

## Capsaicin-induced Pain and Tourniquet Constriction

*To the Editor:*—Recently, Byas-Smith *et al.*<sup>1</sup> reported that tourniquet constriction expands and exacerbates pain during intradermal injection of capsaicin in humans. The underlying mechanism was unclear. It is suggested herein that excitation of paravascular nociceptors is involved in expansion of pain.

Capsaicin has been shown to evoke pain from skin,<sup>2</sup> muscle,<sup>3</sup> and paravascular tissue, but not from veins.<sup>4</sup> In the latter study, one of the authors had a disconcerting experience. Capsaicin was perfused through a vascularly isolated hand vein segment to test capsaicin for its property to excite vascular nociceptors. It definitively did not, but strong pain occurred distant from the perfusion site and spread to the entire forearm. In fear of spreading pain to the entire body, a tourniquet was installed quickly to the upper arm, which, however, increased pain further, up to an unbearable intensity. It was determined that capsaicin solution had drained *via* a previously unnoticed side branch of the isolated vein segment into the venous system. From there, capsaicin apparently had gained access to the paravascular space (capsaicin does not evoke pain in veins). The substantial increase in capsaicin-induced pain during tourniquet inflation is unknown. A recruitment of myelinated fibers during ischemia has been discussed;<sup>5</sup> however, fostering by venous congestion of transendothelial crossing of capsaicin to the paravascular tissue also may play a role. Thus, the spread of capsaicin from the site of application to the paravascular

space may have contributed, at least in part, to the observations made by Byas-Smith *et al.*<sup>1</sup>

\*Holger Holthusen, M.D., Joachim Arndt, M.D. \*Heinrich-Heine-University, Duesseldorf, Germany. Holthusen@med.uni-duesseldorf.de

## References

1. Byas-Smith MG, Bennett GJ, Gracely RH, Max MB, Robinovitz E, Dubner R: Tourniquet constriction exacerbates hyperalgesia-related pain induced by intradermal capsaicin injection. *ANESTHESIOLOGY* 1999; 91:617-25
2. Simone DA, Baumann TK, LaMotte RH: Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. *Pain* 1989; 67:99-107
3. Marchettini P, Simone DA, Caputi G, Ochoa JL: Pain from excitation of identified muscle nociceptors in humans. *Brain Res* 1996; 740:109-16
4. Arndt JO, Kindgen-Milles D, Klement W: Capsaicin did not evoke pain from human hand vein segments but did so after injections into the paravascular tissue. *J Physiol* 1993; 463:491-9
5. Handwerker HO, Ringkamp M, Schmelz M: Neurophysiological Basis for Chemogenic Pain and Itch, Touch, Temperature and Pain in Health and Disease: Mechanisms and Assessments, vol 3, Progress in Pain Research and Management. Edited by Boivie J, Hansson P, Lindblom U. Seattle, IASP Press, 1994, pp 195-200

(Accepted for publication May 26, 2000.)

*In Reply:*—We are gratified to learn that Arndt *et al.*<sup>1</sup> and Handwerker *et al.*<sup>2</sup> have observed independently the dramatic increase of pain caused by tourniquet inflation above a capsaicin injection site. Their description of the response is consistent with our findings and encourages further investigation to determine its clinical relevance. Drs. Holthusen and Arndt's suggestion that pain is caused by the spread of capsaicin to the paravascular space does not explain the sudden onset of pain, which occurs within seconds of tourniquet inflation. We agree that capsaicin may spread from the site of injection to the area around some blood vessels (small vessels must be in the injection area), but we expect this entirely extravascular spread to be an ongoing process not increased by tourniquet inflation. Alternatively, capsaicin taken up into veins might diffuse out of the vein after venous occlusion, as shown in the article by Arndt *et al.*<sup>1</sup> but we would expect this to begin after minutes, not seconds.

\*Michael Byas-Smith, M.D., Gary Bennett, Ph.D., Mitchell B. Max, M.D. \*Emory University School of Medicine, Atlanta, Georgia. Michael\_Byas-smith@emory.org

## References

1. Arndt JO, Kindgen-Milles D, Klement W: Capsaicin did not evoke pain from human hand vein segments but did so after injections into the paravascular tissue. *J Physiol* 1993; 463:491-9
2. Handwerker HO, Ringkamp M, Schmelz M: Neurophysiological Basis for Chemogenic Pain and Itch, Touch, Temperature and Pain in Health and Disease: Mechanisms and Assessments, vol 3, Progress in Pain Research and Management. Edited by Boivie J, Hansson P, Lindblom U. Seattle, IASP Press, 1994, pp 195-200

(Accepted for publication May 26, 2000.)

## Recombinant Hirudin as Anticoagulant during Cardiopulmonary Bypass

*To the Editor:*—In the 92nd volume of *ANESTHESIOLOGY*, Latham *et al.*<sup>1</sup> reported the use of recombinant hirudin (r-hirudin) as a cardiopulmonary bypass (CPB) anticoagulant in two patients with a history of heparin-induced thrombocytopenia of type II. Based on our experiences with the use of r-hirudin in this clinical setting, we would like to comment. Latham *et al.*<sup>1</sup> used the activated partial thromboplastin time for intraoperative monitoring of hirudin. We have recently shown that activated partial thromboplastin time is not an adequate method to monitor plasma concentrations of r-hirudin greater than 1  $\mu\text{g/ml}$ ; ecarin clotting time is the method of choice to monitor hirudin during CPB.<sup>2</sup> Another promising device is the HMT TAS analyzer (Cardiovas-

cular Diagnostics, Raleigh, NC)<sup>3</sup> for measurement of ecarin clotting time and activated clotting time, which is now commercially available.

Latham *et al.*<sup>1</sup> described that the blood in the extracorporeal circuit clotted immediately after discontinuation of CPB. R-hirudin blood concentrations at this time might have been borderline. To keep r-hirudin blood concentration greater than 2.5  $\mu\text{g/ml}$ , we administer additional 5-mg boluses during CPB. When CPB is stopped, 5 mg r-hirudin is administered into the CPB system, which is then run as a closed circuit until the blood can be returned to the patient. Any remaining volume in the machine is prepared by a cell saver to eliminate r-hirudin. In patients with renal impairment or high r-hirudin blood concentrations,

we use hemofiltration with a cellulose acetate filter membrane and a cutoff point of 50,000 Da toward the end of CPB.<sup>4,5</sup>

The first patient described in the case report<sup>1</sup> had a history of heparin-induced thrombocytopenia type II 6 yr previously. Although the platelet factor 4 enzyme-linked immunosorbent assay was negative before surgery, r-hirudin was chosen as anticoagulant during CPB. Our strategy in patients with a history of heparin-induced thrombocytopenia type II but negative heparin-induced platelet aggregation test results is to treat these patients with unfractionated heparin during CPB and standard protamine protocol. After the end of surgery, we initiate an r-hirudin infusion for the first postoperative days to keep the activated partial thromboplastin time values between 40 and 60 s. Using this protocol, we treated six patients without thromboembolic, bleeding, or allergic complications.

**\*Friedrich-Christian Riess, M.D., Joachim Kormann, M.D., Bernd Poetsch, M.D.** \*Cardiac Center Hamburg, Albertinen-Hospital, Hamburg, Germany. Herzchirurgie@albertinen.de

Anesthesiology 2000; 93:1552

*In Reply:*—We appreciate the letter from Dr. Riess *et al.* and fully agree that ecarin clotting time (ECT) is the method of choice for monitoring the anticoagulant effectiveness of recombinant hirudin (r-hirudin) in cases that necessitate cardiopulmonary bypass (CPB). However, ECT is not available in many institutions, including ours, and, in an emergent case, it may be necessary to use the activated partial thromboplastin time (aPTT) as an alternative method of monitoring.

Potsch *et al.*<sup>1</sup> clearly demonstrated that plasma concentrations of free r-hirudin correlate much better with ECT than with aPTT, and that there is a poor relation between aPTT prolongation and plasma concentrations of free r-hirudin.<sup>1</sup> Consequently, use of the aPTT makes it difficult to assess accurately the degree of anticoagulation after r-hirudin administration. Thrombotic complications from inadequate anticoagulation during CPB are severe and potentially lethal; therefore, it seems prudent to err on the side of over-anticoagulation if forced to rely on aPTT monitoring. Based on our experience, we recommend maintaining the aPTT around 200 s, a level higher than was recommended previously.<sup>2</sup>

Despite the benefits of monitoring ECT, it is not in widespread use in the United States for several reasons. ECT is not yet approved by the Food and Drug Administration, and its use may necessitate previous

## References

1. Latham P, Revelis AF, Joshi GP, DiMaio JM, Jessen ME: Use of recombinant hirudin in patients with heparin-induced thrombocytopenia with thrombosis requiring cardiopulmonary bypass. *ANESTHESIOLOGY* 2000; 92:263-6
2. Poetsch B, Madlener K, Seelig C, Riess FC, Greinacher A, Müller-Berghaus G: Monitoring of r-Hirudin anticoagulation during cardiopulmonary bypass: Assessment of the whole blood ecarin clotting time. *Thromb Haemost* 1997; 77:920-5
3. Mertzluft FO, Kuppe H, Koster A: On-line monitoring of r-hirudin via ecarin clotting time: In vitro findings for CPB (abstract). *Anesth Analg* 2000; 90:S73
4. Riess FC, Poetsch B, Jaeger K, Bleese N, Schaper W, Müller-Berghaus G: Elimination von rekombinantem Hirudin aus der Blutzirkulation mittels Haemofiltration. Untersuchungen im Schweinemodell. *Haemost* 1997; 17:200-4
5. Riess FC, Poetsch B, Bader R, Bleese N, Greinacher A, Loewer C, Madlener K, Mueller-Berghaus G: A case report on the use of recombinant hirudin as an anticoagulant for cardiopulmonary bypass in open-heart surgery. *Eur J Cardiothorac Surg* 1996; 10:386-8

(Accepted for publication July 11, 2000.)

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

approval from the Food and Drug Administration (for individual patients) or from the institutional review board. Hospital laboratories do not have protocols for ECT monitoring, and it is still labor intensive necessitating a calibration curve for each patient, and relatively expensive. Therefore, further information and education is needed so that hospitals anticipate the need for ECT, protocols are established, and the equipment is available before an urgent r-hirudin-requiring CPB case.

