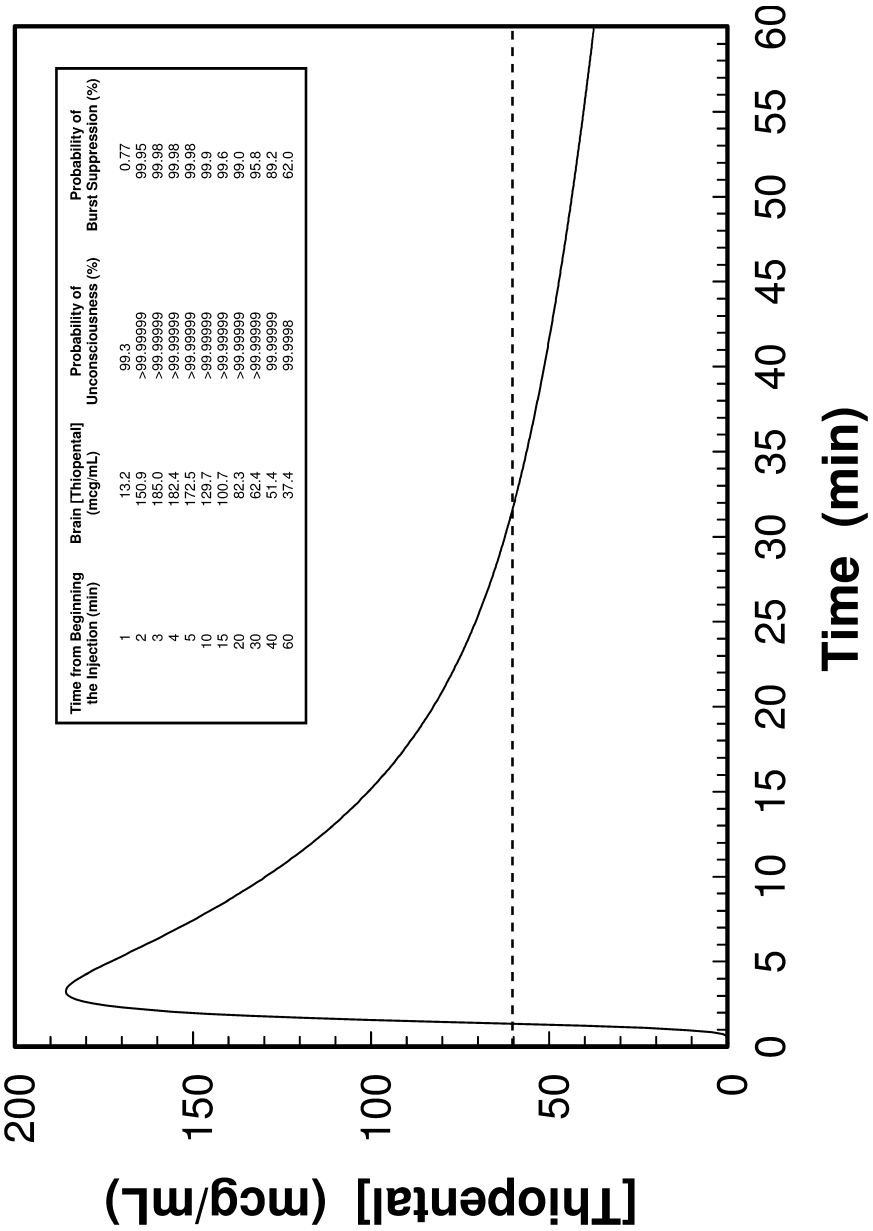


Figure 2: The predicted brain concentration of thiopental following the administration of a dose of 5000 mg given at a rate of 167 mg/sec to an average 80-kg person. The dashed line indicates the brain concentration above which 95% of persons will experience burst suppression on the EEG.[17]

17. *See* Dershwitz & Rosow, *supra* note 6, at 850.

