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Susi Vassallo
New York University School of Medicine

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THIOPENTAL IN LETHAL INJECTION

Susi Vassallo, M.D.*

I. INTRODUCTION

In the United States, the current protocols for execution by lethal injection call for the administration of the combination of three drugs: the anesthetic thiopental, a barbiturate;¹ the paralyzing agent, pancuronium bromide; and potassium chloride, the drug that interrupts electrical cardiac conduction. States differ in the doses and methods of administration; however, the most common dosing regimens call for the administration of a sequence of intravenous drugs by bolus administration; first, a single injection of two to five grams of thiopental; next, an injection of sixty milligrams of pancuronium bromide; finally, an injection of 240 milliequivalents of potassium chloride, or less, depending on the protocol.

An inmate must be unconscious in order to avoid the sensation of suffocation from paralysis caused by the second drug, or the pain caused by the intravenous infusion of concentrated potassium. A critical question in this regard is whether the dose and method of administration of thiopental is adequate to reliably render the inmate unconscious until death occurs.

On January 7, 2008, the United States Supreme Court heard oral arguments in Baze v. Rees.² One of the issues raised is whether the procedures in place are capable of adequately assuring successful administration of death to meet the constitutional standards of the Eighth Amendment. An important part of the argument rested on


². Baze v. Rees, No. 07-5439, 2008 WL 63222 (U.S. argued Jan. 7, 2008). Baze, a case brought by two Kentucky death row inmates, challenges the state's lethal injection protocol as well as questions what the appropriate standard should be for lower courts to apply to assess whether the Eighth Amendment's prohibition against cruel and unusual punishment has been violated.
the qualities and attributes of the anesthetic thiopental. Mr. Verrilli, counsel for the petitioner, conceded that if the dose of the anesthetic thiopental was "always" properly administered into the condemned inmate there would be no "risk." In other words, the inmate would not suffer the terror of suffocation or the pain of intravenous potassium chloride. Of course, he continued, there could be no guarantee and one could not assure successful administration of the thiopental unless proper monitoring was involved. Justice Scalia quickly pointed out that medical doctors cannot participate in executions according to the ethics guidelines of the American Medical Association, and therefore could not serve as monitors. At this point in the testimony, Mr. Verrilli put forth a highly contentious assertion that thiopental alone was an alternative method of lethal injection:

Well, Your Honor, of course, that's why there is another practical alternative here, which solves that problem, which is the single dose of barbiturate, which does not require the participation of a medically trained professional. . . . Thiopental is a barbiturate and by definition will inflict death painlessly. The record in this case establishes—each expert, the Petitioner's expert and Respondents' expert, testified that it is guaranteed at the three gram dose to cause death.

Later, Chief Justice Roberts inquired, "that method has never been tried, correct?" Mr. Verrilli replied, "Well, it has never been tried on humans. That is correct." Interrupted at that point, it is left to speculation what Mr. Verrilli would have said had he been allowed to continue. Mr. Verrilli is correct that sodium thiopental is unstudied as a single killing agent for humans. It is also not the agent of choice in animal euthanasia. It is sodium pentobarbital that is most commonly used to euthanize animals.7

The proposal of a single drug protocol using thiopental as an effective new method of execution by lethal injection, and the basis on which that proposal is put forth, namely, Mr. Verrilli's invocation of the testimony of the medical experts on both sides of the arguments in Baze v. Rees, demands scrutiny. It is highly unlikely that the medical experts in Baze, Mark Dershwitz, M.D., testifying