**Paige Latham, M.D., \*Girish P. Joshi, M.B., B.S., M.D., F.F.A.R.C.S.** \*University of Texas Southwestern Medical Center, Dallas, Texas. girish.joshi@email.swmed.edu

## References

1. Pöttsch B, Madlener K, Seelig C, Riess F-C, Greinacher A, Müller-Berghaus G: Monitoring of r-hirudin anticoagulation during cardiopulmonary bypass: Assessment of the whole blood ecarin clotting time. *Thromb Haemost* 1997; 77:920-5
2. Latham P, Revelis AF, Joshi GP, DiMaio JM, Jessen ME: Use of recombinant hirudin in patients with heparin-induced thrombocytopenia with thrombosis requiring cardiopulmonary bypass. *ANESTHESIOLOGY* 2000; 92:263-6

(Accepted for publication July 11, 2000.)

Anesthesiology 2000; 93:1552-3

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Neostigmine as the Fourth Spinal Component for Labor Analgesia?

*To the Editor:*—We read with much interest the article of Owen *et al.*<sup>1</sup> These authors found a significant prolongation of labor analgesia when adding clonidine-neostigmine to a “standard” bupivacaine-fentanyl mixture or when adding clonidine alone. Unfortunately, the occurrence of nausea was a major drawback.

In the November 1999 issue of *ANESTHESIOLOGY*, Nelson *et al.*<sup>2</sup> from Wake Forest University reported that neostigmine may reduce the ED<sub>50</sub> value of sufentanil by 25%. A prolongation of analgesia was suggested by an equal duration of pain relief when administering twice the ED<sub>50</sub> dose of sufentanil (9 µg) alone or twice the ED<sub>50</sub> dose of sufentanil (6 µg) with 10 µg neostigmine.

However, during the annual Society for Obstetric Anesthesia and Perinatology meeting in Denver, Colorado (May 19-22, 1999), D’Angelo *et al.*<sup>3</sup> (from the same study group) reported no benefit with a similar study design as used in the study from Owen *et al.*<sup>1</sup> comparing sufentanil-bupivacaine-clonidine with and without 10 µg neostigmine. Because of the high incidence of nausea, even the use of

neostigmine was strongly dissuaded. Although we realize that Dr. Owen performed her study with a Turkish group, we are amazed that her findings are in contradiction with those of her colleagues at Wake Forest University.

Dr. Eisenach<sup>4</sup> and Dr. D’Angelo,<sup>5</sup> who are experts in the use of neuraxial adjuvant drugs, wrote two editorials commenting on two studies mixing clonidine with other epidural mixtures.<sup>6,7</sup> Because they were critical about triple or quadruple combinations, it is surprising again to notice that they perform studies with an identical design, even while using the more vulnerable intrathecal route. In both our university hospitals (University Hospital Antwerp, Edegem, Belgium, and Catholic University Hospitals of Louvain, Leuven, Belgium), a standard epidural mixture is prepared by the pharmacist under laminar flow in vials containing 0.125% bupivacaine, 0.75 µg/ml sufentanil, and 1:800,000 epinephrine. This mixture does not contain preservatives and is used not only for epidural, but also for intrathecal analgesia.<sup>8</sup> An intrathecal bolus of 2 ml corresponds with 2.5 mg bupivacaine, 1.5 µg

sufentanil (less pruritus and limited rostral spread), and 2.5  $\mu\text{g}$  epinephrine. Although this way of preparing drug mixtures may reduce the risk of contamination and mistakes, we do not wish to add other components with undeniable drawbacks. The publication of controversial results and confusing editorials by the same authors or group makes it difficult for the reader to find out what to believe.

\***Marcel P. Vercauteren, M.D., Ph.D., Marc Van de Velde, M.D.**  
\*University Hospital Antwerp, Edegem, Belgium.

## References

- Owen MD, Ozsarac O, Sahin S, Uckunkaya N, Kaplan N, Magunaci I: Low-dose clonidine and neostigmine prolong the duration of intrathecal bupivacaine-fentanyl for early labor analgesia. *ANESTHESIOLOGY* 2000;92: 361-6
- Nelson KE, D'Angelo R, Foss ML, Meister GC, Hood DD, Eisenach JC:

*Anesthesiology* 2000; 93:1553

*In Reply:*—We thank Drs. Vercauteren and Van de Velde for their interest in our work using intrathecal neostigmine combinations for labor analgesia. We wish to comment on several points raised in their letter. Drs. Vercauteren and Van de Velde are “amazed” that findings from several of our recent studies appear to be contradictory. In one study,<sup>1</sup> the addition of 10  $\mu\text{g}$  neostigmine to intrathecal bupivacaine-sufentanil-clonidine did not prolong labor analgesia, yet in a similar study<sup>2</sup> using bupivacaine-fentanyl-clonidine, it did. Although these results may appear to be conflicting, they are not.

Drs. Vercauteren and Van de Velde fail to mention that the clonidine dose used in the first study was 50  $\mu\text{g}$ , enough to produce 215 min of analgesia (and an 87% incidence of hypotension).<sup>1</sup> This larger dose of clonidine may have overshadowed any benefits that might have been seen from the intrathecal neostigmine. In the second study,<sup>2</sup> 30  $\mu\text{g}$  clonidine was used to minimize hypotension, which was successful (27% incidence).<sup>2</sup> By using a lower clonidine dose, the addition of 10  $\mu\text{g}$  neostigmine significantly increased the duration of labor analgesia from 123 to 165 min, but it also produced an unacceptable level of nausea (40%). With the lower dose of clonidine, we were able to observe the analgesic benefits of neostigmine, consistent with other studies from our institution.<sup>3,4</sup> Had we used the same clonidine dose for both studies (either 30 or 50  $\mu\text{g}$ ) and found varying results, this would imply that the effect of neostigmine was small or variable or that differences existed between study populations.

Our research team works closely together to design complementary studies to expand the pharmacologic knowledge base, with an emphasis on improving the duration and quality of labor analgesia. Although we believe drug combinations offer the best hope of producing prolonged labor analgesia with minimal side effects, we acknowledge the risks of contamination and dilution errors in multiple drug therapy, and we do not advocate this practice for general patient care, as pointed

Intrathecal neostigmine and sufentanil for early labor analgesia. *ANESTHESIOLOGY* 1999; 91:1293-8

- D'Angelo R, Dean L, Meister G, Nelson K, Eisenach J: Labor analgesia from spinal neostigmine combined with spinal sufentanil, bupivacaine and clonidine (abstract). *ANESTHESIOLOGY* 1999; 90(SOAP suppl):A17
- Eisenach J: Additives for epidural analgesia for labor: Why bother? *Reg Anesth Pain Med* 1998; 23:531-2
- D'Angelo R: Should we administer epidural or spinal clonidine during labor? *Reg Anesth Pain Med* 2000; 25:3-4
- Claes B, Soetens M, Van Zundert A, Datta S: Clonidine added to bupivacaine-epinephrine-sufentanil improves epidural analgesia during childbirth. *Reg Anesth Pain Med* 1998; 23:540-7
- Paech MJ, Favy TJ, Orlikowski CE, Evans SF: Patient-controlled epidural analgesia in labor: The addition of clonidine to bupivacaine-fentanyl. *Reg Anesth Pain Med* 2000; 25:34-40
- Vercauteren M, Bettens K, Van Springel G, Schols G, Van Zundert J: Intrathecal labour analgesia: Do we need another combination than used epidurally? *Int J Obstet Anesth* 1997; 6:242-6

(Accepted for publication July 11, 2000.)

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

out in editorials by Drs. Eisenach<sup>5</sup> and D'Angelo.<sup>6</sup> Determining whether drug combinations might be useful and recommending the routine use of such combinations are two different things. If we discover a useful intrathecal or epidural drug combination, we agree with Drs. Vercauteren and Van de Velde—these combinations should be prepared carefully by a hospital pharmacy (which occurs at our institution) or marketed by the pharmaceutical industry, not the individual clinician. It is important to clarify the difference between clinical research and the routine use of a drug combination, and we thank Drs. Vercauteren and Van de Velde for bringing this issue to light.

\***Medge D. Owen, M.D., Robert D'Angelo, M.D., James C. Eisenach, M.D.** \*Wake Forest University Medical Center, Winston-Salem, North Carolina. mowen@wfubmc.edu

## References

- D'Angelo R, Dean L, Meister G, Nelson K, Eisenach J: Labor analgesia from spinal neostigmine combined with spinal sufentanil, bupivacaine, and clonidine (abstract). *ANESTHESIOLOGY* 1999; 90(SOAP suppl):A17
- Owen MD, Özsarac O, ahin S, Uçkunkaya N, Kaplan N, Magunaci I: Low dose clonidine and neostigmine prolong the duration of intrathecal bupivacaine-fentanyl for labor analgesia. *ANESTHESIOLOGY* 2000;92: 361-6
- Nelson KE, D'Angelo R, Foss ML, Meister GC, Hood DD, Eisenach JC: Intrathecal neostigmine and sufentanil for early labor analgesia. *ANESTHESIOLOGY* 1999; 91:1293-8
- Hood DD, Mallak KA, Eisenach JC, Tong C: Interaction between intrathecal neostigmine and epidural clonidine in human volunteers. *ANESTHESIOLOGY* 1999; 91:315-25
- Eisenach J: Additives for epidural analgesia for labor: Why bother (editorial)? *Reg Anesth Pain Med* 1998; 23:531-2
- D'Angelo R: Should we administer epidural or spinal clonidine during labor (editorial)? *Reg Anesth Pain Med* 2000; 25:3-4

(Accepted for publication July 11, 2000.)

*Anesthesiology* 2000; 93:1553-4

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Intrathecal Morphine in Chronic Pain Management

*To the Editor:*—We commend the work of Dougherty and Staats,<sup>1</sup> which provides an update for the reader regarding pending advances in intrathecal drug therapy for chronic pain. We also commend their effort to provide us with a view of therapeutic horizons in chronic pain management. Their review, however, may not be completely accurate about the status of intrathecal morphine in the treatment of chronic pain.

The authors state that morphine is the “gold standard” for intrathecal drug administration because it has been approved for “long-term”

intrathecal treatment of pain by the United States Food and Drug Administration. The *Physician's Desk Reference*<sup>2</sup> reflects the Food and Drug Administration's position on intrathecal morphine (Duramorph; Elkins-Sinn, Cherry Hill, NJ). The 1999 *Physician's Desk Reference* states that “Repeated intrathecal injections of Duramorph are not recommended.” Furthermore, the *Physician's Desk Reference* states that if pain recurs after single intrathecal injection, “alternative routes of administration should be considered, since repeated doses of mor-

phine by the intrathecal route is limited." The *Physician's Desk Reference* has no comment about the safety and effectiveness of intrathecal morphine for long-term constant infusions.

The authors also state that long-term intrathecal morphine "has fewer side effects than do systemic opioids." To substantiate their claim, the authors cite eight reports. However, none of these reports compare long-term systemic morphine with long-term intrathecal morphine in well-controlled trials in patients with chronic pain.