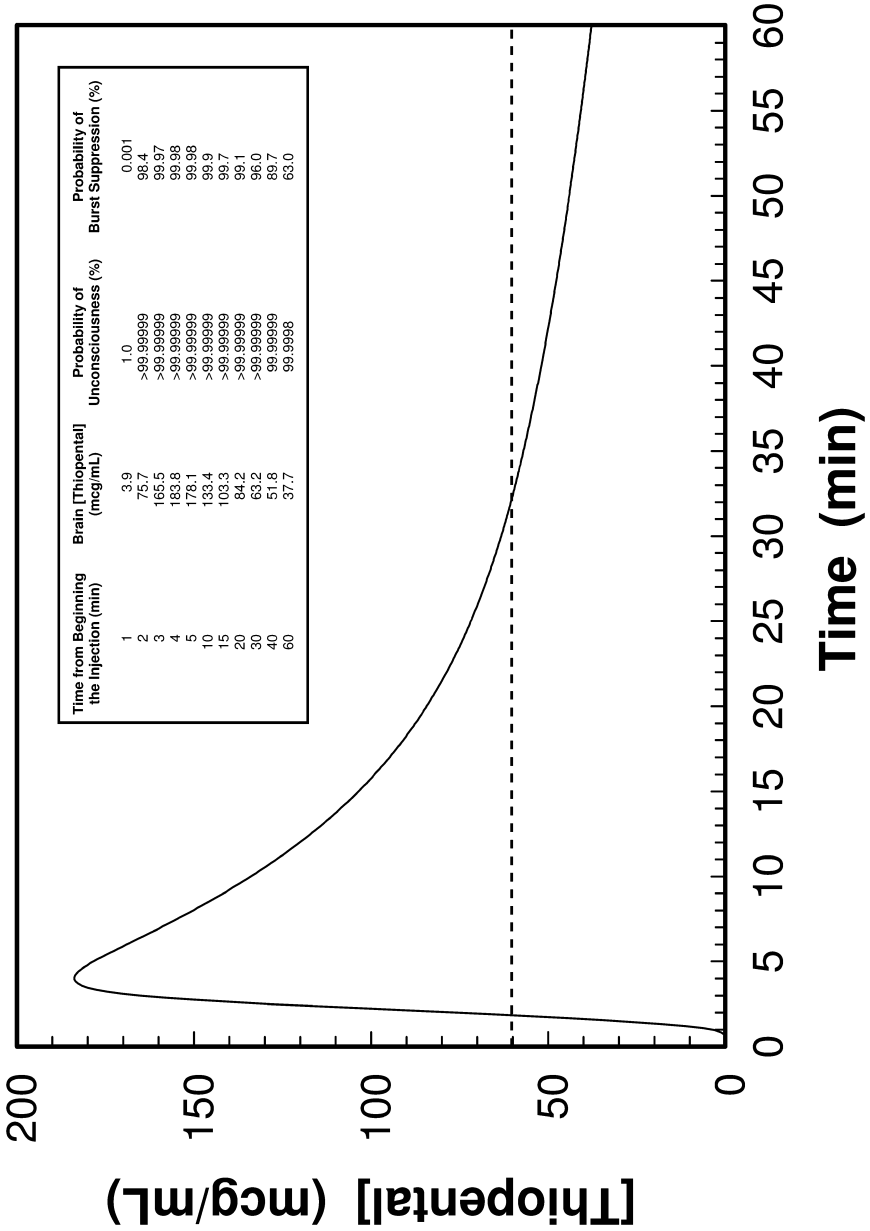


Figure 3: The predicted brain concentration of thiopental following the administration of a dose of 5000 mg given at a rate of 50 mg/sec to an average 80-kg person. The dashed line indicates the brain concentration above which 95% of persons will experience burst suppression on the EEG.[18]

18. The pharmacodynamic model for unconsciousness is in Telford et al., *supra* note 4, at 523-29. See Shanks et al., *supra* note 4, at 309-21 for the pharmacodynamic model for burst suppression. R

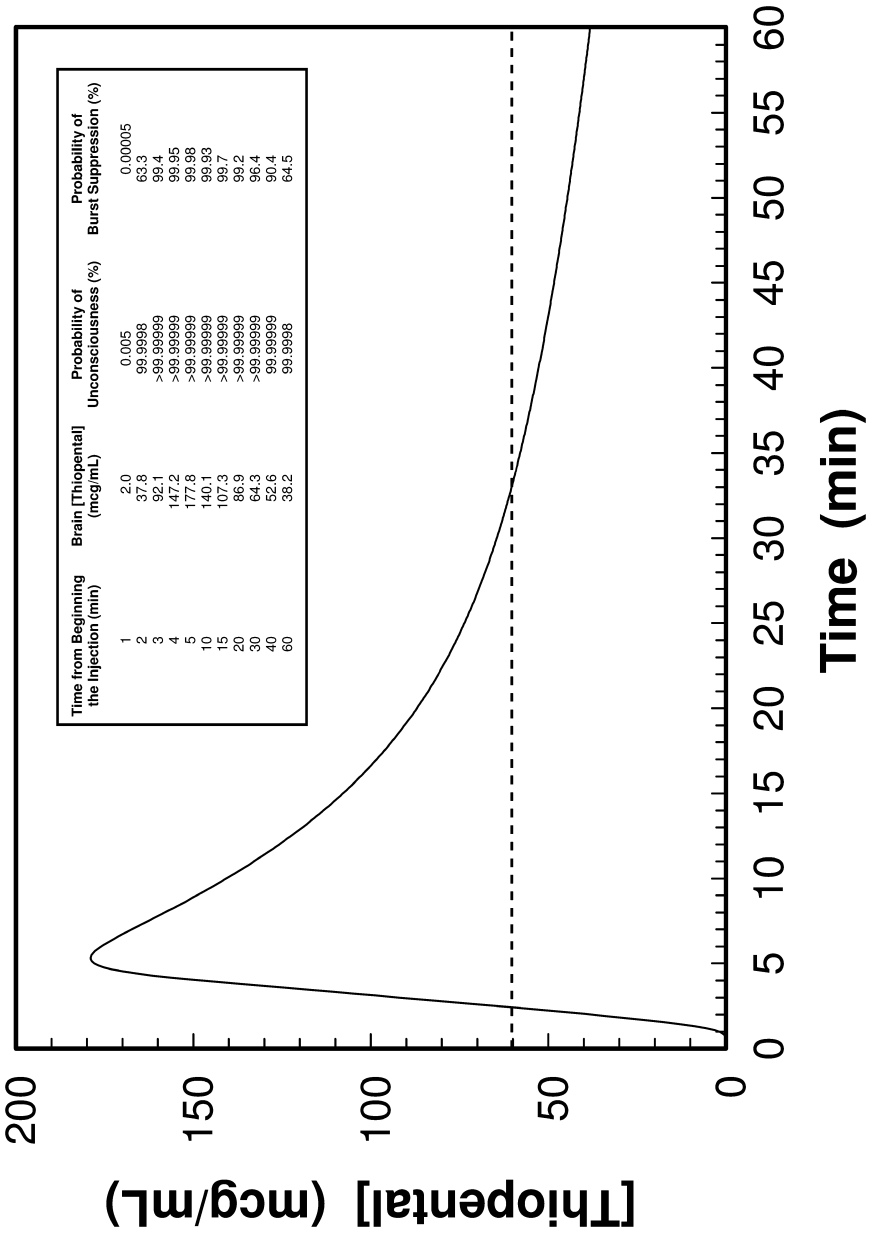


Figure 4: The predicted brain concentration of thiopental following the administration of a dose of 5000 mg given at a rate of 25 mg/sec to an average 80-kg person. The dashed line indicates the brain concentration above which 95% of persons will experience burst suppression on the EEG.[19]

