

Preemptive Analgesic Effect or Short Delay for Inflammation?

To the Editor:—We read with interest the report by Norman *et al.* on preemptive analgesic effect of ketorolac.¹ The authors observed that for 48 patients undergoing ankle fracture surgery that 30 mg of intravenous ketorolac administered before tourniquet inflation offered a better analgesia than after tourniquet inflation at 2 and 4 h after surgery. Can we conclude that it is preemptive analgesia? The effect of ketorolac is mainly peripheral and the tourniquet inflation is probably an adequate technique to compare pre- and postoperative administration. However, the benefit between the two administrations is short-lived (4 h after surgery) and totally compatible with the effect of a single dose of ketorolac. Because preemptive analgesia has to do with limitation of nervous system sensitization,² these results (similar to previous ones^{3,4}) do not support a preemptive analgesic effect. Rather, they suggest that preoperative administration of nonsteroidal antiinflammatory drugs may reduce or delay the development of peripheral inflammation and therefore improve immediate postoperative analgesia. This effect is transient and vanishes a few hours after surgery, which is totally different from preemptive analgesia observed after some studies using ketamine⁵ or local anesthetic.^{6,7}

Bertrand Du Manoir, M.D., Dominique Fletcher, M.D., Ph.D.
Département d'Anesthésie Réanimation, Hôpital Raymond Poincaré, Garches, France. dominique.fletcher@rpc.ap-hop-paris.fr

References

1. Norman PH, Daley MD, Lindsey RW: Preemptive analgesic effects of ketorolac in ankle fracture surgery. *ANESTHESIOLOGY* 2001; 94: 599–603
2. Coderre TJ, Katz J, Vaccarino AL, Melzack R: Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; 52:259–85
3. Fletcher D, Zetlaoui P, Monin S, Bombart M, Samii K: Influence of timing on the analgesic effect of intravenous ketorolac after orthopedic surgery. *Pain* 1995; 61:291–7
4. Rogers JEG, Fleming BG, Macintosh KC, Johnston B, Morgan-Hughes JO: Effect of timing of ketorolac administration on patient-controlled opioid use. *Br J Anaesth* 1995; 75:15–8
5. Menigaux C, Fletcher D, Dupont X, Guignard B, Chauvin M: The benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair. *Anesth Analg* 2000; 90:129–35
6. Pasqualucci A, De Angelis V, Contardo R, Colo F, Terroso G, Donini A, Pasetto A, Bresadola F: Preemptive analgesia: Intraperitoneal local anesthetic in laparoscopic cholecystectomy: A randomized, double-blind, placebo-controlled study. *ANESTHESIOLOGY* 1996; 85:11–20
7. Gottschalk A, Smith DS, Jobses DR, Kennedy SK, Lally SE, Noble VE, Grugan KF, Seifert HA, Cheung A, Malkowicz SB, Gutsche BB, Wein AJ: Preemptive epidural analgesia and recovery from radical prostatectomy: A randomized controlled trial. *JAMA* 1998; 279:1076–82

(Accepted for publication September 8, 2001).

Is the Administration of Ketorolac Associated with Preemptive Analgesia?

To the Editor:—Norman *et al.*¹ presented evidence supporting the concept of possible preemptive analgesic effects based on differences in VAS pain at 2 and 4 h after tourniquet inflation in patients receiving the same dose of ketorolac intravenously before and immediately after tourniquet inflation. Their experimental design was carefully conceived, randomized and placebo controlled to minimize the difference between the prestimulus and poststimulus ketorolac plasma concentration. Although they did not measure ketorolac plasma concentration, they probably achieved their goal.

Katz and Siffert² demonstrated that the concentration of antibiotics under the tourniquet was lower when injected intravenously immediately after tourniquet inflation than before inflation. These findings have dictated the way antibiotics are administered in orthopedics. Indeed, to maximize the concentration at the effector site, antibiotics are injected, preferably before tourniquet inflation, or if this is not done, after tourniquet deflation but not immediately after tourniquet inflation.

The effector site of nonsteroidal antiinflammatory drugs, including ketorolac as one of the antibiotics, is the surgical site. Therefore, Katz and Siffert's² finding suggests that tissue concentrations of ketorolac below the tourniquet would be significantly lower when the drug is

intravenously administered after tourniquet inflation. In these conditions, the difference in VAS pain reported by Norman *et al.*¹ may have reflected the difference in ketorolac concentrations at the effector site, rather than evidence of the preemptive properties of nonsteroidal antiinflammatory drugs. Indeed, VAS pain was higher in patients who received ketorolac immediately after tourniquet inflation, as compared with those who received ketorolac before tourniquet inflation.

Although, like the authors, we intuitively believe that nonsteroidal antiinflammatory drugs have preemptive analgesic effects, Norman *et al.* may want to modulate their conclusions.¹

Tameem Al-Samsam, M.D., Jacques E. Chelly, M.D., Ph.D., MBA
Department of Anesthesiology, The University of Texas Medical School at Houston, Houston, Texas. Jacques.E.Chelly@uth.tmc.edu

References

1. Norman PH, Daley MD, Lindsey RW: Preemptive analgesic effects of ketorolac in ankle fracture surgery. *ANESTHESIOLOGY* 2001; 94:599–603
2. Katz JF, Siffert RS: Tissue antibiotic levels with tourniquet use in orthopedic surgery. *Clin Orthop* 1982; 165:261–4

(Accepted for publication September 8, 2001).