It is well-recognized that a single injection of morphine into the intrathecal space produces a selective pain-blocking effect on the spinal cord, sparing the patient many of the serious side effects caused by morphine when it is administered orally (e.g., sedation).<sup>3</sup> Soon after this discovery, enthusiasm developed to implant permanent morphine pumps to treat non-cancer-related chronic pain, especially after Medicare began to approve this surgical procedure for reimbursement. Implantation of a morphine pump is a relatively invasive and expensive treatment modality.<sup>4</sup> Despite almost 20 yr of testing, no well-controlled studies have emerged that indicate that long-term use of the morphine pump offers an advantage over oral morphine for treating various chronic pain syndromes. In fact, many patients with the implanted morphine pump are prescribed oral opioid at the same time. The same complications sometimes associated with oral morphine use are found with the morphine pump, such as development of drug tolerance, nausea, constipation, weight gain, decreased sexual desire (libido), swollen legs (edema), and increased sweating.<sup>5,6</sup> In addition, malfunc-

tion of the pump system (dislodgment of the catheter) or surgical complications may present a significant problem.<sup>6</sup>

In the era of managed care, our strength as a specialty will depend more and more on our willingness to compare safer and more cost-effective therapeutic options with anesthetic procedures in well-controlled clinical trials.

\***Anthony F. Kirkpatrick, M.D., Ph.D., Michael P. Herndon, M.D.**  
University of South Florida, College of Medicine, Tampa, Florida.  
akirkpat@com1.med.usf.edu

## References

1. Dougherty PM, Staats PS: Intrathecal drug therapy for chronic pain. *ANESTHESIOLOGY* 1999; 91:1891-1918
2. *Physician's Desk Reference*, edition 53. Montvale, Medical Economics, 1999
3. Cousins MJ, Bridenbaugh PO: *Neural Blockade*, 2nd edition. New York: Lippincott Press, 1988, pp 975-9
4. Krames E: Intraspinal opioid therapy for chronic nonmalignant pain: Current practice and clinical guidelines. *J Pain Symptom Manage* 1996; 11:333-52
5. Doleys D, Dinoff B, Page L, Tutak U, Willis K, Coletton M: Sexual dysfunction and other side effects of intraspinal opiate use in the management of chronic non-cancer pain. *Am J Pain Management* 1998; 8:5-11
6. Paice J, Penn R, Shott S: Intraspinal morphine for chronic pain: A retrospective, multicenter study. *J Pain Symptom Manage* 1996; 11:71-80

(Accepted for publication July 3, 2000.)

Anesthesiology 2000; 93:1554

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

*In Reply:*—We appreciate the comments of Drs. Kirkpatrick and Herndon regarding the safety and effectiveness of intraspinal morphine for the relief of chronic pain. We noted that they specifically objected to our reference to morphine as the "gold standard" for intrathecal analgesic therapy. They also highlight the fact that long-term intraspinal administration of this compound involves managing certain well-known complications and necessitates attention to the potential for unknown risks. In reply, we assert that, because morphine is the only drug approved for intraspinal delivery by the Food and Drug Administration for pain and is used widely in this context to treat acute pain successfully worldwide, it is, by default, the standard against which all other intrathecal analgesics are compared. For example, opiates were used as the reference analgesics in 37 of 50 clinical studies we found that were published in 1999 and 2000, and morphine was the reference drug in 19 of these studies. Yet, as we noted in the introduction to our review and as Drs. Kirkpatrick and Herndon reiterate in their letter, the medical complications, scientific uncertainties, and socioeconomic questions regarding long-term use of intrathecal morphine motivate the desire to identify new drugs or drug combinations that may qualify as improved "platinum standards" for the treatment of pain. The main goal of our review was to inform readers of potential candidates for this future role. Finally, Drs. Kirkpatrick and Herndon note that studies that directly compare the effectiveness of systemic *versus* intraspinal analgesics for long-term control of chronic pain, both cancer- and non-cancer-related, are needed. At least one such study, a randomized, controlled trial comparing maximal medical therapy *versus* intrathecal therapy in patients with cancer pain, is now in progress at 26 centers worldwide.<sup>1</sup> The study compares pain relief, quality of life, and cost effectiveness of the two drug administration approaches (systemic and intrathecal). Seventy-four cancer patients, whose pain is not controlled adequately with 200 mg systemic morphine equivalent or who have uncontrolled side effects, have been randomized to receive maximal medical therapy or intrathecal therapy. It is hoped that this project will be completed by the end of 2001 and will help to define better the role of intraspinal analgesics for chronic pain.

Dennis M. Fisher, M.D., was acting Editor-in-Chief for this correspondence.

As an addendum to our previous work, readers should note that new potential targets for intrathecal analgesia regimens have been introduced in the literature during or after publication of our review. Potential neurotransmitter targets now also include the cannabinoid and vanilloid receptor systems. Intrathecal administration of WIN55,2122, an agonist for the cannabinoid 1 receptor, had no effect on baseline paw withdrawal latency to punctate mechanical stimuli in rats but reduced mechanical hyperalgesia after paw inflammation.<sup>2</sup> Resiniferatoxin, an ultrapotent agonist for the vanilloid (capsaicin) 1 receptor, produced thermal analgesia 4-6 h after epidural administration in rats, which lasted more than 7 days.<sup>3</sup> The list of potential neuromodulator targets also has been extended. Intrathecal administration of [Phe<sup>1</sup>(CH<sub>2</sub>NH)Gly<sup>2</sup>]nociceptin(113)NH<sub>2</sub>, a pseudopeptide analog of nociceptin, produced a dose-dependent increase of tail flick latency in rats that lasted up to 1 h.<sup>4</sup>

We appreciate the comments of Drs. Kirkpatrick and Herndon. Although it is clearly the clinical standard, we agree that morphine may not qualify as "gold." The main point of our review, however, was not to evaluate morphine rigorously but to inform readers that there are many agents that, alone or in combination, may become new, improved "platinum standards" for the intraspinal treatment of pain.

\***Patrick M. Dougherty, Ph.D., Peter S. Staats, M.D.**  
The University of Texas M. D. Anderson Cancer Center, Houston, Texas.  
pdougherty@mdanderson.org

## References

1. Staats PS: A multicenter, randomized controlled trial of intrathecal *versus* systemic therapy for chronic cancer pain. *American Pain Society Abstracts* 1999; 18:181
2. Martin WJ, Loo CM, Basbaum AI: Spinal cannabinoids are anti-allodynic in rats with persistent inflammation. *Pain* 1999; 82:199-205
3. Szabo T, Olah Z, Iadarola MJ, Blumberg PM: Epidural resiniferatoxin induced prolonged regional analgesia to pain. *Brain Res* 1999; 840:92-8
4. Wang Y-Q, Zhu C-B, Cao X-D, Wu G-C: Supraspinal hyperalgesia and spinal analgesia by [Phe<sup>1</sup>Ψ(CH<sub>2</sub>-NH)Gly<sup>2</sup>]nociceptin-(1-13)-NH<sub>2</sub> in rat. *Eur J Pharmacol* 1999; 376:R1-3

(Accepted for publication July 3, 2000.)

Anesthesiology 2000; 93:1555

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams &amp; Wilkins, Inc.

## Measurement of Cerebral Blood Flow at the Bedside

*To the Editor:*—The paper by Wietasch *et al.*<sup>1</sup> describes a new technique, transcerebral thermodilution, to evaluate cerebral blood flow (CBF) at the bedside based on a double-indicator method (dye and iced water). The agreement of this new technique with the Kety-Schmidt reference method, with use of argon as a tracer gas, in patients undergoing coronary bypass surgery is reported as reasonable. In fact, the agreement of transcerebral thermodilution technique with the Kety-Schmidt method is poor, with a bias of  $7 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ , which is 14% of the normal value for CBF ( $50 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ), with 95% limits of agreement of  $\pm 26 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ , which are 50% of the normal values for CBF. Moreover, the authors do not report the *in vivo* variability for repeated measurements with the transcerebral thermodilution technique. In the intensive care setting, continuous jugular thermodilution has a better agreement with the Kety-Schmidt reference method (bias  $-0.9 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ , with 95% limits of agreement of  $\pm 7.2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ).<sup>2</sup> More important is the inaccuracy of the measurement at low CBF. If we look at the Bland and Altman diagram, figure 5 in the article by Wietasch *et al.*,<sup>1</sup> it is obvious that the transcerebral thermodilution technique as compared with the Kety-Schmidt method underestimates CBF below  $30 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ .

Anesthesiology 2000; 93:1555-6

*In Reply:*—We appreciate the interest of Dr. Mélot *et al.* in our recent report on a new method of bedside measurement of cerebral blood flow.<sup>1</sup> In principle, we agree with Dr. Mélot *et al.* that, according to their publication,<sup>2</sup> the accuracy of their methodology for measurement of cerebral blood flow is better, and we congratulate them on their impressive results. However, we would like to point out some principal differences between the method of cerebral blood flow measurement in the jugular bulb by continuous thermodilution, as described by Mélot *et al.*,<sup>2</sup> and the method of cerebral blood flow measurement by transcerebral thermodilution, as applied in our investigation. The technique of Dr. Mélot *et al.*<sup>2</sup> measures jugular bulb flow in a manner similar to that developed previously for coronary sinus outflow measurements.<sup>3</sup> This methodology is based on the principle of mass conservation<sup>4</sup> and, therefore, yields blood flow measurements in absolute terms (ml/min). To convert this blood flow measurement into physiologically and pathophysiologically relevant organ-specific blood flow (*i.e.*, into  $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ), brain weight must be estimated. In the investigation of Dr. Mélot *et al.*,<sup>2</sup> this was done by assuming a proportional relation to body height, which was assumed to be different for men and women, according to the work of Spann *et al.*<sup>5</sup> However, as described in the same investigation, the weight of the brain varies significantly interindividually. Spann *et al.*<sup>5</sup> also present several cases in which the brain weight was 6.1 g/cm in one individual and 11.6 g/cm in another individual. Thus, by measuring absolute flow in the jugular vein and converting this flow to organ blood flow in terms of  $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$  based on an estimated brain weight, this variability should contribute to the accuracy of the methodology. Therefore, we opted for a methodology that is based on a transit time principle and, therefore, measures weight-normalized organ blood flow directly. With use of an intravascular tracer and a diffusible tracer simultaneously, cerebral blood volume also can be determined principally.