19. The pharmacokinetic model for thiopental used in Figures 2-8 is in Shanks et al., *supra* note 4, at 309-21. **R**

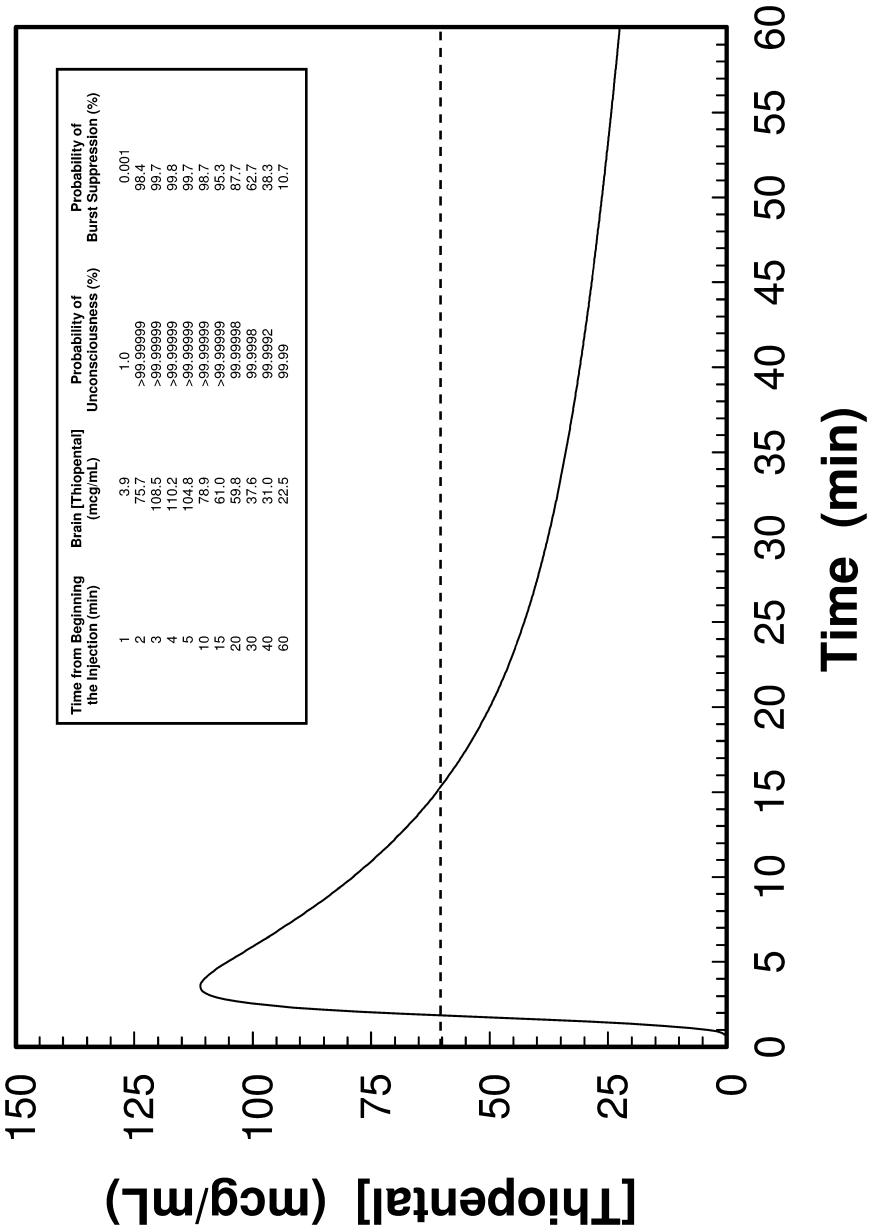


Figure 5: The predicted brain concentration of thiopental following the administration of a dose of 3000 mg given at a rate of 50 mg/sec to an average 80-kg person. The dashed line indicates the brain concentration above which 95% of persons will experience burst suppression on the EEG.[20]

20. *See id.*

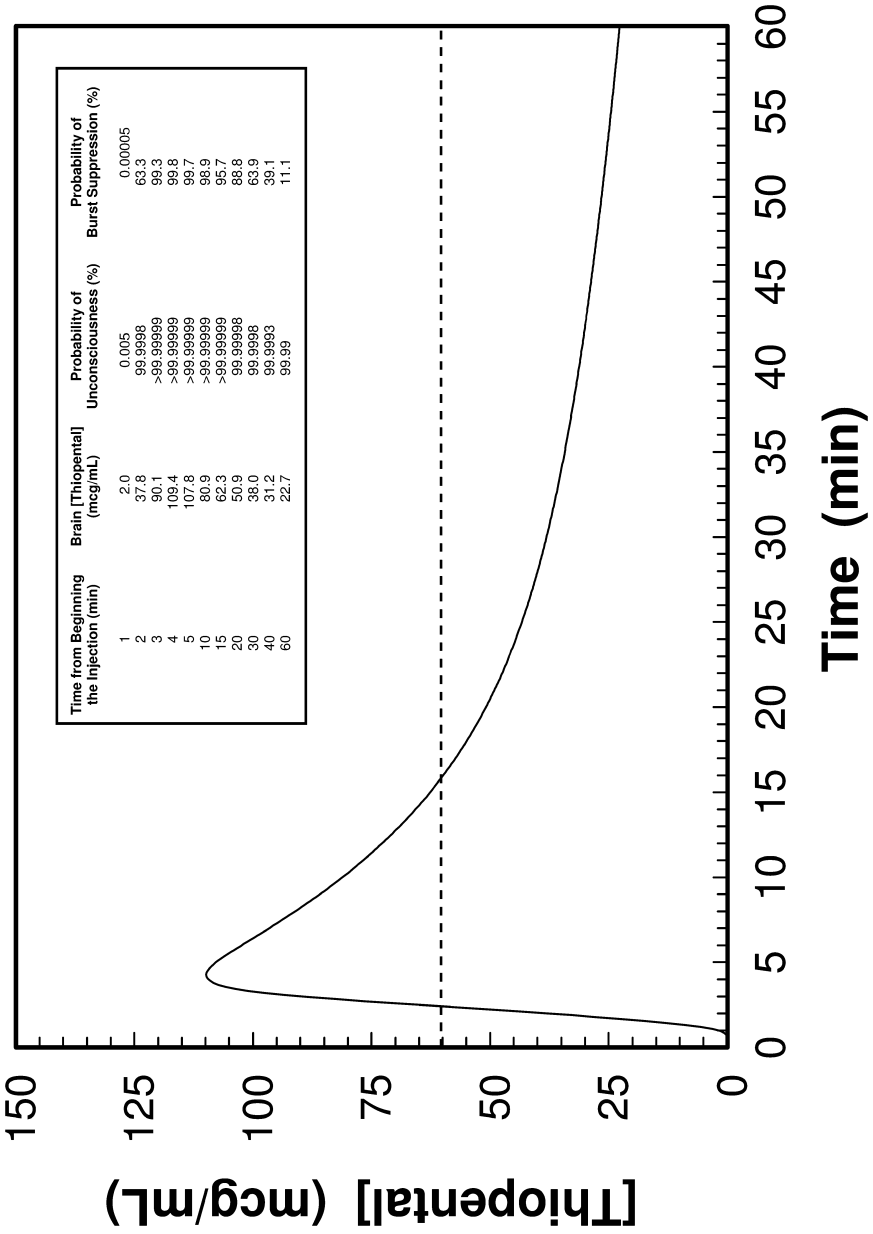


Figure 6: The predicted brain concentration of thiopental following the administration of a dose of 3000 mg given at a rate of 25 mg/sec to an average 80-kg person. The dashed line indicates the brain concentration above which 95% of persons will experience burst suppression on the EEG.[21]