In Reply:—Drs. Al-Samsam and Chelly have suggested that a study by Katz and Siffert¹ invalidates our model. To the contrary, the Katz and Siffert study actually helps support our model. Although it may be unreliable to compare a nonrandomized, unblinded laboratory study of

cefazolin kinetics (human half-life 90–150 min) in 10 mongrel dogs to a blinded, randomized, controlled-trial of ketorolac tromethamine (half-life 120–480 min) in humans, it is nice to have confirmation that drugs administered systemically after tourniquet inflation do not reach

the target limb in any significant amount. This was a major point of our study design. To quote, "because ketorolac exerts its analgesic effects primarily at the peripheral level,² the latter dose would function as a poststimulus dose, since it would not reach the site of action until *after the tourniquet was deflated at the end of surgery*" (emphasis added). The tourniquets in Katz and Siffert's study were never deflated because this study was undertaken to determine if cefazolin administered after tourniquet inflation reached the tissues in significant amounts. This study did not examine tissue drug levels after tourniquet deflation, hence we see no need to "modulate" our conclusions.

Drs. Manoir and Fletcher suggest that our results cannot be attributed to preemptive analgesia because they are not long-lived. We disagree. The definition of preemptive analgesia is the phenomenon by which analgesia administered before a painful stimulus decreases the intensity of the subsequent pain.³ There is no requirement that these effects must persist for a certain period of time. Our paper presents several possible explanations for the relatively short duration of the observed preemptive analgesic effects. Particularly important are the

effects of ongoing tissue inflammation caused by surgical trauma. This inflammation, like repeat injury, will obscure preemptive effects, as discussed by Woolf and Chong.³ Optimal preemptive analgesia may necessitate continuing therapy into the postoperative period.

Peter H. Norman, M.D., F.R.C.P.C., M. Denise Daley, M.D., F.R.C.P.C. Department of Anesthesiology, Division of Anesthesiology, Critical and Palliative Care, University of Texas MD Anderson Cancer Center, Houston, Texas. phnorman@mdanderson.org

References

1. Katz JF, Siffert RS: Tissue antibiotic levels with tourniquet use in orthopedic surgery. *Clin Orthop* 1982; 165:261-4
2. Souter AJ, Fredman B, White PF: Controversies in the perioperative use of nonsteroidal anti-inflammatory drugs. *Anesth Analg* 1994; 79(6):1178-90
3. Woolf CJ, Chong MS: Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993; 77(2):362-79

(Accepted for publication September 8, 2001).

Anesthesiology 2002; 96:515

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

High Incidence of Cardiac Arrest following Spinal Anesthesia

To the Editor:—I read with great interest the article by Drs. Liu and McDonald published in the May 2001 issue of ANESTHESIOLOGY.¹ They report that the incidence of cardiac arrest during spinal anesthesia is from 1/10,000 to 1/250,000 cases. Their own references do not support these incidences. They reference Auroy *et al.* who reported 26 cardiac arrests in a prospective study of 40,640 spinal anesthetics for an incidence of 1/1600 cases.² The other reference cited is also problematic because it was a study of insurance claims for damages following anesthesia.³ Since only a small fraction of adverse events lead to claims for damages, this greatly underestimates the true incidence of these arrests. Other studies confirm a cardiac arrest rate during spinal anesthesia of close to 1/1000 cases.⁴⁻⁶

Having more accurate information about the incidence of cardiac arrest during spinal anesthesia is important because it makes it clear that this problem is common enough to warrant more attention. Further proof of the immediacy of this problem comes from the observation that there are now more claims in the American Society of Anesthesiologists (ASA) Closed Claims Database for cardiac arrest during spinal or epidural anesthesia (170 cases), than there are for aspiration related injury.⁷ The severity of injury has remained high with death or brain damage in approximately 90% of these claims.

It is important to emphasize that the worst outcomes may be avoided if patients receive appropriate treatment.^{5,8} Often this treatment should include use of a strong vagolytic agent. Liu and McDonald acknowledge that there can be a shift in cardiac autonomic balance toward the parasympathetic system related to a sudden decrease in volume.¹ They also allude to increases in baroreflex activity but there is no mention of the potential benefits of vagolytic therapy during spinal anesthesia. The first two prophylactic measures that they discussed can help decrease vagal tone partially, but may be inadequate by when used alone. Gratadour *et al.*⁹ reported that neither volume loading nor infusion of a mixed α - and β -agonist during spinal anesthesia was sufficient to prevent three study patients from experiencing

bradycardia and hypotension associated with an increase in baroreflex activity. To help prevent an overwhelming vagal response, prophylactic treatment with atropine should also be considered for patients at risk for severe bradycardia and cardiac arrest during spinal anesthesia. With the popularity of spinal anesthesia and the reported frequency of these arrests, increased use of all three of these interventions to decrease vagal tone could enhance the safety of spinal anesthesia.