Dr. Mélot *et al.* correctly point out that the limits of agreement with the Kety-Schmidt method, which we used as a reference method, were not as good as the method used for continuous jugular thermodilution in their investigation. Some of the possible explanations for the observed scatter have been discussed in the paper in more detail.<sup>1</sup> In

This point is of crucial importance for a technique proposed for use at the bedside in a critical care unit to monitor patients with low cerebral blood flow, which occurs in most brain-injured comatose patients.<sup>3</sup>

\*Christian Mélot, M.D., Ph.D., M.Sci.Biostat., Jean-Jacques Moraine, P.T., Ph.D., Jacques Berré, M.D. \*School of Medicine, Free University of Brussels, Brussels, Belgium. cmelot@ulb.ac.be

## References

1. Wietasch GJK, Mielck CK, Scholtz M, von Spiegel T, Stephan H, Hoef A: Bedside assessment of cerebral blood flow by double-indicator dilution technique. *ANESTHESIOLOGY* 2000; 92:367-75
2. Mélot C, Berré J, Moraine JJ, Kahn RJ: Estimation of cerebral blood flow at bedside by continuous jugular thermodilution. *J Cereb Blood Flow Metabol* 1999; 16:1263-70
3. Moraine JJ, Berré J, Mélot C: Is cerebral perfusion pressure a major determinant of cerebral blood flow during head elevation in comatose patients with severe intracranial lesions? *J Neurosurg* 2000; 92:606-14

(Accepted for publication July 11, 2000.)

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams &amp; Wilkins, Inc.

comparison with the work of Dr. Mélot *et al.*, we would like to add some further comments. The reference Kety-Schmidt method, which they used in their study, is slightly different from our Kety-Schmidt methodology. We used Argon as a tracer and a sampling system (Unit I; B. Braun, Melsungen, Germany), which draws blood continuously from arterial and jugular bulb catheters, thereby averaging the concentration time courses at these sites "in the syringe." The advantage of this approach is less analytical effort as opposed to serial blood samples, which are necessitated by the classic Kety-Schmidt methodology. However, it seems that the price paid for this sparing of blood samples might be less accuracy as compared with the classic Kety-Schmidt methodology, in particular when viewed with the clearly better results of Dr. Mélot *et al.*<sup>2</sup> On the other hand, we clearly pointed out in our article that the reference method used in our investigation is most likely a significant source for the scatter between methods, which has to be taken into account.

Another limitation of blood flow measurement with use of transcerebral thermodilution, pointed out by Dr. Mélot *et al.*, is the limited accuracy at low blood flow rates, which has also been addressed in their publication. We agree that, in some critically ill patients, low blood flow rates might be of particular interest, and, therefore, we tried to improve the methodology of transcerebral thermodilution in this respect. The crucial problem is the duration of data sampling, which was only 5 min in our investigation. For low blood flow rates, the sampling periods should be prolonged, an option that is being investigated in our department.

We thank Dr. Mélot *et al.* for their interest in our work. As with all clinical methods of measurements, each methodology has its advantages and disadvantages. We believe that, particularly in combination with transcranial Doppler measurements of blood flow velocities, transcerebral double-indicator dilution might add to the armamentarium of cerebral monitoring, especially when longer sampling periods are used.

\*Andreas Hoefl, M.D., Ph.D., Götz Wietasch, M.D. \*University of Bonn, Bonn, Germany. wietasch@mail.meb.uni-bonn.de

## References

1. Wietasch GJK, Mielck CK, Scholtz M, von Spiegel T, Stephan H, Hoefft A: Bedside assessment of cerebral blood flow by double-indicator dilution technique. *ANESTHESIOLOGY* 2000; 92:367-75
2. Melot C, Berre J, Moraine JJ, Kahn RJ: Estimation of cerebral blood flow at bedside by continuous jugular thermodilution. *J Cereb Blood Flow Metab* 1996; 16:1263-70
3. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJ: Measure-

- ment of coronary sinus blood flow by continuous thermodilution in man. *Circulation* 1971; 51:181-95
4. Lassen NA, Pearl WA: *Tracer Kinetic Methods in Medical Physiology*. New York, Raven Press, 1979, pp 76-101
5. Spann W, Dustmann HO: Das menschliche Hirngewicht und seine Abhängigkeit von Lebensalter, Körperlänge, Todesursache und Beruf. *Dtsch Z Gesamte Gerichtl Med* 1965; 56:299-317

(Accepted for publication July 11, 2000.)

Anesthesiology 2000; 93:1556

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Complications Associated with Intermittent Pneumatic Compression Devices

*To the Editor:*—The article by Siddiqui *et al.*<sup>1</sup> was interesting and informative. Antithrombotic devices have long stood the test as prophylactics against the development of perioperative deep vein thrombosis and pulmonary embolism (PE). It is alarming that they could be a causative factor in the development of that intraoperative complication that all anesthesiologists fear—PE. However, as the authors correctly point out, a cause-effect relation, in the presence of the multiple significant risk factors for pulmonary thromboembolism that the patient had, could not be made justifiably. However, the mere possibility of such an occurrence will make me more vigilant during application of such devices. It is conceivable that more cases of such occurrences will be reported, leading to the establishment of more concrete evidence on causality.

Although the authors mention that no significant complications caused by pneumatic compression devices have been reported previously, I would like to bring to their attention a recent article by Lachmann *et al.*<sup>2</sup> They report postoperative development of acute right lower leg compartment syndrome related to use of an intermittent pneumatic compression device, and they caution its use in patients undergoing prolonged surgery in the lithotomy position. Direct local muscle pressure from intermittent pneumatic compression devices can cause muscle necrosis and loss of capillary integrity, leading to massive edema and increased compartmental pressures. They also report the postoperative development of bilateral common peroneal nerve palsy after use of intermittent pneumatic compression devices in a 65-yr-old man with significant weight loss related to malignancy. Loss of tissue and fat around the common peroneal nerves, leaving them unprotected, and increased anterior compartment pressure from the intermittent pneumatic compression devices contributed to ischemia of the nerves.

Other serious injuries that are reported secondary to use of compression devices include acute compartment syndrome caused by a

malfunctioning pneumatic compression boot<sup>3</sup> and peroneal nerve palsy caused by use of a sequential pneumatic compression device.<sup>4</sup>

Curiously, Cisek and Walsh<sup>5</sup> report a higher incidence of thromboembolic complications after radical retropubic prostatectomy in patients using external sequential compression devices perioperatively. Of 1,300 consecutive patients studied, 516 men had perioperative involvement of sequential compression device prophylaxis. There were 12 (2.3%) thromboembolic complications: 9 (1.7%) cases of PE and 3 (0.6%) cases of deep vein thrombosis. Of the 784 men with no perioperative sequential compression device prophylaxis, there were 9 (1.1%) thromboembolic complications: 7 (0.9%) cases of PE and cases of (0.3%) deep vein thrombosis. In light of the case report by Siddiqui *et al.*,<sup>1</sup> one can but wonder if sequential compression device use played a role in the development of PE in any of these patients.

**Abhay Anand, M.D.**, Medical College of Wisconsin, Milwaukee, Wisconsin. [aanand@mcw.edu](mailto:aanand@mcw.edu)

## References

1. Siddiqui AU, Buchman TG, Hotchkiss RS: Pulmonary embolism as a consequence of applying sequential compression device on legs of a patient asymptomatic of deep vein thrombosis. *ANESTHESIOLOGY* 2000; 92:880-2
2. Lachmann EA, Rook JL, Tunkel R, Nagler W: Complications associated with intermittent pneumatic compression. *Arch Phys Med Rehabil* 1992; 73:482-5
3. Matsen FA: Compartmental syndrome: A unified concept. *Clin Ortho* 1988; 13:8-14
4. Pittman GR: Peroneal nerve palsy following sequential pneumatic compression. *JAMA* 1989; 261:2201-2
5. Cisek LJ, Walsh PC: Thromboembolic complications following radical retropubic prostatectomy: Influence of external pneumatic compression devices. *Urology* 1993; 42:406-8

(Accepted for publication July 13, 2000.)

Anesthesiology 2000; 93:1556-7

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

*In Reply:*—I thank Dr. Anand for bringing to the attention of the readers of *ANESTHESIOLOGY* more complications related to sequential compression devices (SCD) used as prophylaxis against development of deep venous thrombosis.

Regarding complications associated with the use of SCD, such as leg compartment syndrome, common peroneal nerve injury, and others, we believe that, based on the nature of the device, certain patients will experience complications. This prompts us to improve the quality of devices and techniques to make them safer for our patients. Although clinicians should consider these remote complications when they prescribe use of the device, these complications are not life threatening or the cause of immediate concern to anesthesiologists who care for emergency surgery patients.

In his letter, Dr. Anand raised an interesting point in reference to a study by Cisek and Walsh.<sup>1</sup> He wonders if SCD could be a factor in the higher incidence of thromboembolic complications in the patients who underwent retropubic radical prostatectomy. In our case report,<sup>2</sup> we reported a patient who had multiple risk factors for deep venous thrombosis but was asymptomatic, and we suspect that SCD might have been involved in the dislodgment of already established thrombi. An argument can be made against Dr. Anand's concern that SCDs could have played a part in the development of deep venous thrombosis because most retropubic radical prostatectomy patients undergo elective surgery, and the disease process (operable tumor) itself is not a risk factor for deep venous thrombosis. The study suggests increased incidence of thromboembolic complications in patients who had SCDs

on their legs; however, it is difficult to establish a causal relation between these devices and the etiology of deep venous thrombosis. This study shows that SCDs delay thromboembolic complications. Most patients in the Cisek and Walsh study experienced these complications after discharge from the hospital.

\*Ata U. Siddiqui, M.D., Timothy G. Buchman, M.D., Ph.D., Richard S. Hotchkiss, M.D. \*Washington University School of Medicine, Saint Louis, Missouri. atasiddiqui@hotmail.com

## References

1. Cisek LJ, Walsh PC: Thromboembolic complications following retropubic prostatectomy: Influence of external pneumatic compression devices. *Urology* 1993; 42:406-8
2. Siddiqui AU, Buchman TG, Hotchkiss RS: Pulmonary embolism as a consequence of applying sequential compression device on legs of a patient asymptomatic of deep vein thrombosis. *ANESTHESIOLOGY* 2000; 92:880-2

(Accepted for publication July 13, 2000.)

Anesthesiology 2000; 93:1557-8

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Population Pharmacokinetics of Propofol for Target-controlled Infusion (TCI) in the Elderly

*To the Editor:*—Schüttler and Ihmsen<sup>1</sup> have performed a massive task, the evaluation of propofol concentration-time data from a data set that is, in many ways, heterogeneous. The authors start and end their article with the suggestion that the field of target-controlled infusion (TCI) may be broadened by using their results for application of TCI in children and elderly patients. In contrast to this suggestion, and although the results may be well-applicable to children and adults, our evaluation leads us to believe that the described data set should not be used for TCI of propofol in the elderly and even may be harmful to this patient population for various reasons.