21. *See id.*

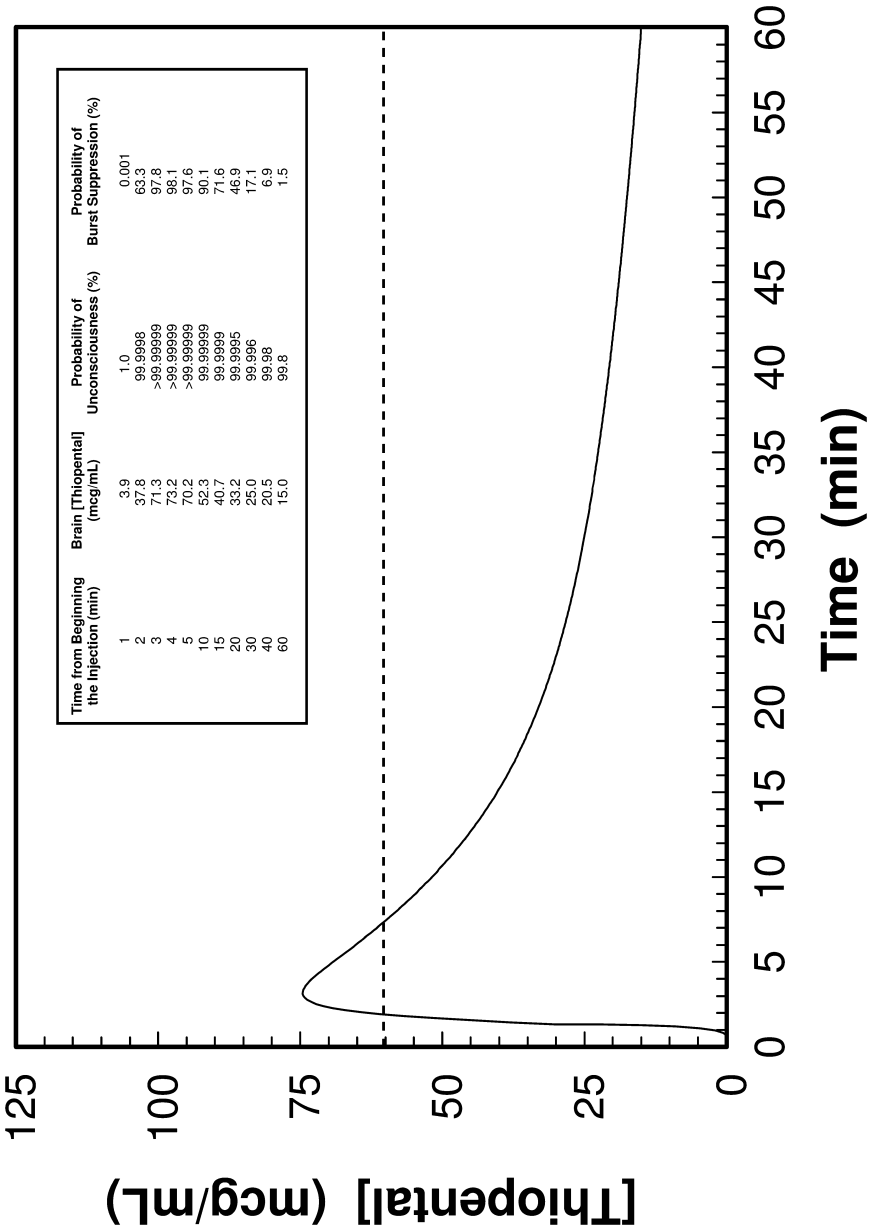


Figure 7: The predicted brain concentration of thiopental following the administration of a dose of 2000 mg given at a rate of 50 mg/sec to an average 80-kg person. The dashed line indicates the brain concentration above which 95% of persons will experience burst suppression on the EEG.[22]

22. *See id.*

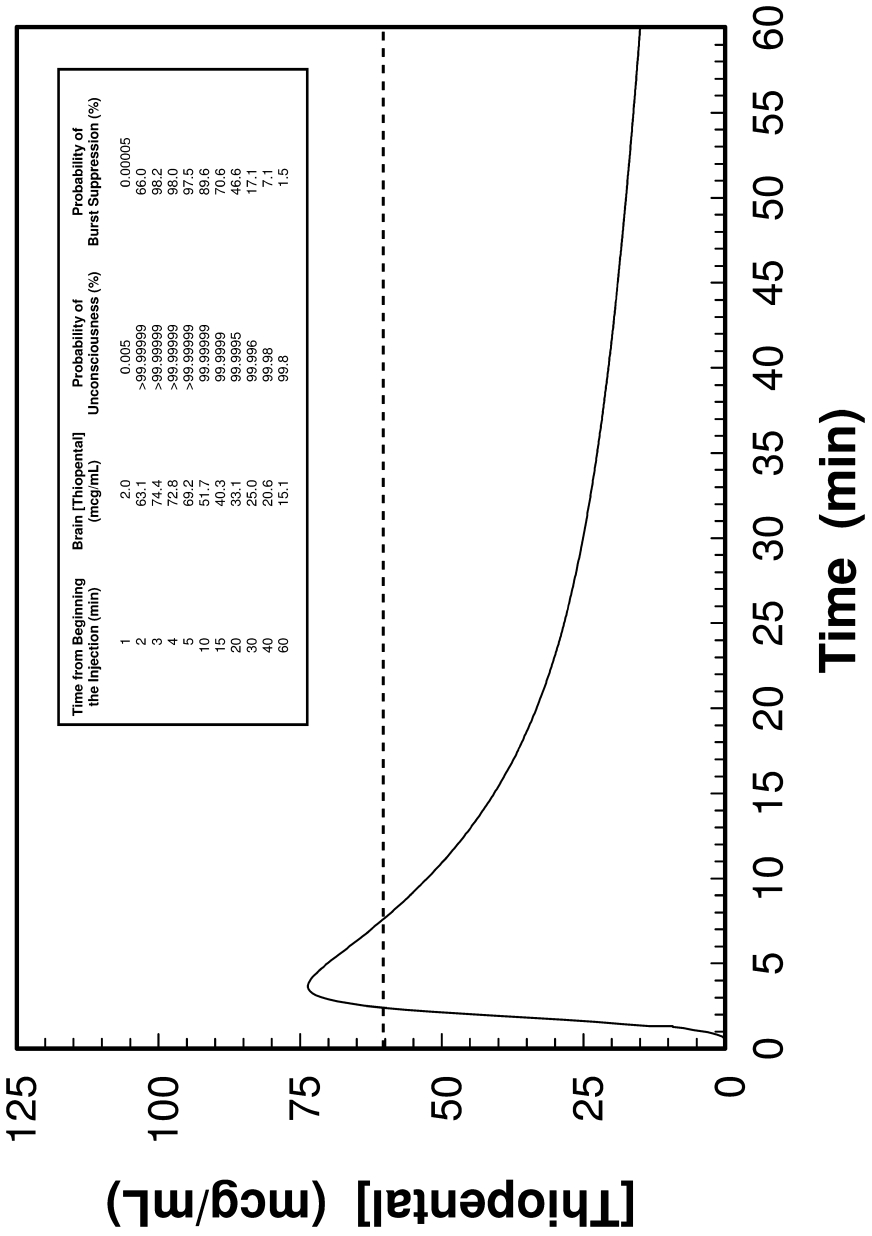


Figure 8: The predicted brain concentration of thiopental following the administration of a dose of 2000 mg given at a rate of 25 mg/sec to an average 80-kg person. The dashed line indicates the brain concentration above which 95% of persons will experience burst suppression on the EEG.[23]