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4. Id. at 6.
5. Id. at 6, 8.
6. Id. at 9.
for the state, and Mark Heath, M.D., testifying on behalf of the plaintiffs, intended to testify that thiopental would serve as an effective single killing agent or to establish thiopental as a new single dose lethal injection protocol. In multiple challenges to lethal injection at the state level, the overwhelming majority of expert testimony by Dr. Dershwitz and Dr. Heath concerned thiopental's ability to assure a state of unconsciousness of adequate duration and depth to last until cardiac arrest occurred, most likely from the potassium chloride. Thiopental is not the agent of death in the current lethal injection protocol. The amicus brief submitted by the American Society of Anesthesiologists states, "there is no dispute that a massive or supraclinical dose of thiopental (as those being considered by the courts), if effectively delivered into the circulation, will reliably produce prolonged and deep unconsciousness." Nowhere does the amicus brief address the lethality of thiopental alone. However, in the Netherlands where euthanasia is legal when certain conditions are met, the use of intravenous thiopental to induce death is addressed. In order to educate physicians and pharmacists regarding the requirements and recommendations for substances used in euthanasia, The Royal Dutch Society for the Advancement of Pharmacy designated a task force which issued the "Report on Euthanasic Agents" in 1987. The report, updated in 1994, concluded that it is not possible to administer enough thiopental intravenously to guarantee a lethal effect.

Studies of thiopental have never been performed using the same dosing or administration regimens as are followed in the current lethal injection protocols. Nonetheless, this Article addresses whether there is adequate scientific evidence on which to base a new single drug protocol using thiopental alone as was recommended to the Supreme Court as a "practical alternative" to the current three-drug protocol.

8. The exact cause of death has been questioned in some executions. See Teresa A. Zimmers, Lethal Injection for Execution: Chemical Asphyxiation?, 4 PUB. LIBRARY SCI. MED. e156, 0647 (2007) (noting that the addition of potassium chloride to a lethal injection protocol in North Carolina was not associated with a statistically significant increase in the speed of death).


II. DIFFICULTIES INVOLVED WITH USING SCIENTIFIC DATA DERIVED FROM THIOPENTAL STUDIES

This Part reviews general studies of thiopental and highlights the limitations of these studies as they relate to lethal injection.

A first issue in the analysis of the scientific literature on the use of thiopental is the method of administration of thiopental. The pharmacodynamic effect\textsuperscript{14} of thiopental varies with the method of administration, either by a single intravenous bolus\textsuperscript{15} (such as is the case in lethal injection in almost all states) or by continuous intravenous infusion. Dr. A. Jay Chapman, chief medical examiner for the state of Oklahoma, recognized this variance when he suggested a continuous infusion of thiopental as one of his recommendations for the first lethal injection protocol for the state of Oklahoma.\textsuperscript{16} If the published studies on thiopental rely on a different means of administration than lethal injection protocols, then it is difficult and/or inappropriate to draw predictions from these studies to the lethal injection context.

Secondly, the total dose of thiopental used\textsuperscript{17} in published studies should be comparable to the doses used in lethal injection. Most studies using thiopental administer smaller amounts of thiopental than those doses used in lethal injection.\textsuperscript{18} Even in studies, however, where the total dose of thiopental administered appears comparable to the total dose administered during lethal injection, the method of administration differed. Administration of thiopental in

\textsuperscript{14} The term "pharmacodynamic" refers to the effects of the drug in the body.

\textsuperscript{15} A bolus injection is a single push on the plunger of the syringe so the drug is delivered over seconds. For example, if 5 grams of thiopental is put into a 60 milliliter (ml) syringe and can be delivered at 2 ml per second, it will take 30 seconds to deliver the drug if there are no difficulties such as resistance to flow in the intravenous line.


\textsuperscript{17} The total dose of thiopental is best expressed as the number of milligrams of thiopental per kilograms of body weight of the subject, or "mg/kg."

\textsuperscript{18} The doses of thiopental used in lethal injection protocols range from 2 to 5 grams. The dose is not based on a milligram per kilogram body weight basis. Depending on the size of the inmate and the protocol, the dose ranges from 6.6 to 75 mg/kg. See Zimmers, supra note 8, at 0649. In comparison, clinical induction doses ranging from 2-15 mg/kg are described in the article by Toner. W. Toner et al., *Another Look at Acute Tolerance to Thiopentone*, 52 BRIT. J. ANAESTHESIA 1005 (1980) (citing John W. Dundee, Henry L. Price & Robert D. Dripps, *Acute Tolerance to Thiopentone in Man*, 28 BRIT. J. ANAESTHESIA 344 (1956)). Brodie infused from 43-67 mg/kg thiopental in four subjects, but did so over time. See Bernard B. Brodie et al., *Acute Tolerance to Thiopentone*, 102 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 215, 215 (1951) [hereinafter Brodie et al., *Acute Tolerance*]. This stands in contrast to the rapid bolus injection frequently used during lethal injection.
these studies is usually by continuous intravenous infusion or by repeated bolus injection over some extended period of time, and not by a single intravenous bolus as is used in the lethal injection context. Thus, as stated above, although the dose of thiopental may appear comparable between these clinical studies and common lethal injection protocols, the pharmacodynamics are likely to differ because of the differences in the means of administering thiopental. Therefore, the conclusions of such studies do not apply in lethal injection.