The pharmacokinetics of propofol during continuous infusion in the elderly have been described by Dyck and Shafer,<sup>2</sup> Schnider *et al.*,<sup>3</sup> and Oostwouder *et al.*<sup>4</sup> A computer simulation of a simple infusion scheme (1.5 mg/kg bolus in 1 min followed by a continuous infusion of  $7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) based on the pharmacokinetics described by the authors shows that the concentration-time data differ significantly from those based on the three other parameter sets (fig. 1). This discrepancy may be the result of the following.

First, the central compartment ( $V_1$ ) of Schüttler and Ihmsen<sup>1</sup> is much larger compared with the previously described data sets. As a result, the initial bolus of the TCI system to reach the desired target concentration is equivalently larger. The "front end kinetics" are missed or misjudged in the Schüttler and Ihmsen<sup>1</sup> parameter set. The larger initial bolus is especially harmful in the elderly in respect to their level of hemodynamic stability during induction. Second, during continuous infusion, the predicted propofol concentration after 360 min of administration is approximately 60% higher based on the data of Schüttler and Ihmsen,<sup>1</sup> compared with the average propofol concentration

as predicted on the basis of the other three parameter sets (fig. 1). This may be caused predominantly by the small metabolic clearance of less than 1 l/min in a typical elderly patient according to the data set by Schüttler and Ihmsen,<sup>1</sup> compared with the 1.5 l/min described by the others.<sup>2-4</sup>

How does this translate to the application in TCI? Obviously, the infusion rate needed to maintain a target propofol concentration of, for example,  $2.5 \text{ } \mu\text{g/ml}$ , is much less when the set of Schüttler and Ihmsen<sup>1</sup> is used compared with any of the other three sets (fig. 2). Implementing the Schüttler and Ihmsen-based infusion scheme needed to maintain a target concentration of  $2.5 \text{ } \mu\text{g/ml}$  in a computer simulation program provided with the Schnider and Ihmsen<sup>3</sup> parameter set (the results are similar when the simulation program is provided with the Oostwouder *et al.*<sup>4</sup> set or the Dyck and Shafer<sup>2</sup> set) shows how low the concentration of propofol in the blood may become ( $1.5 \text{ } \mu\text{g/ml}$ ) when the population pharmacokinetic set is used for TCI in the elderly (fig. 3). Therefore, we conclude that use of the population pharmacokinetic parameter set described by Schüttler and Ihmsen<sup>1</sup> in a TCI setting in the elderly may cause unwanted low blood and effect-site propofol concentrations, increasing the risk of intraoperative awareness.

What may be the cause of this poor description of the propofol pharmacokinetics in the elderly? From table 1, it is clear that, of the 270 patients studied, only a small minority was aged 65 yr or older (approximately 10%), in contrast to, for example, a large group of patients aged 11 yr or younger (approximately 35%). From the groups of patients that contain elderly patients (groups 3, 5, and 7), the patients from group 5 only were administered a bolus dose of propofol. Clearly, from these patients, the evaluation of the concentration-time data is less useful for the application in a continuous infusion setting.

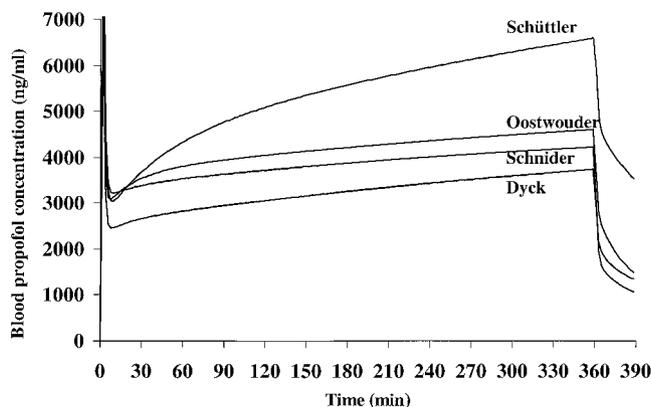


Fig. 1. The predicted propofol concentrations based on pharmacokinetic parameter sets described by Schüttler and Ihmsen,<sup>1</sup> Dyck and Shafer,<sup>2</sup> Schnider *et al.*,<sup>3</sup> and Oostwouder *et al.*<sup>4</sup> in a 73-yr-old man, weighing 75 kg, 180 cm tall, who was administered a 1.5-mg/kg bolus dose of propofol in 1 min followed by  $7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for 359 min.

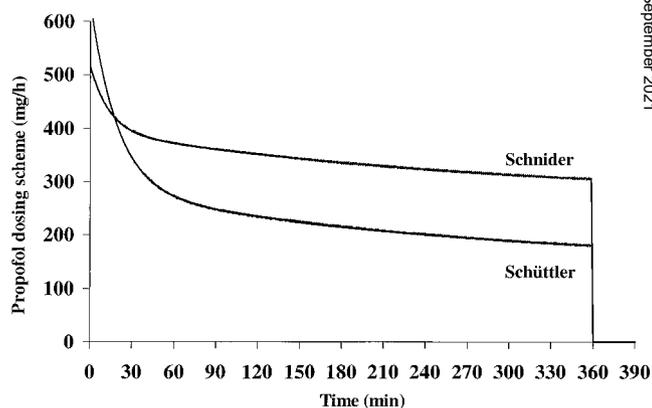
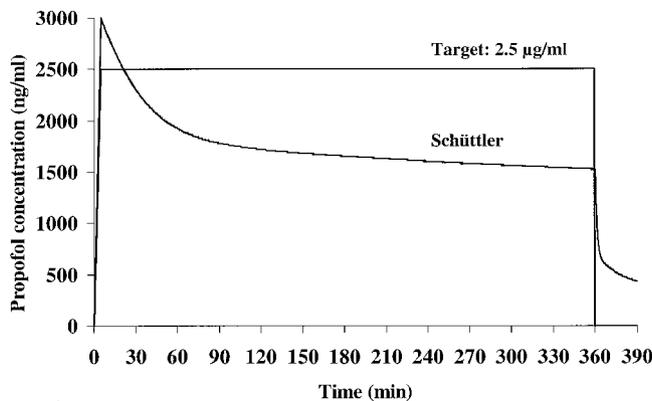


Fig. 2. The infusion rates needed to reach and maintain a target propofol concentration of  $2.5 \text{ } \mu\text{g/ml}$  as based on the pharmacokinetic parameter set of Schüttler and Ihmsen<sup>1</sup> and Schnider *et al.*<sup>3</sup>



**Fig. 3.** The blood propofol concentrations as predicted on the basis of a computer simulation using the pharmacokinetic parameter set of Schnider *et al.*<sup>3</sup> when provided with the infusion rate–time data needed to reach and maintain a target propofol concentration of 2.5 µg/ml on the basis of the Schüttler and Ihmsen<sup>1</sup> parameter set.

such as TCI. From the remaining elderly patients (groups 3 and 7), concentration–time data were gathered only for a mean period of 55 min. From these data, measured over such a short period, it is difficult, if not impossible, to estimate accurately the clearance or slow distribution of propofol.

Last, the article lacks a retrospective or prospective validation of the

Anesthesiology 2000; 93:1558–60

*In Reply:*—Pharmacokinetic modeling has gained more than academic interest because these models can be used for computer-controlled drug administration, which probably will become more and more relevant for clinical practice. This aspect of “applied pharmacokinetics” was one reason for the population pharmacokinetic analysis of propofol published in ANESTHESIOLOGY,<sup>1</sup> and, obviously, it also was the reason for the criticism of Vuyk *et al.* as pointed out in their letter. Because discussion is essential for scientific progress, we appreciate any comment about our work, but we do not believe that the arguments of the authors can justify their conclusions.

Vuyk *et al.* claim that the pharmacokinetic parameter set published in ANESTHESIOLOGY<sup>1</sup> is “unsuitable for application in TCI [target-controlled infusion] in elderly patients.” This statement is, however, nothing but an unproved claim because Vuyk *et al.* did not investigate, either retrospectively or prospectively, the predictability of different parameter sets but simply compared the results of different studies. The cited publications of Dyck and Shafer,<sup>2</sup> Schnider *et al.*,<sup>3</sup> and Oostwouder *et al.*<sup>4</sup> also present estimates of the pharmacokinetic parameters of propofol without any further validation. Therefore, we completely agree with the statement that “nobody knows . . . whether this parameter set predicts the measured propofol concentrations better than previous parameters sets”—nobody, including Dr. Vuyk *et al.*

Therefore, the problem is reduced to the question of the comparability of different data sets: In our population analysis, we studied 270 individuals, with 35 subjects aged 65 yr or older. From these 35 individuals, 9 were administered propofol as a single bolus dose. Thus, there were 26 individuals aged 65 yr or older who were administered propofol as a continuous infusion. This is only 10% of the complete data set, but the absolute number of individuals is still greater than in the study of Schnider *et al.*<sup>3</sup> (9 elderly volunteers of 24 *in toto*) and comparable with the studies of Oostwouder *et al.*<sup>4</sup> (22 elderly) and Dyck and Shafer<sup>2</sup> (20 elderly). Regarding the relatively small fraction of elderly patients in our total population, it should be noted that the

parameter set. As a result, nobody knows, also for the adults and children, whether this parameter set predicts the measured propofol concentrations better than previous parameter sets.

The lack of concentration–time data from a significant number of elderly patients who were administered propofol by continuous infusion and from whom data were gathered for an appropriate period of time (3 times the elimination half-life) resulted in a data set far different from those previously described. As a result, this population pharmacokinetic parameter set is unsuitable for application in TCI in elderly patients.

\*Jaap Vuyk, M.D. Ph.D., Thomas Schnider, P.D., Dr.med., Frank Engbers, M.D. \*Leiden University Medical Center, Leiden, The Netherlands. j.vuyk@lumc.nl

## References

1. Schüttler J, Ihmsen H: Population pharmacokinetics of propofol. ANESTHESIOLOGY 2000; 92:727–38
2. Dyck JB, Shafer SL: Effect of age on propofol pharmacokinetics. Seminars in Anaesthesia 1992; XI(suppl 1):2–4
3. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SH, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. ANESTHESIOLOGY 1998; 88:1170–82
4. Oostwouder CJ, Vuyk J, Vletter AA, Burm AGL, Bovill JG: The pharmacokinetics of propofol in the elderly patient (abstract). ANESTHESIOLOGY 1996; 85(suppl 3A):A326

(Accepted for publication July 14, 2000.)

