

THE ICARUS EFFECT: THE INFLUENCE OF DILUENT WARMING ON DANTROLENE SODIUM MIXING TIME

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Prompt administration of intravenous (IV) dantrolene sodium (DS) is the primary determinant of successful treatment of malignant hyperthermia (MH) syndrome. Because DS has a long reconstitution time for use in treating an MH crisis, we evaluated an alternative technique for hastening the reconstitution.

Simulating real-world conditions, with equipment common to the operating room environment, we conducted a randomized, controlled, single-blind study dividing 16 DS vials into 2 equal groups: warm (41°C) and ambient temperature (22°C). With an IV fluid warmer at 41°C, primed with a 1-L bag of preservative-free sterile water, attached to a 60-mL syringe via a 3-way stopcock, we aspirated and

injected the diluent directly into each DS vial.

The Icarus effect was clearly demonstrated: warmed diluent vs ambient temperature hastened the reconstitution time for DS. The mean time to particulate-free DS solution suitable for IV injection with the warm diluent was 58.88 seconds compared with 93.87 seconds for the ambient temperature group (P < .001). A practical method using a reliable and safe warming device readily available to anesthesiologists and ubiquitous to the operating room environment speeds the time to administration of DS ultimately reducing morbidity and mortality associated with MH.

Key words: Dantrolene sodium, diluent temperature, Icarus effect, particulate-free, malignant hyperthermia.

The diagnosis of malignant hyperthermia (MH) necessitates keen observation followed by swift intervention to reduce associated morbidity and mortality. Succinylcholine and potent inhalational anesthetics can precipitate this devastating pharmacogenetic abnormality. The onset of MH signals the creation of a hypermetabolic state characterized by the disruption of calcium homeostasis in skeletal muscle, which, if not promptly corrected, culminates in death of the patient. Proper identification of MH-susceptible patients and avoidance of triggering agents are fundamental to a safe perianesthetic course. The key to effectively managing an MH crisis includes the rapid administration of dantrolene sodium (DS).

Since its introduction into clinical practice in 1979, the hydantoin derivative, DS, continues to function as first-line therapy against MH.¹ Its widespread use has drastically reduced mortality from nearly 80% in the 1970s to less than 10% today.² By inhibiting calcium release from the defective ryanodine type 1 receptor, DS effectively impairs excitation-contraction coupling, leading to resolution of MH by restoring intracellular calcium balance.³⁻⁵ Additional uses of DS include treatment for neuroleptic malignant syndrome, muscle spasticity, and, possibly, Ecstasy intoxication.¹

The DS molecule is highly lipophilic, which prohibits expedient reconstitution with aqueous diluent.

The intravenous (IV) DS formulation is supplied in 70-mL glass vials that contain the following mixture: 20 mg of lyophilized DS, 3 g of mannitol, and sodium hydroxide. The basic additive yields a final pH of 9.5 after reconstitution with 60 mL of preservative-free sterile water.⁶ Only preservative-free sterile water should be used to reconstitute DS. The addition of 3 g of mannitol offers renal protection against myoglobinemia and increases the solubility of DS in the aqueous diluent.¹ Despite this advantage, DS remains a challenging drug to reconstitute and, as a direct consequence, this labor-intensive process comprises the rate-limiting step in DS administration.

The idea of adjusting temperature to impact the solubility of a substance is hardly revolutionary, and so we cite the tragic tale of Icarus. This mythical story serves as a testament to the ancient Greeks' understanding of the sophisticated nature of physics by illustrating the important relationship between the effect of temperature and the corresponding state of matter. As the story goes, Daedalus and his son Icarus were determined to escape their imprisonment within the Labyrinth of King Minos. Daedalus plotted a clever escape by fashioning 2 pairs of wings to allow them to fly free from their site of captivity on the Isle of Crete to mainland Greece. Icarus' father cautioned his son not to journey too closely to the sun above or the ocean below. Soon after taking flight, Icarus found

Figure 1. Physical set-up of study



himself elated by his newly acquired ability. He failed to heed his father's advice as he unwarily ascended toward the heavens. The sun's radiating heat melted the wax with which Icarus' wings were bound, leaving the child to unexpectedly plummet to his death in the raging sea beneath him.