John B. Pollard, M.D., Veterans Administration Palo Alto Health Care System, Palo Alto, California. John.Pollard@med.va.gov

References

1. Liu SS, McDonald SB: Current issues in spinal anesthesia. *ANESTHESIOLOGY* 2001; 94:888-906
2. Auroy Y, Narchi P, Messiah A, Lit L, Rouvier B, Samii K: Serious complications related to regional anesthesia. *Anesthesiology* 1997; 87:479-86
3. Aromaa U, Lahdensuu M, Cozaniis DA: Severe complications associated with epidural and spinal anesthetics in Finland 1987-1993: A study based on patient insurance claims. *Acta Anaesthesiol Scand* 1997; 41:445-52
4. Palmer SK: What is the incidence of arrest and near arrest during spinal and epidural analgesia? Report of nine years' experience in an academic group practice. *Anesth Analg* 2001; 92:S339
5. Geffin B, Shapiro L: Sinus bradycardia and asystole during spinal and epidural anesthesia: a report of 13 cases. *J Clin Anesth* 1998; 10:278-85
6. Tarkkila PJ, Kaukinen S: Complications during spinal anesthesia: A prospective study. *Reg Anesth* 1991; 16:101-6
7. Pembroke L: Unforeseen, sudden cardiac arrests continue in healthy patients. *Anesthesiology News* 2000;123-5
8. Mackey DC, Carpenter RL, Thompson GE, et al.: Bradycardia and asystole during spinal anesthesia: A report of three cases without morbidity. *ANESTHESIOLOGY* 1989; 70:866-8
9. Gratadour P, Viale JP, Parlow J, Sagnard P, Counieux H, Bugou G, Annat G, Hughson R, Quintin L: Sympathovagal effects of spinal anesthesia assessed by the spontaneous cardiac baroreflex. *ANESTHESIOLOGY* 1997; 87:1359-67

(Accepted for publication September 10, 2001).

Anesthesiology 2002; 96:515-6

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Extrapolating beyond the Data

To the Editor:—In my years as an editor of ANESTHESIOLOGY and a reviewer for numerous journals, I frequently encountered submissions

in which figures contained fitted curves (linear regression or other nonlinear functions) extrapolated beyond the range of measured X

Anesthesiology, V 96, No 2, Feb 2002

values. Authors were often resistant to changing these figures to limit their predictions to the observed range of X values. The folly of extrapolating beyond the observed range is seen in figure 4 in a recent review article in *ANESTHESIOLOGY*.¹ The fitted function indicates that a decrease in blood volume increases cardiac output, certainly an unexpected and unphysiologic finding (and not supported by the data). Fortunately, the authors limited their extrapolation; had they extended their curve further, it would suggest that profound hypovolemia was desirable, certainly not the authors' intention.

Anesthesiology 2002; 96:516

In Reply:— We appreciate the comments by Drs. Pollard and Fisher. Dr. Pollard points out the wide variability in estimated incidence of cardiac arrest in spinal anesthesia. Depending on the data examined, interpretation of data, and definition of cardiac arrest, the incidence could certainly be as common as 1:1,000. We agree with Dr. Pollard that clinicians must maintain vigilance during spinal anesthesia. Dr. Pollard also recommends prophylactic treatment with atropine to reduce sudden baroreflex activity and prevent cardiac arrest in high-risk patients. Although a reasonable suggestion, this intervention has not been definitively studied, and efficacy is unclear. In fact, the cited reference (8) concluded that it was very difficult to prospectively

Dennis M. Fisher, M.D., DURECT Corporation, Cupertino, California. fisher@plessthan.com

Reference

1. Liu S, McDonald SB: Current issues in spinal anesthesia. *ANESTHESIOLOGY* 2001; 94:888-906

(Accepted for publication September 10, 2001).

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

identify patients at risk for sudden increase in baroreflex activity associated with sudden bradycardia and hypotension.

Dr. Fisher's comments on data presentation are appreciated. The figure was reproduced with permission from a previous publication in *ANESTHESIOLOGY* by other investigators. Because we were not involved in the statistical analysis and editorial process for the original publication, we have no additional insight to offer.

Spencer S. Liu, M.D., Susan B. McDonald, M.D. Department of Anesthesiology, Virginia Mason Medical Center, Seattle, Washington. anessl@vmc.org

(Accepted for publication September 10, 2001).

Anesthesiology 2002; 96:516

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

The Intubating Dose of Succinylcholine

To the Editor:— Drs. Heier *et al.* are to be congratulated on a courageous and convincing study.¹ Their conclusion that "spontaneous recovery from succinylcholine-induced apnea may not occur sufficiently quickly to prevent hemoglobin desaturation in subjects whose ventilation is not assisted" is well taken. I was somewhat disappointed, however, that the authors did not take the next logical step in the discussion of their findings. They state, "a smaller dose of succinylcholine would have decreased the duration of muscle paralysis but the results would have been less clinically relevant." I think it is time to question the correctness of the assumption that the intubating dose of succinylcholine must be 1.0 mg/kg. I was taught as a resident back in the early 1960s that if you never exceeded a dose of 40 mg of succinylcholine (to an adult) that most patients would likely survive the experience. In the subsequent four decades I have rarely found it necessary to exceed a dose of 0.50 to 0.60 mg/kg for routine intubations.