23. *See id.*

Injection Rate (mg/sec)	Time to 95% probability of unconsciousness (min, normal C.O.)	Time to 95% probability of burst suppression (min, normal C.O.)	Time to 95% probability of unconsciousness (min, C.O. ↓ by 75%)	Time to 95% probability of burst suppression (min, C.O. ↓ by 75%)
25	1.6	2.6	2.3	3.1
50	1.4	2.1	2.0	2.7
167	1.1	1.5	1.8	2.2

These principles along with published data regarding the timing of drug onset can be used to construct models to simulate the onset of thiopental effect from any given dose or injection speed.[24] Figures 2 to 8 depict the onset of thiopental effect to the endpoints of unconsciousness and burst suppression for 2000 mg, 3000 mg, and 5000 mg doses at varying injection speeds. Since the onset of effect is rate-limited by blood circulation and diffusion, injection speed matters little. The table above shows the times required, from the beginning of the injection process, to reach a 95% probability of unconsciousness or burst suppression as a function of the injection rate for a 5000-mg dose. The standard solution of thiopental as used clinically is a 2.5% solution, or 25 mg/mL.[25] Therefore, injecting this solution at a rate of 1 mL/sec or 2 mL/sec yields injection rates of 25 mg/sec and 50 mg/sec, respectively. An injection rate of 167 mg/sec (6.7 mL/sec) is achieved by administering a 5000-mg dose over 30 seconds.

Since a 5000-mg dose of thiopental is expected to produce a substantial decrease in the cardiac output (C.O.),[26] the table also shows how the times to reach a 95% probability of unconsciousness or burst suppression are prolonged by a 75% decrease in cardiac output.

II. The Duration of Thiopental Following Various Doses

We shall now consider the *duration* of the effect of the thiopental once it has been administered. The duration of its action should exceed the amount of time required to administer the remaining

24. *See id.*
25. *See id.*
26. *See infra* notes 28-29 and accompanying text. R

medications as well as the time required for the potassium chloride to stop the inmate's heart and to cause his or her death.

The amount of time required to administer all of the medications will depend on the doses specified by the protocol as well as the speed of the injection (i.e. how rapidly the executioner injects each syringe) as well as allowing some time to change syringes by removing one from the intravenous tubing and replacing it with the next one. The following hypothetical three-drug protocol involves using doses at the high end of those used by the various states:

- thiopental, 5000 mg (25 mg/mL, 200 mL)
- saline flush, 50 mL
- pancuronium, 100 mg (1 mg/mL, 100 mL)
- saline flush, 50 mL
- potassium chloride, 240 mEq (2 mEq/mL, 120 mL)
- saline flush, 50 mL

The largest commercially-available syringes used in medicine are 60 mL. The above protocol therefore requires eleven syringes. Assuming ten seconds for each syringe change, the total time to change syringes is 100 seconds. Considering the size of the syringes used (it becomes harder to push the plunger of a syringe as its diameter increases) and the length of the intravenous tubing required to go from the "injection room" to the "death chamber," it is difficult to inject such syringes at a rate greater than 2 mL/sec (or 50 mg/sec when the standard 2.5% solution is used). On the other hand, there is no reason to inject more slowly than 1 mL/sec, so the total volume of the drugs and flushes as listed above, 570 mL, should require no more than approximately eleven minutes to inject.

The potassium chloride should cause cessation of cardiac electrical activity within two minutes of its injection (although see below for a discussion on the effects of thiopental on cardiac output). Therefore, a time period of fifteen minutes should be more than enough to complete an execution, from the beginning of the injection of the thiopental until cessation of electrical activity. Some states mandate a period of time, e.g. five minutes, of continuous electrical inactivity on the electrocardiogram ("ECG"), but that additional time does not need to be considered here.[27]

27. North Carolina, for example, requires such a five-minute period of electrical inactivity prior to the pronouncement of death. *See* North Carolina Department of Correction, Execution Method, http://www.doc.state.nc.us/dop/deathpenalty/method.htm (last visited Apr. 15, 2008).

Figures 2 through 4 depict the predicted concentration of thiopental in the brain following a dose of 5000 mg given at various rates of injection. Referring to Figures 2 to 4, it is apparent that fifteen minutes following the beginning of the thiopental injection, an average person will have essentially a 100% probability of being unconscious and having burst suppression on the EEG. These probabilities are not affected by the speed of the injection.

Figures 5 and 6 depict the predicted brain concentration of thiopental following a dose of 3000 mg given at a rate of 25 mg/sec (1 mL/sec) or 50 mg/sec (2 mL/sec). Fifteen minutes following the beginning of the thiopental injection, an average person will have essentially a 100% probability of being unconscious and about a 95% probability of having burst suppression on the EEG. These probabilities are not affected by the speed of the injection.

Figures 7 and 8 depict the predicted brain concentration of thiopental following a dose of 2000 mg given at a rate of 25 mg/sec (1 mL/sec) or 50 mg/sec (2 mL/sec). The 2000-mg dose of thiopental requires less time to inject than the 5000-mg dose (40 seconds vs. 100 seconds using an injection rate of 50 mg/sec). It will also have a lesser effect in decreasing cardiac output permitting the potassium chloride to circulate more quickly. With the 2000-mg dose, the time required to complete the injection and achieve cardiac arrest will be approximately 7 to 10 minutes with injection rates of 25-50 mg/sec and an additional two minutes to observe cardiac arrest on the ECG. At these time points, a person will have essentially a 100% probability of being unconscious, and a 90-95% probability of having burst suppression on the EEG.