By appreciating the legend of Icarus, which clearly exemplifies the Newton Second Law of Thermodynamics, we postulated that warming the aqueous diluent would hasten the development of a clear and particulate-free DS mixture suitable for IV injection. In their elegantly designed study, Mitchell and Leighton⁷ examined this concept despite the shortcoming that their study included only 1 data point at 5 temperatures between 20°C and 40°C. Although they determined the presence of a linear relationship between diluent temperature and solubility, their study lacked the power to adequately support the significance of their findings. After we collected the data for the present study in May 2006, Quraishi et al⁸ reported similar findings in August 2006.

This randomized, controlled study aimed to identify whether sterile water warmed to 41°C hastens DS solubility compared with sterile water at the ambient operating room temperature of 22°C. We devised a

Figure 2. Dantrolene sodium solubility



study with a sufficiently powered sample size, as revealed by the Cohen *d* calculation and based on previously published research, and a method for warming the diluent using materials common to the operating suite and readily available to anesthetists.

Materials and methods

We conducted a randomized, controlled, single-blind study in a closed operating room suite at Virginia Commonwealth University Health Sciences Campus, Richmond, Va. Because we had a finite quantity of DS vials, we conducted a pilot study before our formal study to test and refine our methodology.

We used equipment common to the operating room to best replicate the clinical environment. We prepared 2 Smith Industries Medical Systems (Rockland, Mass) Hotline fluid warmers (reference HL-90, 115V) with the following: a 1-L bag of preservative-free sterile water, 10 gtt/mL IV tubing, an 8-ft Hotline tubing (reference L-70, 0403), a 3-way stopcock, and a 60-mL syringe (Figure 1). One fluid warmer was designated for the warm group (41°C) and the other for the ambient temperature group (22°C), which remained unplugged from the electrical wall outlet. We primed each circuit with preservative-free sterile water and used a 60-mL syringe connected to a 3-way stopcock at the distal end of the circuit to aspirate the diluent. We recorded all temperature measurements with a thermo resistor (reference 81-010400) Skin Temperature Sensor 400 Series (Smiths Medical, Rockland, Mass) connected to a Dräger Infinity Delta Monitor (Delford, Pa). Room temperature was determined by exposing the thermo resistor skin temperature sensor to air for 1 minute. Baseline Hotline tubing measurements were obtained by purging each circuit of its 20-mL priming volume, waiting 2 minutes, and inserting the temperature probe into the distal end of the circuit and allowing 1 minute to record the temperature. Before our study, we found that the temperature probe would elicit a stable reading in less

Table 1. Pilot study: time to suitable injection by temperature condition

Characteristic	n	Time (s)		
		Mean* (median)	SD	Range
Ambient temperature	5	114.00 (120.00)	13.41	90.00-120.00
Warmed	5	81.00 (90.00)	13.41	60.00-90.00

* $P < .05$.

than 1 minute; thus, we chose 1 minute to standardize our process. The mean temperatures for the warm and ambient temperature groups were 41.0°C and 22.3°C, respectively. We used a digital stopwatch to record all time-sensitive events.

We randomly divided 16 DS vials into 2 equal groups, a warm group (41°C) and an ambient temperature group (22°C). We constructed 16 slips of paper, H for “warm” and C for “ambient temperature,” placed them in a bag, manually shuffled them within the bag, and withdrew 1 slip of paper at a time with the individual’s head turned away from the bag at the time of drawing. The drawn slip of paper was discarded after its first and only use. We blindly withdrew the group assignment marker, purged the circuit of its 20-mL priming volume, waited 2 minutes, and then measured the diluent temperature via the distal end of the circuit for 1 minute. We connected a 60-mL syringe to the 3-way stopcock at the distal end of the fluid warmer, aspirated 60 mL of sterile water, and forcefully injected a full 60 mL into the DS vial.