A few facts are worth reviewing:

- The ED₉₅ of succinylcholine is less than 0.30 mg/kg.² Thus, 1.0 mg/kg of succinylcholine represents between 3.5 and 4.0 times the drug's ED₉₅.
- Even when administered in subparalyzing doses, 90% of the blocking effect of succinylcholine (at the adductor pollicis) is still evident within 75 s.³ The time to peak effect at sites more relevant to the adequacy of conditions for intubation such as the masseter, diaphragm, and laryngeal adductors is even more rapid.
- As the intrinsic speed of onset of a neuromuscular blocker becomes more rapid, smaller multiples of the ED₉₅ are required to assure timely ease of intubation. The usually recommended "intubating dose" of cisatracurium (a slow onset drug) is 0.15 to 0.20 mg/kg (3-4xED₉₅). The commonly cited intubation-dose of 0.60 mg/kg for rocuronium represents less than 2xED₉₅, yet the drug's onset profile is slower than that of succinylcholine.

- The notion that laryngoscopy must be initiated within 60 s is not absolute. Rather this dictum is the product of many risk-to-gain factors that must be balanced clinically. Optimal intubating conditions at 60 s are only obtainable by giving doses of hypnotics and relaxants that are larger than would be necessary if a more relaxed intubation sequence was contemplated. I think it can be successfully argued that overall patient safety might be enhanced when the time from loss of consciousness to endotracheal tube placement is lengthened by 15 s, if the "trade-off" is a simultaneous decrease in the duration of succinylcholine-induced apnea of 90 s or more.

The observations of Heier *et al.* are important. Nevertheless I think the authors have perhaps done the anesthesia community a disservice by dismissing the "clinical relevance" of doses of succinylcholine < 1.0 mg/kg so casually. The utility of smaller doses of succinylcholine deserves to be reexamined.

Aaron F. Kopman, M.D., Department of Anesthesiology, St. Vincent's Hospital and Medical Center, New York, New York. akopman@rcn.com

References

1. Heier T, Feiner JR, Lin J, Brown R, Caldwell JE: Hemoglobin desaturation following succinylcholine-induced apnea: A study of the recovery of spontaneous ventilation in healthy volunteers. *ANESTHESIOLOGY* 2001; 94:754-9
2. Kopman AF, Klewicka MM, Neuman GG: An alternate method for estimating the dose-response relationships of neuromuscular blocking drugs. *Anesth Analg* 2000; 90:1191-1197
3. Kopman AF, Klewicka MM, Kopman DJ, Neuman GG: Molar potency is predictive of the speed of onset of neuromuscular block for agents of intermediate-, short-, and ultra-short duration. *ANESTHESIOLOGY* 1999; 90:425-31

(Accepted for publication September 14, 2001)

Anesthesiology 2002; 96:517

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

The Safety of Rapid Sequence Induction

To the Editor:—We read with interest the article by Heier *et al.* entitled “Hemoglobin Desaturation After Succinylcholine-induced Apnea.”¹ In our practice, we are often called on to perform emergency airway management, and after reading this article, it appears that the safety of rapid sequence induction (RSI) has been called into question. The study by Heier *et al.*; demonstrated that there is a potential risk of desaturation with the RSI sequence. We believe, however, that the methodology used by the authors does not permit formulation of a definitive answer in this regard. In the authors’ study, the facemask was removed after induction and remained off throughout the period of apnea. In emergency airway management, when difficult intubation occurs, the bag mask must be applied against the face of the patient with continuous oxygen infusion, but without active ventilation, until oxygen saturation is greater than 90%. Several studies have demonstrated that oxygenation may be maintained for more than 30 min with passive oxygenation in the absence of active ventilation.² The true clinical relevance of the author’s study is apparently in the situation of complete airway obstruction or in the “cannot intubate, cannot ventilate” situation. However, this latter situation is very rare (about 0.01–0.2 per 10,000).³ In short, we believe that the degree of hemoglobin desaturation during apnea from the RSI procedure may be more ap-

propriately assessed with a bag-mask connected to a high-flow oxygen source applied to the face of the patient. The RSI technique was designed to reduce pulmonary aspiration, and, to our knowledge, the combination of a rapid neuromuscular blocker (succinylcholine) and a hypnotic remains the anesthetic procedure of choice in the case of emergency invasive airway management.⁴

Frederic Adnet, M.D., Ph.D., Stephen W. Borron, M.D., M.S., Frederic Lapostolle, M.D. Departement d’Anesthesie-Reanimation, Hopital Avicenne, Bobigny, Cedex, France. frederic.adnet@avc.ap-hop-paris.fr

References

1. Heier T, Feiner JR, Lin J, Brown R, Caldwell JE: Hemoglobin desaturation after succinylcholine-induced apnea. *ANESTHESIOLOGY* 2001; 94:754–9
2. Frumin MJ, Epstein RM, Cohen G: Apneic oxygenation in man. *ANESTHESIOLOGY* 1959; 20:789–98
3. Benumof JL: Management of the difficult adult airway. *ANESTHESIOLOGY* 1991; 75:1087–1110
4. Walls RM: Emergency airway management. Philadelphia, Lippincott Williams & Wilkins, 2000