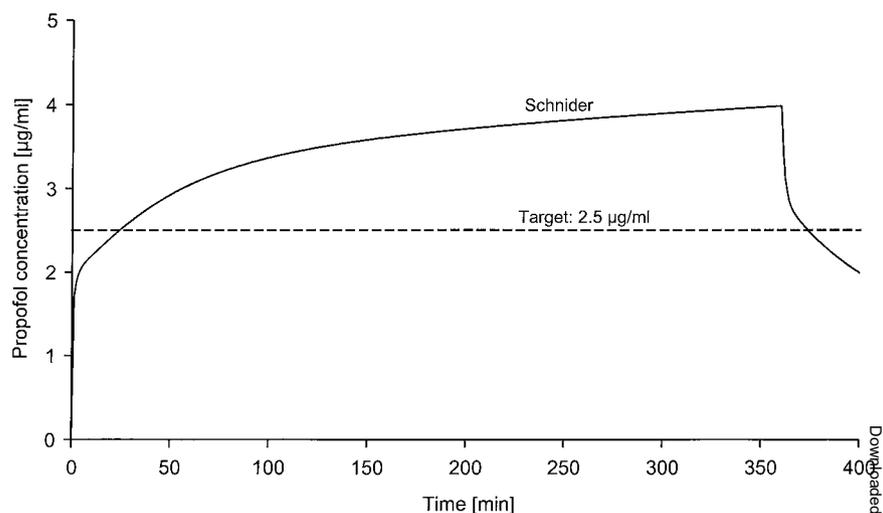
© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

effect of age on elimination clearance was highly significant (age as covariate for clearance led to a significant reduction of the NONMEM objective function) and distinct (reduction by approximately 50% for patient aged 75 yr). If the number of elderly individuals within the total population had been too small, the effect of age should have been much smaller than observed.

When comparing the pharmacokinetic parameters of our study with those from Dyck and Shafer,<sup>2</sup> Oostwouder *et al.*,<sup>4</sup> and Schnider *et al.*,<sup>3</sup> the differences in the estimates of the elimination clearance and the central volume of distribution are obvious. We found relatively small values for clearance (0.9 l/min for a 75-kg patient aged 75 yr) compared with Dyck and Shafer,<sup>2</sup> Oostwouder *et al.*,<sup>4</sup> and Schnider *et al.*<sup>3</sup> (approximately 1.7 l/min). Vuyk *et al.* claim that this is a result of the short sampling period in our data. For short sampling periods, however, the opposite should be observed. Because the distribution into deep peripheral compartments can not be identified under these circumstances, the model should overestimate the elimination clearance.

Regarding the central volume of distribution, Oostwouder *et al.*,<sup>4</sup> Dyck and Shafer,<sup>2</sup> and Schnider *et al.*<sup>3</sup> found extremely small values of approximately 4–6 l, compared with our estimates of 9 l for young adults and 7 l for a 70-yr-old individual, when propofol is administered as a continuous infusion. These differences demonstrate again a widely discussed methodologic problem in pharmacokinetic data analysis. The estimation of central volume of distribution depends on the sampling procedure in the early phase of administration. When samples are drawn too early after the start of administration, the assumption of instantaneous mixing is violated; the concentrations may be higher than expected, and the central volume of distribution may be underestimated. In our data, the first sample was not drawn before 2 min after the start of administration (even in the case of bolus administration), whereas Schnider *et al.*<sup>3</sup> and Dyck and Shafer<sup>2</sup> measured propofol 1 min or even 30 s after the start of infusion. These differences in sampling may explain partially the different estimates of central volume of distribution. For the Oostwouder *et al.*<sup>4</sup> data, the

**Fig. 1.** The blood propofol concentrations as predicted on the basis of a computer simulation using the pharmacokinetic parameter set of Schüttler and Ihmsen<sup>1</sup> when provided with the infusion rate-time data needed to reach and maintain a target propofol concentration of 2.5  $\mu\text{g}/\text{ml}$  on the basis of the Schnider *et al.*<sup>3</sup> parameter set. The calculations were performed for a 73-yr-old man, weighing 75 kg, 180 cm tall.



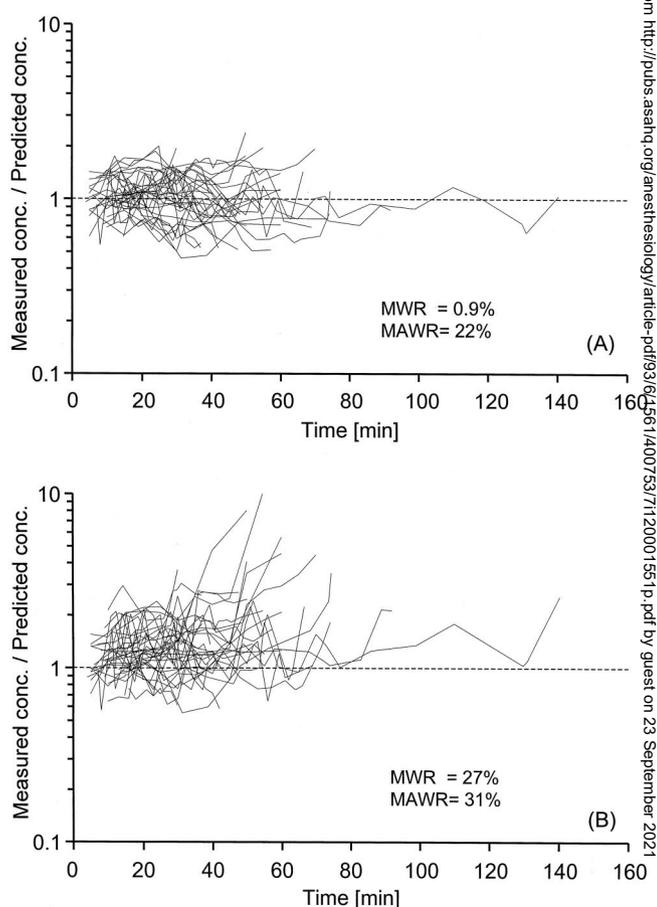
early sampling is unclear because this study has not been published in a peer-reviewed journal but only as an abstract with limited information.

Therefore, we have one parameter set from one study and other parameters from other studies, and it is only a hypothesis that one parameter set is superior to the other. One can turn the arguments of Vuyk *et al.* the other way around. If we calculate a TCI infusion scheme with the Schnider *et al.*<sup>3</sup> data and predict the resulting concentrations with our parameter set, we find an underdosing at the beginning and an accumulation (overdosing) toward the end of anesthesia (fig. 1). If we calculate the ratio (measured concentration)/(predicted concentration) for the elderly individuals of our data set with the parameters of Schnider *et al.*,<sup>3</sup> the concentrations are underestimated (fig. 2). Again, this is not proof that our results are right and the others are wrong, but the reverse claim of Vuyk *et al.* has no more evidence.

The more interesting question, however, is related to the consequences for dosing in clinical practice. Vuyk *et al.* claim that the use of our pharmacokinetic parameters for TCI “even may be harmful” to elderly patients because of an overdosing in the initial infusion phase and the resulting hemodynamic depressive effects of propofol. In many countries (European Union, Australia, New Zealand, South Africa), a commercial TCI system has been available to patients for several years (Diprifusor-TCI; Astra Zeneca Pharmaceuticals, Wilmington, DE). This system, which is approved for patients between 16 and 100 yr, uses the pharmacokinetic data from Gepts *et al.*<sup>6</sup> with a central volume of approximately 17 l for a patient weighing 75 kg, irrespective of the patient’s age. Following the arguments of Vuyk *et al.*, use of this system in elderly patients would be extremely dangerous because of a fourfold overdosing during induction. However, several million applications have been performed with this TCI system in the past 3 yr, but there were no more hemodynamic problems during induction with this system than with conventional dosing strategies (H. Brasch, M.D., Astra Zeneca, written communication, July 2000).

Finally, we would like to focus on a more general aspect of TCI. It often is pointed out that the targeted concentrations are never achieved exactly because the error of such systems is typically in the range of 25–30%. Therefore, the term “target-controlled” is misleading. In contrast, the first description of a computer-controlled infusion device by Schüttler *et al.*<sup>7</sup> as CATIA (Computer Assisted Titration of Intravenous Anesthesia) might have been more appropriate because the aspect of titration was more emphasized. Even with a TCI system, the anesthetist has to find out the optimal dosing by careful titration, and computer-controlled infusion systems can facilitate this process. An experienced anesthetist would never choose the “one and only” optimal value of a fixed blood concentration for every patient, particularly if the patient is elderly or has polymorbidity.

Vuyk *et al.* speculate with more or less reasonable arguments in



**Fig. 2.** Ratio of measured to predicted propofol concentrations versus time for the elderly patients (aged > 65 yr) of the Schüttler and Ihmsen<sup>1</sup> data set who were administered propofol as a continuous infusion. Predictions were calculated with (A) the Schüttler and Ihmsen<sup>1</sup> parameter set and (B) the Schnider *et al.*<sup>3</sup> parameter set. Conc. = concentration; MWR = median weighted residual; MAWR = median absolute weighted residual, with the single residual calculated as (measured concentration – predicted concentration)/predicted concentration.

reflection on our data, but valid proof to support their opinions is missing. However, this letter shows that pharmacokinetic modeling of propofol is still of interest and that there is a need for prospective validation, especially in regard to its application to TCI.

**\*Jürgen Schüttler, M.D., Harald Ihmsen, M.Sc.** \*Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany. juergen.schuetzler@kfa.imed.uni-erlangen.de

## References

- Schüttler J, Ihmsen H: Population pharmacokinetics of propofol. *ANESTHESIOLOGY* 2000; 92:727-38
- Dyck JB, Shafer SL: Effect of age on propofol pharmacokinetics. *Seminars in Anaesthesia* 1992; XI(suppl 1):2-4
- 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
- Oostwouder CJ, Vuyk J, Vletter AA, Burm AGL, Bovill JG: The pharmacokinetics of propofol in the elderly patient (abstract). *ANESTHESIOLOGY* 1996; 85(suppl 3A):A326
- Beal SL, Sheiner LB: *NONMEM Users Guide*. San Francisco, University of California, 1994
- Gepts E, Camu F, Cockshott ID, Douglas EJ: Disposition of propofol administered as constant rate intravenous infusions in humans. *Anaesth Analg* 1987; 66:1256-63
- Schüttler J, Schwilden H, Stoeckel H: Pharmacokinetics as applied to total intravenous anaesthesia: Practical implications. *Anaesthesia* 1983; 38(suppl): 53-6

(Accepted for publication July 14, 2000.)