A third issue facing comparisons between studies of thiopental and lethal injection protocols is that thiopental concentrations are not directly measured in the brain. Instead, thiopental concentrations are measured in an easily obtainable tissue such as blood, plasma, or fat. Subsequently, mathematical derivations are applied to estimate the brain thiopental concentration. The shortcoming of this approach is that the concentration of thiopental in one tissue source does not necessarily reflect the other, and may not reflect the clinical condition of the individual.

In other words, the plasma or blood concentration of thiopental does not necessarily reflect the level of sedation in the brain. To summarize, thiopental drug concentrations obtained from different sites, such as plasma, do not reflect the physiological consequences at the site of interest, such as the brain.

19. Plasma is the liquid portion of blood after centrifugation removes the blood cells.
20. Debra A. Schwinn & Steven L. Shafer, Basic Principles of Pharmacology Related to Anesthesia, in Miller's Anesthesia, supra note 1, at 67
21. Bernard B. Brodie et al., The Fate of Thiopental in Man and a Method for Its Estimation in Biological Material, 1 J. Pharmacology & Experimental Therapeutics 85, 93-94 (1950) [hereinafter Brodie, Fate of Thiopental] (noting that in canine subjects, significant portions of thiopental administered intravenously is stored in fat, and indicating that to “what extent [thiopental] content of each tissue depends on the proportion of fat is now under study”).
22. See Dundee, Price & Dripps, supra note 18, at 350 (“These observations show that there is a wide variation in the blood [thiopental] levels at which normal patients awake from the doses of the drug used in clinical anaesthesia. The blood [thiopental] level thus is not a reliable guide to the depth of anaesthesia.”); Brodie et al., Acute Tolerance, supra note 18, at 216 (noting a statistically significant difference in the plasma levels of thiopental at the time of recovery of normal patients and suggesting that tolerance to thiopental might account for this variation).
23. Thomas K. Henthorn, Michael J. Avram & Tom C. Krejcie, Intravascular Mixing and Drug Distribution: The Concurrent Disposition of Thiopental and Indocyanine Green, 45 Clinical Pharmacology & Therapeutics 56, 62 (1989) (noting that kinetic models of distribution of thiopental indicate multiple physiological compartments with varied kinetic features and that the equilibration of thiopental between these compartments and the blood is not clearly equivalent).
Finally, there are studies of thiopental that apply pharmacokinetic-pharmacodynamic parameters and combine infusion quantal\textsuperscript{24} dose-response data.\textsuperscript{25} In some studies, these models are used to predict a clinical endpoint such as loss of consciousness. The ability to accurately predict thiopental dose-response relationships (the loss of consciousness at a certain dose of thiopental) through computer modeling demands many values for thiopental doses derived from average populations of young healthy men. Average population-based values for pharmacokinetic parameters, drug administration rate, and derived rate constants quantifying concentrations in various tissue compartments, may not reflect the physiology of an individual inmate.\textsuperscript{26} The data used to estimate these population-based parameters derive largely from studies in healthy men devoid of premedication with benzodiazepines or opiates in the acute prestudy period.\textsuperscript{27} Use of other centrally-acting drugs excluded these men from the study.\textsuperscript{28} Age, cardiac output, body weight, or lean body mass, were all-important determinants of thiopental dose requirements in one such study.\textsuperscript{29} In dogs, obesity affected model predictions of plasma thiopental concentrations.\textsuperscript{30} In another study, the observed effective dose of thiopental needed to achieve the chosen end-point, of loss of consciousness, increased significantly with increasing infusion rates.\textsuperscript{31} There was a thirteen percent error in the predictions based on one model at the higher infusion rates.\textsuperscript{32} As stated in a recent paper, physiologically-based models, while useful in explaining some factors of thiopental disposition using model simulation, are too com-

\textsuperscript{24} Quantal: the plural of quantus, Latin for “how many”, signifies two experimental alternatives i.e. response or no response.