(Accepted for publication September 14, 2001)

Anesthesiology 2002; 96:517

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

In Reply:—We appreciate the responses by Dr. Kopmen and by Dr. Adnet *et al.* to our article.¹ Dr. Kopman raised the pertinent clinical question about what is the correct dose of succinylcholine necessary to facilitate tracheal intubation. We used 1 mg/kg of succinylcholine because that is the standard recommended dose.² We did not devote much discussion to the question of dose because it was not a focus of our study. Dr. Kopman argues that smaller doses than 1 mg/kg are adequate for intubation because the ED 95 of succinylcholine is less than 0.3 mg/kg.³ This estimate of potency was obtained using the dorsal interosseous muscle of the hand, a muscle which is not as relevant to quality of tracheal intubation as are the laryngeal adductor muscles. In particular, the duration of action of succinylcholine at the laryngeal adductor muscles is several minutes shorter than at the intrinsic muscles of the hand.⁴ As a consequence, with small doses of succinylcholine recovery of the laryngeal adductors may occur so rapidly that the “window of opportunity” for tracheal intubation is very short. Consequently, delaying intubation may, in fact, lead to a diminished, not increased, chance of successful intubation. This may explain why a dose of 0.5 mg/kg results in worse conditions for intubation than a dose of 1.5 mg/kg.⁵ Dr. Kopman eloquently identifies the need for a definitive study on the relationship of dose of succinylcholine to timing and quality of tracheal intubation; we look forward to the results of such a study.

Regarding the comments by Dr. Adnet *et al.* on rapid-sequence intubation (RSI), our study did not address RSI nor call its safety into question. Our intent was solely to investigate the validity of a clinical belief, namely that recovery from succinylcholine occurs sufficiently rapidly to permit a margin of safety in airway management. We sought to replicate conditions in the “can’t intubate and can’t ventilate” situation, and while the incidence of this problem is low, the potential for a catastrophic outcome elevates its importance. In this situation, passive transfer of oxygen into the lungs will not take place, therefore, to approximate this circumstance we removed the oxygen mask from the subject’s face. The argument by Adnet *et al.* that in the absence of

ventilation, passive oxygenation will maintain hemoglobin saturation for 30 min is misleading. In the study they cite subjects had an endotracheal tube placed, and their lungs were ventilated with 100% oxygen for 30 min before apnea was induced.⁶ This does not resemble in any meaningful way the clinical situation of managing a difficult airway with a face mask in a paralyzed patient whose lungs cannot be effectively ventilated. In addition, in that study, during the time of passive oxygenation P_{aCO_2} increased to between 130 and 250 mmHg and pH decreased to between 6.72 and 6.97.⁶ We believe we have provided important new information that clinicians can use in their decision-making processes, whether that is for an elective and uncomplicated or an emergent rapid-sequence intubation.

James E. Caldwell, M.B.Ch.B.,* Tom Heier, M.D., Ph.D. *Department of Anesthesia and Perioperative Care, University of California, San Francisco, California. caldwell@anesthesia.ucsf.edu

References

1. Heier T, Feiner JR, Lin J, Brown R, Caldwell JE: Hemoglobin desaturation after succinylcholine-induced apnea: A study of the recovery of spontaneous ventilation in healthy volunteers. *ANESTHESIOLOGY* 2001; 94:754–9
2. Savarese JJ, Caldwell JE, Lien CA, Miller RD: Pharmacology of muscle relaxants and their antagonists, *Anesthesia*, 5th Edition. Edited by Miller RD. New York, Churchill Livingstone, 2000, pp 412–90
3. Kopman AF, Klewicka MM, Neuman GG: An alternate method for estimating the dose-response relationships of neuromuscular blocking drugs. *Anesth Analg* 2000; 90: 1191–7
4. Wright PMC, Caldwell JE, Miller RD: Onset and duration of rocuronium and succinylcholine at the adductor pollicis and laryngeal adductor muscles in anesthetized humans. *ANESTHESIOLOGY* 1994; 81:1110–5
5. McLoughlin C, Leslie K, Caldwell JE: Influence of dose on suxamethonium-induced muscle damage. *Br J Anaesth* 1994; 73:194–8
6. Frumin JM, Epstein RM, Cohen G: Apneic oxygenation in man. *ANESTHESIOLOGY* 1959; 20:789–98

(Accepted for publication September 14, 2001)

Prediction of Propofol Induction Dose Using Multiple Regression Analysis

To the Editor:—We read with great interest the article by Kazama *et al.*¹ They clarified the relationship between initial blood distribution volume and propofol induction dose using continuous infusion during the induction of anesthesia. The results are consistent with those of our study,² and the study protocols differed in only two parameters: the infusion rate, and its basis. Kazama *et al.* administered propofol at $40 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ as a function of lean body mass (LBM), whereas we administered it at $15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ as a function of total body weight. Using multiple linear regression analysis, Kazama *et al.* report that the induction dose can be determined from four variables, age, LBM, central blood volume (CBV), and hepatic blood flow (HBF), whereas we selected age, body weight, cardiac output (CO), and the plasma disappearance rate of indocyanine green (k) as our variables.