One member of our research team was designated as the observer. During the pilot study, we incorporated a test trial of several randomly selected DS vials to train the observer to identify particulate vs particulate-free solutions suitable for IV injection (Figure 2). The observer was blinded to the aspiration of fluid and temperature measurement technique, and then was permitted to view the DS vial after it was injected with sterile water (time = 0). At no time was the observer allowed to touch the bottle to determine its temperature. A designated manual agitator performed a continuous series of mixing the vial by hand. This person vigorously agitated the vial in an up-and-down manner between the range of his waist and shoulders by maintaining a fixed elbow position. The same person agitated each and every vial in a standardized manner to eliminate any variance that might occur with multiple mixers. Each mixing cycle consisted of rapid injection of sterile water into the DS vial, manual agitation for 10 seconds, and a stop period of 3

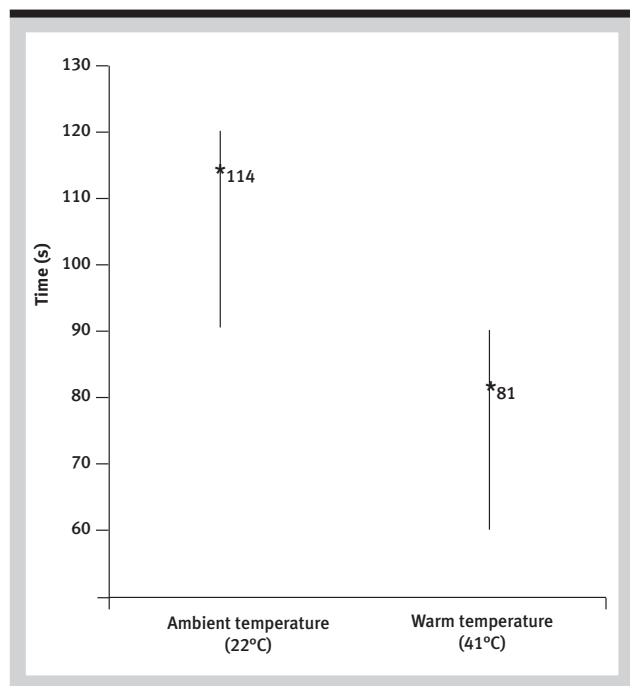
seconds. The observer continuously inspected the vial, but the 3-second stop period was incorporated to more fully appreciate when we reached our endpoint. After the observer declared the presence of a clear particulate-free solution, an end time was determined by a digital stopwatch and recorded.

Results

We compared the time required to produce a clear, particulate-free DS mixture suitable for IV injection when using warm vs ambient temperature diluent. We made use of SPSS 13.0 (SPSS, Chicago, Ill) for all statistical analysis. The *t* test compares the means of 2 independent populations while ignoring individual differences within each group, so we used this test to compare diluent warmed to 41°C with the diluent at the ambient temperature of the operating room (22°C). We set statistical significance at a *P* value of less than .05. We chose the Levene Test for Equality of Variance to test whether the variation around the independent variable was similar between the warm and ambient temperature groups. We selected the Cohen *d* statistic to measure effect size and the magnitude of difference between groups.

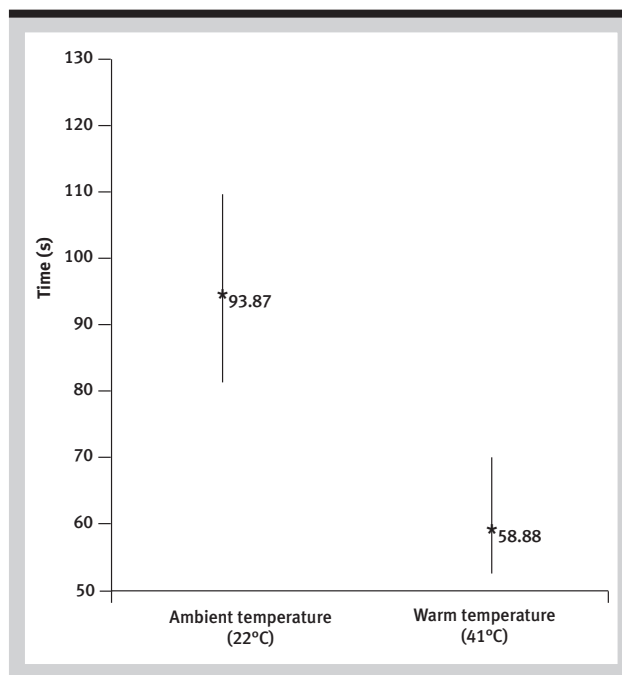
Our pilot study results revealed the mean time to achieve a clear particulate-free mixture suitable for IV injection for the warm group vs the ambient temperature group was 1 minute and 21 seconds vs 1 minute and 54 seconds (Table 1). The Levene test indicated that the variance between groups was equal and insignificant. The Cohen *d* statistic was 2.46, signifying that the mean time to obtain a clear solution between the groups differed by 2.46 SD, demonstrating a large effect size, relevant to statistical power considerations. Warming the diluent gave way to a large effect on dissolution time (Figure 3). At the conclusion of the pilot study, we decided to revise the observation frequency downward in efforts to further increase effect size and to obtain a more accurate account of dissolution time. Despite the wide interval between observations in the pilot study, we obtained statistically significant results ($P < .005$).