III. Other Effects of Thiopental

The aforementioned predictions of duration of unconsciousness are based upon the persons continuing to breathe (or have their breathing assisted as during surgery). The doses of thiopental used in lethal injection will cause most persons to stop breathing and to have their blood pressures substantially decreased.[28] Thus, even in the absence of the administration of pancuronium and/or potassium chloride, doses of thiopental of 2000 mg and above will be lethal in most persons due to the impairment of delivery of oxygen to critical organs such as the heart and brain. The largest dose of thiopental used in clinical medicine, about 3000 mg, is occasionally used for "brain protection" when there is the planned and deliber-

28. *See generally*, Dershwitz & Rosow, *supra* note 6, at 853. R

ate interruption of blood flow to the brain.[29] Such an interruption of blood flow may occur during certain brain surgeries to repair an aneurysm or arteriovenous malformation. During such surgical procedures, patients are mechanically ventilated so that the effect of thiopental on ventilation is not relevant. However, a dose of 3000 mg of thiopental will decrease the cardiac output and the blood pressure to a dramatic, and dangerous, degree. Such patients require the aggressive administration of medications to maintain adequate blood pressure and oxygen delivery to organs. While neither of us, nor any other physician we know, has ever given a 3000-mg dose of thiopental to a patient who was not mechanically ventilated nor had his or her circulation supported, it is difficult for us to imagine that the administration of 3000 mg of thiopental to an inmate, by itself, is survivable.

We are unaware of any indication in clinical medicine in which a 5000-mg dose of thiopental is given to an 80-kg patient. The negative cardiac effects of such a huge dose of thiopental are necessarily larger than those following a 3000-mg dose. In fact, there is circumstantial evidence that a 5000-mg dose of thiopental may have caused, in some inmates, virtual cessation of the circulation. California is one of the states that uses a 5000-mg dose of thiopental as well as an ECG to monitor the electrical activity of the heart. There have been several executions in California in which a second dose of potassium chloride was given, as mandated by the protocol, because cessation of electrical activity on the ECG did not occur after the first dose.[30] One possible explanation is that the potassium chloride was not injected through a working intravenous catheter. Another more plausible explanation is that the potassium chloride did not circulate to the heart from the site of the intravenous injection.

IV. Assessing the Presence or Absence of Consciousness

As previously described, all of the lethal injection protocols that we have reviewed are intended to render the inmate unconscious prior to the administration of pancuronium and potassium chloride

29. *See* W.A. Kofke, *Protection of the Central Nervous System in Surgical Patients*, in ANESTHESIOLOGY, *supra* note 3, at 1939-40. R

30. For example, the execution log of Robert L. Massey, who was executed on March 27, 2001, indicates he was given a second dose of potassium chloride five minutes after the first dose failed to produce a flat ECG, and the execution log of Stephen Wayne Anderson who was executed on January 29, 2002, indicates he was given a second dose of potassium chloride four minutes after the first dose failed to produce a flat ECG.

and to maintain unconsciousness until death occurs.[31] The greatest risk to the inmate, in terms of the humaneness of an execution, is the administration of pancuronium and/or potassium chloride to an inmate who is conscious. Based upon the history of those executions that did not go as intended, the most frequent problem in such executions has been an intravenous catheter that was not actually within a vein.[32]

If the intravenous catheter was not positioned correctly from the beginning, all of the medications will be delivered to the subcutaneous tissues and the inmate will not lose consciousness as rapidly as expected. A less plausible, but still possible, scenario is one in which the thiopental is delivered subcutaneously but then the intravenous catheter begins functioning properly and the remaining medications are delivered intravenously. In such a scenario, the inmate could be conscious and experience the paralytic effects of pancuronium and the pain associated with the injection of potassium chloride.

Such a risk could be lessened if the inmate were demonstrated to be unconscious following the administration of thiopental and before the administration of the pancuronium and potassium chloride. This sort of assessment is mandated by some protocols and makes use of either a physical examination or an EEG monitor.[33]

Assessing the *depth* of anesthesia is a complex examination requiring both significant training and experience, which is obligatory in clinicians who administer anesthesia. Assessing the *presence of unconsciousness*, in contrast, is something many paramedical personnel do routinely. Such an examination typically involves the application of graded stimuli and the assessment of the response to:

- a spoken command (e.g. "open your eyes")
- a tactile reflex (e.g. gently stroking an eyelash)
- gentle shaking
- a noxious stimulus (e.g. a strong pinch)

31. *See supra* note 2 and accompanying text. **R**

32. The executions of Joseph Clark on May 2, 2006, in Ohio and of Angel Diaz on December 13, 2006, in Florida were characterized by prolonged periods following the administration of thiopental during which the inmates did not lose consciousness as would have been expected had the medication been introduced intravenously.

33. For example, the protocols used by Missouri and the federal government include an assessment of consciousness by physical examination. The protocol used by North Carolina employs a type of EEG monitor. *See, e.g.*, Connor v. N.C. Council of State, Nos. 07-GOV-0238, 07-GOV-0264 (N.C.O.A.H. Aug. 9, 2007) (describing North Carolina's lethal injection protocol).

The lack of any response to these graded stimuli is strong evidence that a person is indeed unconscious.

One state, North Carolina, uses the bispectral index ("BIS") monitor in its lethal injection protocol.[34] This is a type of EEG monitor commonly used by anesthesiologists to assess the depth of anesthesia and decrease the incidence of intraoperative awareness.[35] It involves placing an electrode array on the forehead and connecting these electrodes to the monitor. Although the monitor displays much neurophysiological information, the parameter of greatest interest is the bispectral index, or BIS. This is a dimensionless number that ranges from zero to 100.[36] Zero corresponds to complete electrical inactivity of the EEG (i.e. "flatline") while 100 corresponds to the completely awake state.[37] Many clinical studies have shown that a BIS value of 40-60 is associated with a clinically appropriate depth of anesthesia and a very low probability of intraoperative awareness.[38]

North Carolina has utilized the BIS monitor in several executions. The monitor is viewed by a nurse. The executioner pauses after the administration of thiopental (3000 mg in this state) and awaits a signal from the nurse before giving the pancuronium and potassium chloride. In each execution in which it has been used, the BIS value was 0-10 *before* the thiopental administration was complete.

V. Postmortem Determination of Thiopental

Some states routinely perform autopsies on executed inmates and such autopsies may include drawing blood for the measurement of the thiopental concentration.[39] Unfortunately, in far too many of these autopsies the blood samples have been improperly

34. *See id.*; Brown v. Beck, 2006 U.S. Dist. LEXIS 60084, at *4 (E.D.N.C. Apr. 7, 2006).

35. *See* Paul S. Myles et al., *Bispectral Index Monitoring to Prevent Awareness During Anaesthesia: The B-Aware Randomised Controlled Trial*, 363 Lancet 1757, 1757 (2004); Y. Punjasawadwong et al., *Bispectral Index for Improving Anaesthetic Delivery and Postoperative Recovery*, 1 The Cochrane Library 1, 2 (2008) (reprinted by The Cochrane Collaboration).