\textsuperscript{25} See Colin A. Shanks, A Pharmacokinetic-Pharmacodynamic Model for Quantal Responses with Thiopental, 21 J. PHARMACOKIN. BIOPHARMACEUT. 309 (1993).

\textsuperscript{26} W. Brooks Gentry et al., Effect of Infusion Rate on Thiopental Dose-Response Relationships, 81 ANESTHESIOLOGY 316 (1994).

\textsuperscript{27} Michael J. Avram et al., Determinants of Thiopental Induction Dose Requirements, 76 ANESTHESIOLOGY & ANALGESIA 10, 10-11 (1993); Gentry et al., supra note 26, at 317 (“Patients chronically using central nervous system active drugs . . . were excluded from the study as were patients receiving either benzodiazepines or opiates acutely . . . .”).

\textsuperscript{28} Id.

\textsuperscript{29} Avram et al., supra note 27, at 11.

\textsuperscript{30} Michael Weiss, Tom C. Krejcie & Michael J. Avram, A Minimal Physiological Model of Thiopental Distribution Kinetics Based on a Multiple Indicator Approach, 35 DRUG METABOLISM & DISPOSITION 1525 (2007).

\textsuperscript{31} Gentry et al., supra note 26, at 319.

\textsuperscript{32} Id.
plex to be applied to plasma concentration-time data. Currently, the shortcomings of modeling studies limit their utility in understanding thiopental in execution by lethal injection. New modeling methods continue to be developed to further define the action of thiopental in the clinical setting.

A. Continuous Infusion Studies of Thiopental

Many studies of thiopental are performed by administering thiopental by short continuous infusion or by repeated boluses over time. Short continuous infusion of thiopental results in a model that does not mimic the single bolus injection of thiopental in lethal injection protocols. Models, studies, and clinical scenarios where repeated bolus injections are given, or short or continuous infusions are administered, do not equate to the situation in lethal injection where a single bolus injection is administered. For example, the long continuous infusions used to maintain coma in brain-injured patients for many hours to days, and the attendant large doses of thiopental, result in steady state conditions. This situation has no relationship to the single bolus injection used during execution.

In one continuous infusion study in humans using doses of thiopental comparable to the total doses used in lethal injection, doses of 2.3 grams were administered intravenously over 25 minutes.

33. See Weiss, Krejcie & Avram, supra note 30.
34. Id.
35. Hélène Russo & Françoise Bressolle, Pharmacodynamics and Pharmacokinetics of Thiopental 35 Clinical Pharmacokinetics 95, 107 (1998) (describing the differences on dosage requirements as a function of infusion rate).
39. See Brodie et al., Acute Tolerance, supra note 18, at 215.
Larger doses of 3.9 grams were administered over 50 minutes. In the study, four male study subjects received 3.3 to 3.9 grams, or 43 to 67 mg/kg, of thiopental by continuous infusion. Anesthesia, defined by the “conjunctival reflex and eyeball motion,” lasted from four to five hours. Awakening, arbitrarily defined as the ability of the study subject to stick out his tongue, occurred at plasma concentrations of 16.8 to 32.6 mg/L. Interestingly, as the dose of thiopental increased, the plasma concentration of thiopental at awakening was increased, such that the blood concentrations of thiopental at awakening were sixty-seven percent higher following the high doses of thiopental than after the small doses. In their discussion, the authors concluded that the central nervous system’s response to thiopental may have depended on the initial peak concentration, or the length of time thiopental persisted in the brain. The authors called this “acute tolerance”, and they offered several possible explanations, including increased drug metabolism, or altered permeability of the blood-brain barrier to the drug. The most likely mechanism, according to the authors, was some sort of tissue adaptation refractory to the depressant effects of thiopental in the brain. Other authors concluded that acute tolerance is present but some have questioned its origins; one hypothesized that acute tolerance may simply reflect the differences in thiopental concentrations measured at different sampling sites, i.e. the peripheral blood vessel versus a more central blood vessel such as the jugular vein, bringing blood directly from the brain back to the heart.