Figure 3. Pilot study: mean time to suitable injection for ambient and warm conditions with associated 95% confidence intervals



* Mean values differed at $P < 0.05$.

Figure 4. Final study: mean time to suitable injection for ambient and warm conditions with associated 95% confidence intervals



* Mean values differed at $P < 0.05$.

Table 2. Final study: time to suitable injection by temperature condition

Characteristic	n	Time (s)		
		Mean* (median)	SD	Range
Ambient temperature	8	93.87 (93.00)	8.39	83.00-108.00
Warmed	8	58.88 (55.50)	6.24	53.00-67.00

* $P < .05$.

We performed the formal study, based on our experiences with the pilot study, using 16 vials of DS (Table 2). The mean time to dissolve DS with the warm diluent was 58.88 seconds compared with 93.87 seconds for the ambient temperature group ($P < .001$). The Levene test indicated that the variance between groups was equal and insignificant. Increasing the frequency of observations to once every 10 seconds yielded a larger effect size ($d = 4.73$) (Figure 4).

Discussion

Chartrand⁹ was the first to make reference to the use of an IV fluid-warming device to facilitate DS reconstitution. By using an IV fluid warmer at 41°C, we demonstrated a favorable reduction in the time

required to achieve a clear, particulate-free DS solution suitable for IV injection ($P < .001$). At the first sign of an impending MH crisis, 2.5 mg/kg of IV DS is repeated every 5 minutes up to a recommended maximum dose of 10 mg/kg or until symptoms subside. This translates into a significant mixing burden in an adult patient. For example, in a 72-kg patient, 36 vials of DS are required to reconstitute the maximum recommended dose of 10 mg/kg.

At first inspection, one may liken the idea of supplying an additional heat burden to a patient experiencing an MH crisis to adding fuel to the proverbial fire. Closer analysis reveals the time savings conferred by quickly mixing and administering DS at the onset

Table 3. Dantrolene sodium (DS) mixing time by dose and diluent temperature*

	DS dose			
	2.5 mg/kg		10 mg/kg	
	A diluent	W diluent	A diluent	W diluent
Time (s)†	94	59	94	59
No. of vials	9	9	36	36
1 mixer (min)	14	9	56	35
3 mixers (min)	5	3	19	12

A indicates ambient temperature; and W, warmed diluent.

* Calculated for a 72-kg adult.

† Comparative study results; mean times from Table 2.

of MH symptoms will likely more than compensate for the heat burden imposed by the warmed diluent.^{1,6} Mitchell and Leighton⁷ calculated that an initial 2 mg/kg dose of DS in a 70-kg patient using sterile water warmed to 40°C would fail to generate a net heat gain if one saved 5.1 seconds of mixing time per vial and would create a net heat reduction if more time were saved. Our data suggest a time savings of about 35 seconds per vial when the diluent is warmed to 41°C, translating to a significant net reduction in patient temperature. Precious time saved can be used to attend to other life-saving measures. The time savings afforded by mixing DS with warmed diluent vs ambient temperature sterile water for 1 and 3 mixers is summarized in Table 3.