36. *See* Lee A. Kearse et al., *Bispectral Analysis of the Electroencephalogram Predicts Conscious Processing of Information During Propofol Sedation and Hypnosis*, 88 Anesthesiology 25, 25-34 (1998).

37. *Id.*

38. *See* Myles et al., *supra* note 35, at 1757, 1763; Punjasawadwong et al., *supra* note 35, at 6. R R

39. Leonidas G. Koniaris et al., *Inadequate Anaesthesia in Lethal Injection for Execution*, 365 Lancet 1412, 1412-14 (2005).

obtained and the results have therefore been erroneously interpreted.

Thiopental undergoes postmortem redistribution. This means that the blood concentration of thiopental continues to decrease even after the inmate's death and the cessation of circulation.[40] There is unfortunately very little information on the postmortem kinetics of thiopental because historically thiopental has been of little importance to forensic toxicologists. There are no peer-reviewed papers in the medical literature that have evaluated the postmortem redistribution of thiopental. Medical examiners in several jurisdictions have drawn paired blood samples following executions in order to assess the presence and degree of postmortem redistribution.[41] The first blood sample was obtained soon after the execution, while the second blood sample was obtained hours later at the time of autopsy. We are aware of the following sets of paired blood samples that demonstrate that postmortem redistribution of thiopental does indeed occur:

Jurisdiction	Inmate	Date	[Thiopental] mcg/mL Obtained soon after death	[Thiopental] mcg/mL Obtained at autopsy
CT	Ross	5/13/05	29.6	9.7
NC	McHone	11/11/05	21	1.5
NC	Syriani	11/18/05	12	4.4
NC	Boyd	12/2/05	29	11
NC	Simpson	1/20/06	42	12
MT	Dawson	8/11/06	21	3

In each case, "soon" after death means that the blood sample was drawn within an hour of completing the execution. Autopsies were performed at various times following the executions, ranging from about seven to eighteen hours.

Some persons have argued that this table represents nothing more than a group of random numbers.[42] There are indeed *pooled* data that are purported to demonstrate no time-dependent de-

40. *See* A.L. Pélissier-Alicot et al., *Mechanisms Underlying Postmortem Redistribution of Drugs: A Review*, 27 J. ANAL. TOXICOL. 533, 533-44 (2003).

41. Such postmortem analyses have been performed following executions in Connecticut, Montana, and North Carolina.

42. *See generally* Susi Vassallo, *Thiopental In Lethal Injection*, 35 FORDHAM URB. L.J. 957 (2008); Teresa A. Zimmers & Leonidas Koniaris, *Peer-reviewed Studies Iden-*

crease in the thiopental concentration in blood following death.[43] The table above is, however, the only example of *paired* data in which blood samples were drawn from the *same* inmate at *different* times following death. Applying Student's t-test for paired data to the data in the above table yields a *p* value of 0.0013. The interpretation of this statistical result is that there is a 99.9987% probability of a significant *decrease* in the blood thiopental concentration as a function of time following death by lethal injection where death closely follows a single rapid infusion of the drug and pseudoequilibrium with the majority of the body's tissues did not have time to be completed.[44] These data confirm the process of postmortem redistribution and would suggest that a rise in blood thiopental concentrations would be seen if similar paired postmortem samples were obtained when death occurred much longer after a dose of thiopental (as might occur in a clinical situation) at a time well after pseudoequilibrium between blood and tissue drug concentrations when the concentration gradient would be expected to be reversed.

In addition to the process of postmortem redistribution, another possible source of misleading postmortem thiopental data is the difference in the concentration of thiopental in arteries and veins. Pathologists most commonly draw postmortem blood samples from the femoral vein in the groin. Located immediately next to the femoral vein is the femoral artery. During life, it is usually easy to locate the femoral artery because it is typically the strongest peripheral pulse in the body. Following death, this landmark is lost. Since the femoral vein has a greater diameter, when a needle is inserted blindly in the groin, the femoral vein is more likely to be entered. However, Figure 9 shows that there may be substantial and clinically meaningful differences between the arterial and venous concentrations of thiopental. Assuming a normal cardiac output, differences between the arterial and venous concentrations of thiopental are expected for approximately four minutes following the beginning of thiopental administration. In contrast, if thiopental were to cause a large decrease in cardiac output (as is expected with the large doses used in lethal injection protocols), the differ-

tifying Problems in the Design and Implementation of Lethal Injection for Execution, 35 FORDHAM URB. L.J. 919 (2008).

43. *See* Koniaris et al., *supra* note 39, at 1412-14; Teresa A. Zimmers et al., *Authors' Reply*, *Inadequate Anaesthesia in Lethal Injection for Execution*, 366 LANCET 1073, 1074-76 (2005). R

44. *See* Stanton Glantz, PRIMER OF BIOSTATISTICS 322-25 (McGraw-Hill, 6th ed. 2005).

ence in the arterial and venous concentrations will persist until well after the expected occurrence of death.

The accurate differentiation between the femoral artery (lacking a pulse) and the femoral vein following death requires dissection and visualization of both vessels. Many medical examiners are unwilling to perform such a procedure at a prison on an inmate who has just been executed. Were a state to decide that the acquisition of a blood sample from a known blood vessel is a prudent idea, they might consider hiring a funeral director to perform the procedure. Since the process of embalming involves dissection and visualization of arteries and veins so that the embalming fluid can be injected, funeral directors should readily be able to obtain accurately femoral arterial and femoral venous blood for analysis.

We believe that there should be as much transparency as possible in the lethal injection procedure. Therefore, we support the practice of obtaining postmortem blood samples for thiopental analysis as a routine procedure. It is, however, crucial to obtain the blood sample properly and that means drawing it soon after the inmate's death, preferably within a few minutes and definitely within an hour.

VI. CONCLUSIONS

In summary, our pharmacokinetic and pharmacodynamic predictions of the effects of thiopental as used in the lethal injection protocols we have reviewed suggest that these protocols, if implemented as written, will result in the rapid death of the inmate without undue pain or suffering.