Multiple linear regression analysis in the study of physiologic systems provides a powerful statistical tool for sorting out the relationships among several variables in such experiments. However, there are many potential pitfalls when using regression analysis, including multicollinearity, which can lead to numerical problems in estimating the parameters in regression equations.³ Ideally, all selected predictive variables must be uncorrelated. When multiple regression analysis was applied to our results using the variables of Kazama *et al.*,¹ age, LBM, CO, BV, and HBF were identified as significant factors for predicting the induction dose of propofol ($P < 0.01$, table 1). However, our statistical analysis (NCSS2000, Kaysville, UT) detected possible multicollinearity among the selected predictive variables.

In our results, age did not demonstrate any correlation with BV or CBV, consistent with Kazama *et al.*, whereas age showed marked correlation with HBF, and CBV was significantly correlated with LBM and BV. Age has been reported as a predictive variable for HBF.⁴ Normalization of accurate BV measurement using LBM has been recommended in a clinical setting,⁵ because LBM is an absolute predictive factor for CBV. These relationships might become sources of multicollinearity, and ordinary least squares multiple linear regression can give nonsensical results for the estimated parameter magnitude, sign, or standard error. Hepatic blood flow is a cross-product of BV and clearance slope (K^{-1}); thus, it might become another source of artificial multicollinearity.

The results of Kazama *et al.* clearly demonstrate the predictive variables for propofol induction dose. Age and other circulatory variables play an important role in determining the dose, which is consistent with our results. The interpretation of the results using multiple regression analysis (including our study), however, might leave room for attention and discretion. Although multicollinearity can be avoided

Table 1. Coefficients Entered in Multiple Linear Regression Model for Patient Baseline Variables and Propofol Induction Dose at the Rate of $15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$

Variable Entered in Model	Regression Coefficient	SE	Standardized Regression Coefficient
Age (yr)	-0.42	0.12	-0.30
Sex (0 M, 1 F)	*		
LBM (kg)	0.84	0.30	0.33
Hemoglobin (mg dl^{-1})	*		
Cardiac output (1 min^{-1})	3.2	1.1	0.23
Blood volume (l)	-4.8	1.7	-0.32
Central blood volume (l)	*		
Hepatic blood flow (1 min^{-1})	23	6.1	0.36
Intercept	35	14	
Adjusted R ²	0.43 ⁺		

* Not selected as a predictor variable in the multiple linear regression model using the variables of Kazama *et al.*¹

⁺ $P < 0.0001$.

LBM = lean body mass; SE = standard error; M = male; F = female.

with good experimental design, not all interesting questions can be studied without encountering multicollinearity.

Yushi U. Adachi, M.D.* Hideyuki Higuchi, M.D., Ph.D.,
*Medical Clinic of Kumagaya Base, Japan Air Self Defense Force, Kumagaya City, Japan. grd1117@gr.ndmc.ac.jp

References

1. Kazama T, Ikeda K, Morita K, Ikeda T, Kikura M, Sato S: Relation between initial blood distribution volume and propofol induction dose requirement. *ANESTHESIOLOGY* 2001; 94: 205-10
2. Adachi YU, Watanabe K, Higuchi H, Satoh T: The determinants of propofol induction of anesthesia dose. *Anesth Analg* 2001; 92:656-61
3. Slinker BK, Glantz SA: Multiple regression for physiological data analysis: The problem of multicollinearity. *Am J Physiol* 1985; 249:R1-12
4. Zoli M, Magalotti D, Bianchi G, Gueli C, Orlandini C, Grimaldi M, Marchesini G: Total and functional hepatic blood flow decrease in parallel with ageing. *Age Ageing* 1999; 28:29-33
5. Wright RR, Tono M, Pollycove M: Blood volume. *Semin Nucl Med* 1975; 5:63-78

(Accepted for publication September 24, 2001.)

In Reply:—Dr. Adachi did not make the important distinction between administration rates of 15 and $40 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. However, propofol administration rate has a critical impact on induction dose.¹ The pharmacokinetics are not stationary. Distribution volumes and clearances vary over time. Schneider *et al.*² administered propofol at the very slow infusion rate of $15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Although this slow propofol administration rate is useful for studying pharmacokinetic parameters, it is not suitable for investigation of clinical induction doses and times. As I previously reported, induction doses are highly variable at administration rates of less than $20 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.¹ At these low rates, propofol metabolized during infusion may have important effects. As a

consequence, the selected parameters in our study were age, lean body mass (LBM), central blood volume (CBV), and hepatic blood flow (HBF) at the rate of $40 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.³

The propofol administration rate of $15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ that Dr. Adachi used is not clinically acceptable because it takes over 5 min for loss of consciousness. Moreover, I was very surprised to see that cardiac output (CO) was selected as a parameter of induction dose at this slow administration rate. Although CO was also correlated with induction dose, it could not be identified as a significant variable in the multiple linear regression model in our study.³ I could not explain the difference clearly.