The authors writing about acute tolerance shared the conclusions that plasma thiopental levels serve as a poor indicator of depth of

40. Id.
41. Id.
42. Id.
43. Id.
44. Id. at 216.
45. Id. at 217.
46. Id.
47. The blood-brain barrier is a collection of cells tightly formed around the brain blood vessels that forms an interface between the blood and the brain, limiting the passage of molecules with certain physiochemical characteristics.
48. See Brodie et al., Acute Tolerance, supra note 18, at 217-18.
50. See Dundee, Price & Dripps, supra note 18, at 47 (noting that differences in thiopental concentrations are not different between the brachial artery and the jugular vein, but that there might be some difference between arterial and venous blood in more distal sites, such as the forearm); Toner et al., supra note 18, at 1005.
anesthesia, and isolated plasma thiopental levels are meaningless.\textsuperscript{51} This is important in the lethal injection debate for two reasons; first, post-mortem studies using peripheral plasma measurements as a means of establishing level of consciousness at the time of death are meaningless; second, the literature is replete with studies demonstrating that plasma thiopental levels do not correlate with level of consciousness.\textsuperscript{52}

\textbf{B. Estimating Brain Thiopental Concentrations and Sedation}

Many studies of thiopental used limited tissue samples such as blood or plasma to create a hypothetical mathematical model to predict the duration and depth of sedation. In the classic article by Price, six patients were studied preoperatively.\textsuperscript{53} One or two doses of 50-100 mg thiopental were administered for anesthesia for the placement of catheters into the carotid artery and jugular vein.\textsuperscript{54} A single injection of 150-350 mg of intravenous thiopental was then administered.\textsuperscript{55} A thiopental brain concentration was estimated by simultaneously measuring the flow rate of blood and the difference between the concentration of thiopental in blood going into the brain (the carotid artery) and the concentration of thiopental in blood coming from the brain (jugular vein).\textsuperscript{56} Based on calculations, the brain showed rapid uptake of thiopental such that the peak brain concentrations occurred less than one minute after the end of the intravenous injection.\textsuperscript{57} After the first minute, however, the brain concentration of thiopental began to decline and the calculated brain concentrations decreased.\textsuperscript{58} At the end of five minutes, only approximately forty percent of the total intravenous


\textsuperscript{53} Henry L. Price et al., \textit{The Uptake of Thiopental by Body Tissues and Its Relation to the Duration of Narcosis} 1 \textit{Clinical Pharmacology & Therapeutics} 16 (1960).

\textsuperscript{54} \textit{Id.} at 17. The carotid artery is the major artery bringing blood from the heart to the brain. The jugular vein is the major vein draining the brain of blood and carrying the blood back to the heart.

\textsuperscript{55} \textit{Id.}

\textsuperscript{56} \textit{Id.} at 19-20.

\textsuperscript{57} \textit{Id.} at 21 fig.3. This figure represents the calculated thiopental concentrations based on kinetic data that the authors had obtained empirically. In the figure, the central nervous system was included with other tissues in this figure and labeled "viscera."

\textsuperscript{58} See \textit{id.}
dose of thiopental remained in the brain according to the calcula-
tions.\textsuperscript{59} The authors concluded that this decrease in brain thiope-
tal represented the rapid redistribution of thiopental from the
brain to other different body tissues, primarily the muscle and later
on, fat.\textsuperscript{60} The calculated concentration values for various tissues
were compared with actual measurements of thiopental concentra-
tions from fat and muscle taken during surgical procedures.\textsuperscript{61} The
measured decrease in brain thiopental concentration in human pa-
tients mirrored the calculated results: the concentration of thiopen-
tal in the brain dropping from approximately fourteen percent of
the total dose at one minute after infusion to approximately one
percent after one hour. Therefore, the duration of sedation from
thiopental after a single intravenous injection was limited by the
distribution of thiopental out of the brain to lean body tissues.
There are models of the distribution and elimination of thiopental
using a compartmental system where body tissues are grouped
based on similar characteristics of blood perfusion and drug
solubility.\textsuperscript{62}