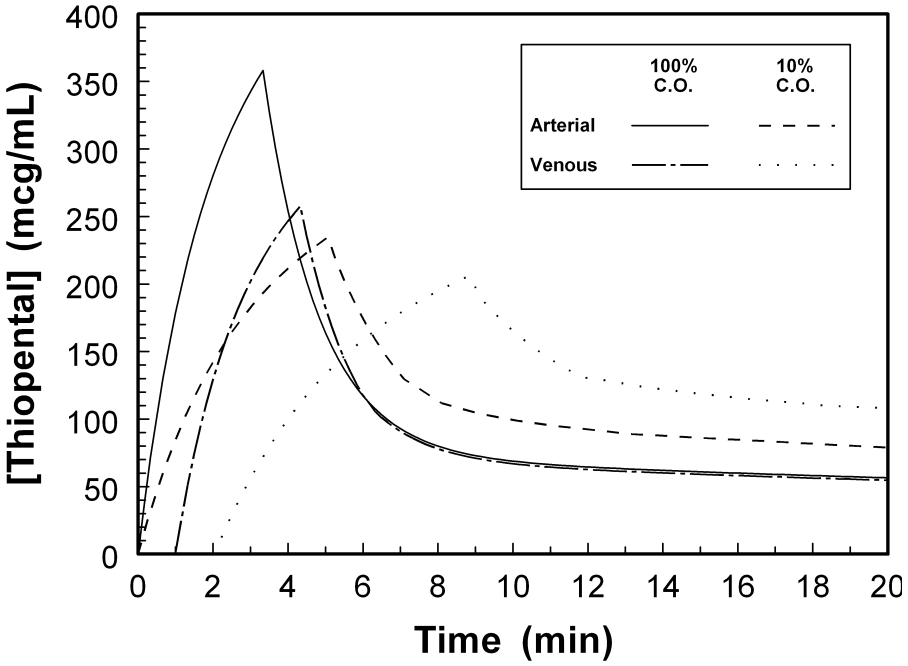


Figure 9: The effect of thiopental-induced decrease in cardiac output on the time course of the arterial and venous concentrations of thiopental. The predicted arterial blood concentration of thiopental following the administration of a dose of 5000 mg given at a rate of 1 mL/sec to an average 80-kg person is depicted by the solid line. The simultaneous venous blood concentration is depicted by (— - —). The two other lines assume a 90% decrement in cardiac output caused by thiopental. The dashed line depicts the predicted arterial concentration, while the dotted line depicts the predicted venous concentration.[45]

Implementing a protocol as written means the correct doses of the correct medications are administered in the correct order into a properly functioning intravenous delivery system and allowing sufficient time for thiopental to produce its effect.

We previously discussed that the cardiovascular and respiratory effects of thiopental given by itself in doses of 2000 mg and above are likely to be lethal in virtually everyone. Much has been written and said about adopting lethal injection protocols that rely on a single drug alone such as thiopental. As clinical pharmacologists, we can describe the advantages and disadvantages in comparing the current three-drug protocol with a protocol consisting of thio-

45. The pharmacokinetic model for thiopental used in Figure 9 is in T.D. Homer & D.R. Stanski, *The Effect of Increasing Age on Thiopental Disposition and Anesthetic Requirement*, 62 ANESTHESIOLOGY 714, 714-24 (1985). Some of the cardiovascular modeling was performed using the program A-ware, Springer Electronic Media.

pental as the only medication. We cannot, however, state which option is "better" because in this context "better" is based not upon pharmacological considerations but is actually a public policy decision best made by well-informed policy makers.

Some persons have contended that a large dose of thiopental given by itself does not reliably produce death.[46] In the Netherlands, where euthanasia and physician-assisted suicide are both legal, the Royal Dutch Society for the Advancement of Pharmacy wrote, "For intravenous administration, thiopental receives most consideration. It is not possible to administer so much of it that a lethal effect is guaranteed, but the substance is quite suitable for producing coma, after which termination may be effected using a muscle relaxant."[47] In the same article, the thiopental dose to be used was stated as, "intravenous administration of 1 g thiopental sodium, if necessary, 1.5-2 g of the product in case of strong tolerance to barbiturates."[48] Apparently the largest dose of thiopental used in the Netherlands was only 2 g (or 2000 mg) and it is therefore not surprising that such a dose was found to be less than 100% lethal.

The primary advantage of the three-drug protocol is that there is a definite and rapid end-point to the protocol and that is the onset of a flat-line ECG that can be assessed remotely by viewing an ECG monitor. The primary disadvantage is that there is the risk that the inmate could experience pain and suffering if the dose of thiopental is not properly administered for whatever reason and the pancuronium and potassium chloride are then administered to a conscious person. Another disadvantage to the three-drug protocol is that the potassium chloride, in addition to its action in stopping the heart, also causes widespread stimulation of nerve and muscle tissue throughout the body. Such stimulation is often manifested as involuntary muscle contractions that may have in the past been misperceived by lay witnesses as consistent with pain or suffering, or experiencing a seizure. In fact, it is most unlikely that someone given a large dose of thiopental, an excellent anticonvulsant medication, could suffer a seizure. One action of the pancuronium is to mitigate these involuntary muscle contractions.

46. Teresa A. Zimmers et al., *Lethal Injection for Execution: Chemical Asphyxiation?* 4(4) PLoS Medicine 646, 646-47 (2007).

47. For an English translation of the article, see *Administration and Compounding of Euthanasic Agents*, The Hague (Royal Dutch Society for the Advancement of Pharmacy 1994), *available at* http://wweek.com/html/euthanasics.html.

48. *Id.*

The primary advantage of a protocol in which a large dose of thiopental is given by itself is that there is no risk whatsoever of the inmate experiencing pain or suffering due to the effects of pancuronium or potassium chloride. If the intravenous catheter were to malfunction and the thiopental were deposited next to, instead of inside of, the vein, the inmate might experience some pain at the injection site but in fact this is a potential risk to which any patient given thiopental for anesthesia is subjected. The primary disadvantage of this single-drug protocol is that, although the inmate will likely die within a few minutes, his death will not be immediately reflected on the ECG monitor. In fact, following a large dose of thiopental that causes the inmate to stop breathing, experience a huge drop in blood pressure, and therefore a fatal decrease in oxygen delivery to critical tissues, it might very well take a half hour or longer for the ECG to become flat. In this case, it would be imprudent to wait for the ECG to become flat, and death would need to be ascertained by a physical examination that demonstrated the absence of a heartbeat or evidence of circulation. Whether this physical examination is performed by a physician or a paraprofessional credentialed to pronounce death (such as a nurse or a paramedic), either the person would be visible to the witnesses or the curtains in the death chamber would need to be drawn for the pronouncement of death to maintain this person's anonymity. Once again, we are unable to state, based upon pharmacological principles, which of these options is "better," however, we believe that those policy makers responsible for making such decisions are entitled to accurate scientific information in order to make an informed policy decision.