Anesthesiology 2000; 93:1560

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Warning: Carbon Dioxide Absorption Capacity of Amsorb Was Unexpectedly Low in Low-flow Anesthesia

*To the Editor:*—Amsorb (Armstrong Medical Ltd., Coleraine, United Kingdom) is a new carbon dioxide (CO<sub>2</sub>) absorbent that does not degrade the inhalation anesthetics into compound A and carbon monoxide. According to the report by Murray *et al.*, the CO<sub>2</sub> absorptive capacity of Amsorb was retained at 85-90% of that of currently available CO<sub>2</sub> absorbents.<sup>1</sup> However, we had unexpected clinical occurrences of CO<sub>2</sub> rebreathing caused by rapid exhaustion of Amsorb during low-flow anesthesia.

We studied the CO<sub>2</sub> absorption capacity of Amsorb and of two currently available brands of soda lime: Medisorb (Datex Ohmeda, Bromma, Sweden) and Dragorsorb800plus (Dräger, Lübeck, Germany) in a model semiclosed breathing system at low flow rates of fresh gas. This study has been performed in two anesthetic machines, Excel (Ohmeda, Madison, WI) and Cato (Dräger). Before each trial, two Excel canisters and one Cato canister were filled with 2.4 kg and 1.2 kg of each absorbent, respectively. Oxygen was used as fresh gas at flow rates of 0.5, 1.0, and 2.0 l/min. The anesthetic ventilator was set at an inspiratory:expiratory ratio of 1:2, a respiratory rate of 12 breaths/min, and a tidal volume of 500 ml. A 3-l reservoir bag with a CO<sub>2</sub> inflow of 0.2 l/min was ventilated mechanically with an anesthetic ventilator. Gas was sampled from the Y-piece at a speed of 200 ml/min and analyzed with use of a capnograph (BP-508; Nihon Colin, Komaki, Japan). The data were recorded at 5-min intervals. The sampling gas was sent to the inspiratory limb of the circuit, and CO<sub>2</sub> absorptive capacity was determined as the time taken for the inspired CO<sub>2</sub> tension (P<sub>CO<sub>2</sub></sub>) to increase from 0 to 5 mmHg. The time interval of CO<sub>2</sub> absorption in Amsorb was approximately 50% less than the conventional absorbents with the previously mentioned fresh gas flow rates and anesthetic machines (table 1).

In the report of Murray *et al.*,<sup>1</sup> the CO<sub>2</sub> absorptive capacity was measured simply by continuously administering CO<sub>2</sub> containing fresh gas through the canister, and CO<sub>2</sub> tension was measured at the exit port of the canister. We believe that our model, the mechanically ventilated semiclosed breathing system, is more reasonable for the estimation of CO<sub>2</sub> absorptive capacity because it is based on clinical practice. Although Amsorb is chemically unreactive with inhalational anesthetics, the CO<sub>2</sub> absorptive capacity is far less from conventional absorbents in low-flow anesthesia.

It is well-known that change of color in soda lime is not a good indicator when it is exhausted in low-flow anesthesia.<sup>2</sup> Therefore, the use of Amsorb in cases in which high expiratory CO<sub>2</sub> is expected, such as in laparoscopic surgeries, must be performed with caution.

**Table 1. CO<sub>2</sub> Absorption Capacity in Three Absorbents**

Absorbent (Anesthesia Machine)	Flow (l/min)	Time (n = 2) (min)
Amsorb (Cato)	0.5	360 ± 15
Medisorb (Cato)	0.5	705 ± 20
Dragorsorb (Cato)	0.5	790 ± 15
Amsorb (Cato)	1	425 ± 15
Medisorb (Cato)	1	870 ± 10
Dragorsorb (Cato)	1	995 ± 20
Amsorb (Cato)	2	563 ± 20
Medisorb (Cato)	2	1,165 ± 50
Dragorsorb (Cato)	2	1,230 ± 30
Amsorb (Excel)	0.5	900 ± 20
Medisorb (Excel)	0.5	1,755 ± 35
Dragorsorb (Excel)	0.5	1,825 ± 30
Amsorb (Excel)	1	1,025 ± 30
Medisorb (Excel)	1	2,050 ± 15
Dragorsorb (Excel)	1	2,158 ± 60
Amsorb (Excel)	2	1,315 ± 35
Medisorb (Excel)	2	2,460 ± 85
Dragorsorb (Excel)	2	2,590 ± 50

Data are given as mean ± SD.

CO<sub>2</sub> = carbon dioxide; time = time for inspired CO<sub>2</sub> tension to increase from 0 to 5 mmHg.

**\*Hiroshi Ueyama, M.D., Masaki Takashina, M.D., Takahiro Suzuki, M.D., Varathan Sriranganathan, M.D., Takashi Mashimo, M.D.** \*Osaka University Medical School, Suita, Japan. ueyama@hp-op.med.osaka-u.ac.jp

## References

- Murray JM, Renfrew CW, Bedi A, McCrystal CB, Jones DS, Fee JP: Amsorb: A new carbon dioxide absorbent for use in anesthetic breathing systems. *ANESTHESIOLOGY* 1999; 91:1342-8
- Ohm M, Gravenstein N, Good ML: Duration of carbon dioxide absorption by soda lime at low rates of fresh gas flow. *J Clin Anesth* 1991; 3:104-7

(Accepted for publication July 14, 2000.)

Anesthesiology 2000; 93:1561

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams &amp; Wilkins, Inc.

*In Reply:*—We thank Ueyama *et al.* for their interest and comments regarding Amsorb (Armstrong Medical Ltd., Coleraine, Northern Ireland) and our recent report.<sup>1</sup> Although the absolute carbon dioxide (CO<sub>2</sub>) absorptive capacity of Amsorb is less than that of conventional absorbents, we must emphasize that the true performance of any CO<sub>2</sub> absorbent is its ability to facilitate low-flow anesthesia safely.<sup>2</sup> Retaining a strong base, as within conventional soda lime, carries the risk of carbon monoxide poisoning and the formation of compound A,<sup>3,4</sup> both of which substances, unlike CO<sub>2</sub>, are not detectable in clinical practice.

Major differences exist between our study and the study reported by Ueyama *et al.* They used significantly larger canisters and a different study method than those described in our paper.<sup>1</sup> Beyond this initial work, we have used a model similar to that of Ueyama *et al.* and have shown that changes in canister size and design significantly alter the CO<sub>2</sub> absorptive capacity of both soda lime and Amsorb by almost sixfold.<sup>5</sup> Comparing Ueyama *et al.*'s data for the two reported canister designs (Dräger, Lübeck, Germany, and Datex Ohmeda, Bromma, Sweden), it is clear that there are marked intracanister differences in CO<sub>2</sub> absorption capacity for Amsorb and Medisorb both, highlighting potential inefficient use of all absorbents caused by shortcomings in canister design. The convenience of a smaller-sized canister is always a trade-off against efficient use of a CO<sub>2</sub> absorbent. We argue that a CO<sub>2</sub> absorption capacity of 900 min (15 h) for 2.4 l Amsorb at a flow rate of 500 ml/min is more than adequate for 1–2 days of anesthesia.

Ueyama *et al.* state that their model of determining CO<sub>2</sub> absorptive capacity is based on clinical anesthetic practice. However, in routine practice, the life of a conventional CO<sub>2</sub> absorbent is limited by safety concerns and the United States Food and Drug Administration Center for Disease Control recommendation regarding this subject is that "All soda lime that has been dormant in the anesthesia machine for more than 24 hours should be changed, and dated."<sup>6</sup> Such a restriction does not apply to Amsorb. The authors also state that color change is not a good indicator of exhaustion of soda lime, and, for conventional limes, this is correct because the strong alkali allows regeneration of pH changes within the indicator after the calcium hydroxides' capacity for CO<sub>2</sub> absorption has been exceeded. Amsorb does not contain strong alkali, so color change is not reversible and does indicate exhaustion.

With concurrent use of capnography, unexpected rebreathing does not occur.

We wish to draw the authors' attention to a cost analysis of the use of Amsorb in clinical low-flow anesthesia that has shown that the life of the Amsorb (ignoring Anesthesia Patient Safety Foundation recommendations for the changing of soda lime) is about two thirds that of conventional limes.<sup>7</sup>

We thank the authors for their interest in our new absorbent, but we stress that to measure this product against soda lime purely on absorptive capacity ignores safety issues and is a retrograde step for low-flow anesthesia.

\*James M. Murray M.D., Amit Bedi, F.R.C.A., J.P., Howard Fee, M.D., Ph.D. \*The Queen's University of Belfast, Belfast, United Kingdom. jmmurray@compuserve.com

## References

1. Murray JM, Renfrew CW, Bedi A, McCrystal CP, Jones DS, Fee JPH: Amsorb: A new carbon dioxide absorbent for use in anesthetic breathing systems. *ANESTHESIOLOGY* 1999; 91:1342–8
2. Stabernack CR, Brown R, Laster MJ, Dudziak R, Eger EI II: Absorbents differ enormously in their capacity to produce Compound A and carbon monoxide. *Anesth Analg* 2000; 90:1428–35
3. Fang ZX, Eger EI II, Laster MJ, Chortkoff SB, Kandel L, Ionescu I: Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme®. *Anesth Analg* 1999; 80:1187–93
4. Fang ZX, Kandel L, Laster MJ, Ionescu P, Eger EI II: Factors affecting production of compound A from the interaction of sevoflurane with Baralyme and soda lime. *Anesth Analg* 1996; 82:775–81
5. Bedi A, Murray JM, Fee JPH: The *in vitro* performance of carbon dioxide absorbents with and without strong alkali. Presented at: ASA Annual Scientific Meeting; October 2000; San Francisco, CA
6. Lentz RE: CO poisoning during anesthesia poses puzzles: New agent used in Florida case. *Anesthesia Patient Safety Foundation Newsletter* 1994; 9:13–24
7. Baum J, Van Aken H: Calcium hydroxide lime: A new carbon dioxide absorbent: A rationale for judicious use of different absorbents (editorial). *Eur Anaesthesiol* 2000; 17:1–5

(Accepted for publication July 14, 2000.)

Anesthesiology 2000; 93:1561

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams &amp; Wilkins, Inc.