The total R^2 of hypnotic dose by Dr. Adachi was 0.468. This means that only 46.8% of induction dose can be explained with their selected parameters of age, body weight, CO, and k (the plasma disappearance rate of indocyanine green). Our total R^2 for induction dose was 0.85 (at $40 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$).³ Dr. Adachi reanalyzed his data using the parameters identified in our study. However, the R^2 was still less than 0.5. The small total R^2 of Dr. Adachi might be a result of the large variability in the induction dose and the slow administration rates.

There are no complete independent variables among age, sex, body weight, height, LBM, hemoglobin, CO, BV, CBV, and HBF. It is important to select parameters that make R^2 close to 1.0 in multiple linear regressions. Multicolinearity among variables makes regression difficult to interpret. We used forward and backward selection to identify the most useful variables for predicting the induction dose. The criterion for adding and deleting variables was a minimum of 4.0 for the F ratio, which was the square of the value obtained from a *t* test with the hypothesis that the coefficient of the variable in question was equal to zero.

Tomiei Kazama M.D., Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, Hamamatsu, Japan. tkazama@hama-med.ac.jp

References

1. Kazama T, Ikeda K, Morita K, Kikura M, Ikeda T, Kurita T, Sato S: Investigation of effective induction doses using a wide range of infusion rates with undiluted and diluted propofol. *ANESTHESIOLOGY* 2000;92:1017-28
2. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *ANESTHESIOLOGY* 1998; 88:1170-82
3. Kazama T, Ikeda K, Morita K, Ikeda T, Kikura M, Sanjo Y, Sato S: The relation between initial blood distribution volume and propofol induction dose requirement. *ANESTHESIOLOGY* 2001; 94:205-10

(Accepted for publication September 24, 2001.)

Anesthesiology 2002; 96:519-20

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Sheath Placement over Transesophageal Probes: A Description of a "Self-Moving" Method

To the Editor:—The use of transesophageal echocardiography (TEE) in the operating room, both for cardiac and noncardiac surgery, is increasing. In our hospital, we use disposable sheaths over the TEE-probe, to prevent nosocomial infections^{1,2}. Placing a Latex sheath over the TEE-probe in the operating room is not easy; it is time-consuming and the limited space can necessitate bending of the probe, which may decrease its longevity. Polyurethane sheaths are even more difficult to place over the probe. Potentially life-threatening allergic reactions to Latex have forced us to consider the use of polyurethane sheaths.^{3,4}

In order to maximize the ease of sheath placement, we have designed a vacuum tube, mounted on the echo-machine. This consists of two Perspex or Polycarbonate tubes (Polycarbonate exhibits extremely high-impact strength); a smaller tube within a larger tube (Fig. 1). Holes are placed in the inner tube and vacuum is applied between the inner and outer tubes. The exact placement of the holes in the inner tube is crucial; they have been placed, after trial and error, at the section of the inner tube that coincides with the distal 60–80% of the probe, and also at the bottom of the inner tube. After placing the sheath and applying negative pressure, the sheath opens against the wall of the inner tube; starting proximally and extending distally. Once the distal part of the inner tube has been reached, the sheath closes the openings in the inner tube, and the suction force from the holes in the bottom of the inner tube now extends its length (the length of the probe extends a few cm from the last distal opening in the tube). Ultrasound gel is placed on the tip of the probe so that it can be effortlessly placed in the stretched sheath. After removing the negative pressure, the distal part of the sheath retracts first (the proximal side-holes are still occluded by the sheath), thereby fitting tightly around the tip of the probe. The remaining negative pressure is then reduced so that the rest of the sheath retracts around the shaft of the probe. Occasionally, minimal manipulation of the tip of the sheathed probe is needed in order to remove air (the fit of the polyurethane sheath is extremely tight and, in fact, much better). This procedure is quick, easy, and clean, and requires minimal manipulation of the

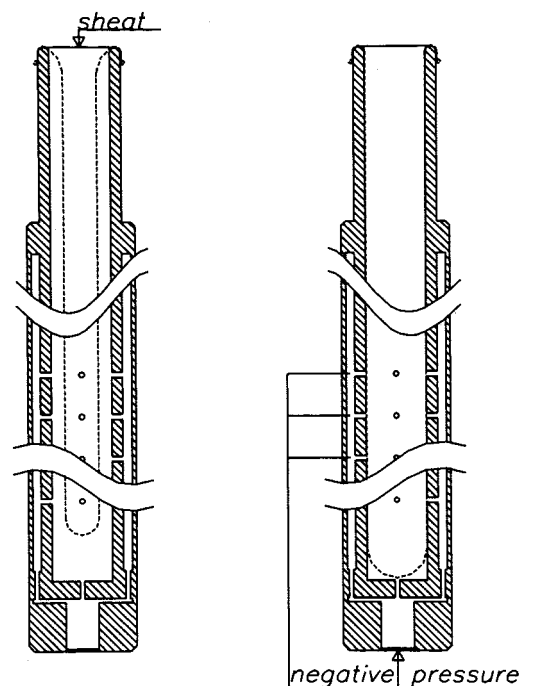


Fig. 1. Inner and outer Perspex or Polycarbonate tubes. Negative pressure is applied to the space between the inner and outer tubes. The suction force is transferred to the inner tubes via holes in the inner tube and at the bottom. The inner tube is sealed airtight to the outer tube.

probe. Readers may be interested in this "self-moving" method, which can quite easily be locally manufactured.