\section{C. Physiologic and Pharmacodynamic Models}

Further studies on thiopental are mathematical models never
validated on animals or humans. In the article by Price discussed
in the section above, the textbook figures\textsuperscript{63} showing distribution of
thiopental in body tissues over time is based on a mathematical
equation and physiological assumptions. It uses data from a single
dose and applies a mathematical equation to predict the percent of
dose in the tissues at various times after administration.\textsuperscript{64}

In another example of mathematical modeling, Dr. Mark
Dershwitz has constructed several graphs to demonstrate hypothet-
cal concentrations of thiopental in the blood at various times after
thiopental administration. In expert testimony, Dr. Dershwitz uses
blood thiopental levels to predict the probability of conscious-

\textsuperscript{59} See id.
\textsuperscript{60} Id. at 21.
\textsuperscript{61} Id.
\textsuperscript{62} See Henthorn, Avram & Krejcie, supra note 23; Russo & Bressolle, supra note 35.
\textsuperscript{63} Robert J. Fragen & Michael J. Avram, \textit{Barbiturates, in Miller's Anesthesia},
211-15 figs 8-4, 8-8 (Ronald D. Miller ed. 5th ed. 2000)
\textsuperscript{64} See Price et al., supra note 53; Henry L. Price, \textit{A Dynamic Concept of the
ness. The graphs assume a steady state infusion of thiopental and have not been validated in living subjects. The pitfalls of using thiopental blood concentrations to predict level of consciousness have been addressed in multiple scientific articles. Despite the lack of validation by peer review, or demonstration of the appropriateness of generalization of the data to the situation in lethal injection, these graphs have repeatedly been introduced into court during legal arguments concerning lethal injection.

III. CONCLUSION

As a whole, these studies suggest that brain concentrations of thiopental peak early after intravenous administration, and, even in the setting of a continuous infusion, have unpredictable effects on depth and duration of sedation. Although it may be that thiopental must induce and maintain unconsciousness for the duration of the process execution by lethal injection, there is no scientific study to that effect. The mathematical modeling and lack of validation studies in living subjects further limit the interpretation of the data. Finally, none of these studies addresses lethality.

The current lethal injection protocol as created by Dr. A. Jay Chapman years ago, was accepted without scientific review. Today, recommendations for new strategies for lethal injection continue. A future “improved” method of lethal injection—using thiopental alone, no longer requiring the participation of medically trained professionals, and monitoring the depth of anesthesia using the bispectral index, is an illusion. In a recent article, monitoring of awareness during anesthesia using the bispectral index did not reduce the frequency of intraoperative awareness. An accompanying editorial commentary is relevant to the subject at hand. In it, the authors warned against the adoption of new devices and interventions without peer-reviewed data, and advised

65. Declaration of Dr. Mark Dershwitz, M.D., Ph.D., ¶¶ 4-14, Beardslee v. Woodford, No. 5:04CV05381, 2004 WL 5537989 (N.D. Cal 2005); Affidavit of Dr. Mark Dershwitz, M.D., Ph.D., ¶¶ 4-14, Johnston v. Crawford, No. 4:04cv1075, 2005 WL 1474022 (E.D. Mo. 2005); Affidavit of Mark Dershwitz, M.D., Ph.D., ¶¶ 4-15, Perkins v. Beck, No. 5:04-CT-643-BO, 2004 WL 5003233 (N.D. Cal. 2004).

66. See supra notes 50-54 and accompanying text.

67. See supra notes 55-61 and accompanying text.

68. See Denno, Lethal Injection Quandary, supra note 16, at 66-70; Denno, When Legislatures Delegate, supra note 36, at 90-120.

69. A bispectral index is a computerized monitor of brain function.

that strategies that "intuitively appear to be valuable fail to perform as predicted."\textsuperscript{71}

The history of the development of the three-drug lethal injection protocol, the problems associated with its administration today, as well as the characteristics of thiopental, should serve to caution against the acceptance of a new lethal injection protocol relying on thiopental alone.