Neither the DS package insert nor the Malignant Hyperthermia Association of the United States treatment guidelines address the issue of warming the diluent.^{6,10} We were unsuccessful in our efforts to find data specifically about the effectiveness of warmed DS, although anecdotal evidence supports the notion that the drug remains efficacious when warmed. Furthermore, logic dictates that the temperature of an injected drug rapidly equilibrates with the patient's temperature.

A comparison of our study with the work of Mitchell and Leighton⁷ and Quraishi et al⁸ validates the notion that warmed diluent hastens DS solubility, although the methodologies developed to reach this conclusion contrast on several levels. Mitchell and Leighton⁷ demonstrated their ability to reconstitute DS in roughly 30 seconds with diluent warmed to 40°C in a single data point study with a small sample. The results of the study by Quraishi et al⁸ were similar to those of Mitchell and Leighton⁸; Quraishi et al⁸ claimed their data were collected under clinical conditions. Interestingly, they emptied all of their sterile

water vials into a sample cup before mixing the DS. This task devours precious time, challenges aseptic technique, and fails to replicate actions that might take place during an MH crisis. They also incorporated warming closets to heat their sterile water. Many of these devices are not intended to warm IV fluids, and we cannot recommend them for use in this application. In addition, neither of the designs in the aforementioned studies incorporated blinding of the observing party.

We endeavored to simulate real-world clinical conditions, revealing a substantial time savings by warming the aqueous diluent to 41°C. We demonstrated that the use of several 1-L bags of preservative-free sterile water run through an IV fluid warming device is an attractive and clinically useful method to rapidly dissolve DS ($P < .001$). Effect size estimates test the strength of a relationship, helping to determine meaningfulness of statistically significant results. The Cohen d statistic for our findings ($d = 4.73$) reveals a large effect size, imparting practical significance to our findings as well. The use of a larger sample than used by Mitchell and Leighton⁷ and Quraishi et al⁸ extended greater strength to our findings. Blinding the observer reduced bias. Limitations to our study included the use of DS 6 months expired and a single manual agitator.

We conducted a pilot study before our study. During the pilot, we incorporated a test trial of several randomly selected DS vials so that we could calibrate the observer's senses to a defined endpoint—an appreciation for the formation of a clear particulate-free solution that would be suitable for IV injection. We based our pilot in part on the work of Mitchell and Leighton⁷ by conducting repeated cycles of manual agitation for 30 seconds during continuous observation followed by a 5-second rest to facilitate visual

inspection. Although the pilot results suggested a statistically significant difference between the warmed and ambient temperature diluents ($P = .005$), we determined that 30 seconds might have been too long between observations and, in effect, falsely elevated our estimation. We also varied the method of measuring the temperature of the diluent based on our pilot study. We found that withdrawing the warmed diluent from the IV fluid warming device into a syringe led to a time-dependent decrement in the temperature of the diluent. Put another way, the longer we measured the temperature, the greater the decline in the temperature of the warmed diluent. We feared our results would be arbitrarily affected by the time we selected to measure the temperature of the diluent after it was withdrawn from the fluid warmer.

Conclusions

Prompt administration of IV DS is the primary determinant of successful treatment of MH. The time needed to mix an appropriate number of DS vials to successfully treat MH necessitates the assistance of multiple providers during a crisis. Warming the DS diluent to 41°C provides a practical method to rapidly solubilize the drug in a period of crisis. In addition, an IV fluid warming device, a reliable and safe tool approved for patient use, is ubiquitous to the operating room environment. Our study was conducted in an operating room environment where we were able to demonstrate a significant reduction in the time from the start of mixing to the ability to administer IV DS.

The Icarus effect was clearly demonstrated, illustrating the important relationship between the effect of temperature and the corresponding state of matter. Warming the aqueous diluent hastened the development of a clear and particulate-free DS sodium mixture suitable for IV injection. We should take heed from the physical principle underlying Icarus' misfortune to update our practice and impact patient outcomes in a tremendously positive way. This tragic tale illustrates the vital relationship between the effect of temperature and the state of matter. Perhaps our research, in addition to the work of Mitchell and Leighton⁷ and Quraishi et al,⁸ will lay the groundwork

for changing MH treatment protocols and ultimately reducing morbidity and mortality.

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