Hendrikus H. M. Korsten, M.D., Ph.D.,* Cathinka H. Peels, M.D., Piet Heesakkers, Kees Rommelse *Department of Anesthesiology, Catharina Hospital, Eindhoven, The Netherlands. korsten@chello.nl

Support was provided solely from institutional sources.

References

1. Mayinger B, Strenkert B, Martus P, Kunz B, Hahn EG, Hochberger J: Disposable protection for flexible gastroenterologic endoscopy: Prospective comparative evaluation of a new gastroscopy system (endosheath) compared to the standard fiberglass gastroscopy. *Z Gastroenterol* 1998; 36:501-7
2. MacGowan SW: Intra-operative transoesophageal echocardiography is a potential source of sepsis in the intensive care. *Eur J Cardiothorac Surg* 2000; 7:768-9

3. Nawa Y, Imaizumi H, Masuda Y, Hazama K, Sato M, Namiki A, Asai Y: A case of anaphylactic shock due to latex glove used on internal examination and on the probe of intrauterine echogram. *Masui* 2000; 49:1027-9

4. Laxenaire MC: Drugs and other agents involved in anaphylactic shock occurring during anesthesia: A French multicenter epidemiological inquiry. *Ann France Anaesth Reanim* 1993; 12:91-6

(Accepted for publication September 18, 2001.)

Anesthesiology 2002; 96:520

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Malfunction of Syringe Pump Caused by Fluid Infiltration

To the Editor:—The breakdown or dysfunction of syringe pumps can present a serious threat to patient safety when they are used to administer high concentrations of narcotic, vasopressor, or depressor drugs. I report an experience in which the power supply circuit and syringe size sensory were damaged— apparently a result of leakage of intravenous infusion fluids into the housing of the pump.

My institute has had 19 anesthesia syringe pumps (Graseby 3500; Graseby Medical LTD, Watford, Hertfordshire, UK) in service for 4 yr or more, and these have been used exclusively for continuous infusion of Propofol. In recent periodic checks of all units, corrosion in the syringe size sensory springs was found in three syringe pumps, and damage to the power supply by short circuit was found in one. Figure 1 shows a corroded syringe size sensory spring. Because residual liquid or white crystal was found on the bottom of the housing between the syringe size sensor and the power supply circuit board, it is evident that intravenous infusion fluids had infiltrated into the housing from the narrow space between the main body and the syringe plunger, thus causing both corrosion of the spring and a short circuit of the power supply. Infusion fluid occasionally falls onto the syringe pumps because we usually attach them to the infusion stand during surgery. So, this kind of medical instrument should be waterproof by design. The instruction manual for this syringe pump does state in the Specifications section that its electrical safety category is "drip proof IPX1," which guarantees protection against a 10-min exposure to artificial rain of 3-5 mm/min from a 50-cm height.¹ Therefore, it is anomalous that dripping intravenous infusion fluids should result in the observed problems. Although short circuit of the power supply simply results in infusion interruption, corrosion in the syringe size sensory spring is a severe problem, because it may cause incorrect recognition of syringe size, resulting in an unpredictable drug infusion rate.

I suggest that the syringe size sensory spring be made from a material that is not corroded by the electrolytes included in the infusion fluids,

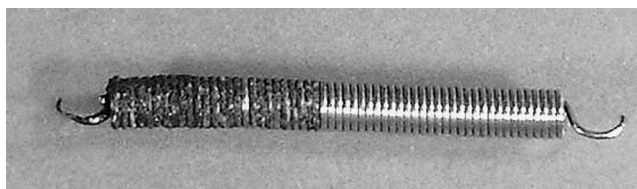


Fig. 1. The damaged spring of the syringe size sensor is shown. The hook was corroded, and the connection with the case has come off.

and that the seal between the main body and the syringe plunger be improved. In this case, the Japanese sales agent was unable to distinguish between the possibilities of a structural defect and an assembly problem after checking the faulty syringe pumps. To prevent recurrence of these problems, Graseby Medical and the Japanese sales agent suggested I install a syringe cover normally used with another of Graseby's products with patient-controlled analgesia function that has a common housing. I accepted this suggestion at the time, but it is notable that such a modification potentially constitutes a warranty violation and exposure to legal problems. At any rate, the improved water resistance is expected to prevent this type of accident in the future.

Masaki Takashina, M.D., Surgical Center, Osaka University Medical School, Osaka University Hospital, Osaka, Japan. takashina@hp-op.med.osaka-u.ac.jp

References

1. Graseby 3500 Anaesthesia Syringe Pump instruction manual. Watford, Hertfordshire, UK, Graseby Medical, 1996, pp 45

(Accepted for publication September 19, 2001.)

Support was provided solely from institutional and/or departmental funds.