## The Use of Intrathecal Fentanyl Is Justified

*To the Editor:*—We read with interest the recent review article by Dahl *et al.*<sup>1</sup> regarding intrathecal opioids in patients undergoing cesarean section. Although our previous work substantiates the claim that intrathecal fentanyl (10 µg) does not allow for adequate postoperative analgesia,<sup>2</sup> we take exception with the comment that the use of intrathecal opioids are "... hardly justified ... if the only purpose is to improve intraoperative analgesia." When patients undergoing cesarean section are not administered intrathecal fentanyl, both intraoperative pain and the need for intraoperative opioid supplementation are higher.<sup>2</sup> When fentanyl (10 µg) was added to spinal anesthetic, the need for intraoperative opioids decreased from approximately 20% to 0%, without any increase in side effects. Therefore, we believe that not only is the use of intrathecal fentanyl justified, but that omitting it is unjustified.

Neil Roy Connelly, M.D., \*Steven M. Dunn, M.D. \*Tufts University School of Medicine, Baystate Medical Center, Springfield, Massachusetts. stevedunn@pol.net

## References

1. Dahl JB, Jeppesen IS, Jorgensen H, Wetterslev J, Moiniche S: Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia. *ANESTHESIOLOGY* 1999; 91:1919–27
2. Connelly NR, Dunn SM, Ingold V, Villa EA: The use of fentanyl added to morphine-lidocaine-epinephrine spinal solution in patients undergoing cesarean section. *Anesth Analg* 1994; 78:912–20

(Accepted for publication August 22, 2000.)

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

## Severe Hypertension following Ephedrine Administration in a Patient Receiving Entacapone

*To the Editor:*—Entacapone belongs to a new therapeutic class, the catechol-O-methyl transferase inhibitors. It is a reversible, specific, and mainly peripherally acting catechol-O-methyl transferase inhibitor designed for concomitant administration with L-dopa-dopa decarboxylase inhibitor therapy for Parkinson disease patients who have severe motor fluctuations.<sup>1</sup> It has been available since August 1999 in Australia (Novartis Pharmaceuticals, Sydney, Australia) and October 1999 in the United States (Orion Corp., Dallas, TX), and we report herein a case that occurred in our institution and highlights the implications of this new class of drug for anesthetic practice.

A 76-yr-old woman with a long history of Parkinson disease and recent occurrences of closed-angle glaucoma was scheduled for phacoemulsification of a cataract and insertion of an intraocular lens to prevent recurrence of the closed-angle glaucoma. During the previous 6 months, she had experienced severe choreoathetoid movements, and, 3 weeks before admission to the hospital, she began to take 200 mg entacapone concomitantly with her 5 daily doses of carbidopa-levodopa to improve control of these movements.

General anesthesia was used to prevent movement during surgery and was induced with use of 80 mg propofol and 25  $\mu$ g fentanyl intravenously. It was maintained with the patient spontaneously breathing nitrous oxide-oxygen (2:1 mix) and 1–1.5% end-tidal sevoflurane. The procedure had been uneventful for 30 min when blood pressure decreased from 145/85 mmHg to 85/35 mmHg. This was treated with a 3-mg intravenous ephedrine bolus. There was an immediate response in blood pressure to 225/125 mmHg, which remained increased despite an increasing sevoflurane concentration. Hydralazine, 2 mg, was administered, and blood pressure returned to 140/85 mmHg. However, after 10 min, blood pressure returned to 240/130 mmHg, necessitating further hydralazine administration. Heart rate remained between 55 and 75 beats/min throughout this period. The procedure was completed, anesthesia was discontinued, and the patient was transferred to the recovery area for further monitoring and treatment. The patient required further doses of hydralazine to control her blood pressure, and, in total, the period of sustained increased blood pressure necessitating treatment was 2 h and 20 min. Her recovery was then uneventful.

Levodopa crosses the blood-brain barrier and is converted to dopamine in the central nervous system by the enzyme dopa-decarboxylase.

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

Dopa-decarboxylase is present in the systemic circulation and tissue, and therapy with levodopa increases systemic dopamine levels, as well. Side effects from chronically increased serum dopamine concentrations include reduced activity of the renin-angiotension system, causing decreased intravascular volume and orthostatic hypotension, which may have contributed to the decrease in blood pressure in the patient described. The concomitant administration of a peripheral decarboxylase inhibitor, carbidopa, allows the total dose of levodopa to be decreased, thus reducing the systemic dose-related effects. It has also been recommended that, if a vasopressor is needed intraoperatively, a dilute direct acting agent should be used, e.g., phenylephrine hydrochloride. In this case, use of ephedrine, which acts directly and indirectly, in the presence of levodopa may have contributed to intraoperative sustained hypertension.<sup>2</sup>

However, we believe that the most likely explanation for the sustained increase in blood pressure was the failure of ephedrine and the resultant catecholamines released to be metabolized by catechol-O-methyl transferase, resulting from the action of entacapone. This case highlights the importance of being aware of the pharmacologic action of all patients' medication, especially if the drug has become available recently. The data sheet for this drug states that "Entacapone should be administered cautiously to patients being treated with drugs metabolized by catechol-O-methyl transferase e.g. adrenaline, isoprenaline and apomorphine. Patients should be carefully monitored if entacapone is administered with any of these drugs." As shown by the case described, there is a prolonged and exaggerated response not only to direct sympathomimetics, but also to indirect sympathomimetics commonly used during anesthesia.

\*Craig Renfrew, M.B., F.R.C.A., Rona Dickson, M.B., F.R.C.A., Craig Schwab, M.B., F.A.N.Z.C.A. \*Royal Perth Hospital, Perth Western Australia. craigrenfrew@hotmail.com

### References

- Holm KJ, Spencer CM: Entacapone: A review of its use in Parkinson disease. *Drugs* 1999; 58:159–77
- Katz J, Benumof JL, Kadis LB: *Anaesthesia and uncommon diseases*, 3rd edition. Philadelphia, WB Saunders, 1990, pp 563–4

(Accepted for publication July 21, 2000.)

## Postoperative Ventilatory Management with Noninvasive Positive-pressure Ventilation in a Child with a Severe Tracheomalacia

*To the Editor:*—Children with tracheomalacia are at high risk of postoperative respiratory distress for non-upper airway surgery and of prolonged tracheal intubation. Noninvasive positive-pressure ventilation (NPPV) via facial mask is a method of providing mechanical ventilatory support without tracheal intubation.<sup>1</sup> We report the case of a 6-month-old, 7.4-kg male patient with severe tracheomalacia in whom respiratory failure developed after surgery for gastroesophageal reflux. The child had a full-term gestation with a type III esophageal atresia that was repaired on the day of birth. He had tracheomalacia

and a tracheolaryngeal cleft (type 2-b) without respiratory insufficiency. For the current procedure, the trachea was intubated with a 3.5-mm ID nasotracheal tube. The procedure was uneventful, and he underwent extubation after completion. He developed signs 1 h later of upper airway obstruction with severe bradycardia, necessitating manual ventilation and atropine. He was administered supplemental oxygen, intravenous steroids, and aerosolized racemic epinephrine, without improvement. To avoid tracheal reintubation, NPPV via facial mask was instituted in the timed spontaneous mode with use of a ventilatory support system (BiPAP; Respironics, Murrysville, PA). Initially, inspiratory positive airway pressure was set at 12 cm H<sub>2</sub>O, and

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

expiratory positive airway pressure was set at 5 cm H<sub>2</sub>O, with a mechanical respiratory rate of 25 breaths/min. Eleven hours later, inspiratory positive airway pressure was increased to 16 cm H<sub>2</sub>O, expiratory positive airway pressure was increased to 10 cm H<sub>2</sub>O, and administration of 1 l/min-flow oxygen with a fraction of inspired oxygen of 0.3 was started *via* the mask. Arterial blood gas measurements showed a pH of 7.33, an arterial carbon dioxide tension of 47.2 mmHg, and an arterial oxygen tension of 63.7 mmHg. The ventilator settings were not changed for 26 h, when respiratory status began to improve. Oxygen supplementation was discontinued. The levels of support were decreased gradually, and NPPV was discontinued on postoperative day 2, with no recurrence of upper airway obstruction. A nasogastric tube placed for surgery allowed reduction of gastric distension. The antireflux procedure probably minimized the risk of aspiration. Analgesia was achieved with use of nalbuphine. Initially, the child required sedation with intravenous diazepam for comfort. Feeding was started on postoperative day 5. The child was discharged to his home on postoperative day 10.

Postoperative respiratory management of children with tracheomalacia can be a major challenge. NPPV has been described widely in

pediatric patients with acute respiratory failure.<sup>2</sup> However, there are few reports about the use of NPPV in the postoperative period in children.<sup>3</sup> Our report indicates that NPPV may be attempted before reintubation in infants requiring airway support, with careful attention given to the risks of aspiration and respiratory muscle fatigue.

\*Jean-Christophe Bouchut, M.D., Didier Stamm, M.D., Daniel Floret, M.D. \*Hôpital Edouard Herriot, Lyon, France. jc.bouchut@wanadoo.fr

## References

1. Mehta S: Noninvasive positive-pressure ventilation in acute respiratory failure. *Intensive Care Med* 1998; 24:1113-4
2. Padman R, Lawless ST, Ketrick RG: Noninvasive ventilation via bilevel positive airway pressure support in pediatric practice. *Crit Care Med* 1998; 26:169-73
3. Hertzog JH, Siegel LB, Hauser GJ, Dalton HJ: Noninvasive positive-pressure ventilation facilitates tracheal extubation after laryngotracheal reconstruction in children. *Chest* 1999; 116:260-3

(Accepted for publication July 26, 2000.)

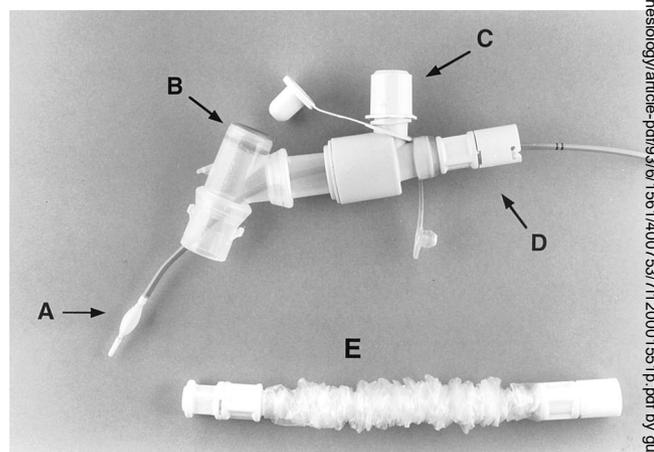
Anesthesiology 2000; 93:1563-4

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## An Improved Technique of Placing a Coaxial Endobronchial Blocker for One-lung Ventilation

*To the Editor:*—One-lung ventilation is used commonly to facilitate intrathoracic surgery. Routinely used techniques include double-lumen endotracheal tubes and Univent tubes (Fuji System Corporation, Tokyo, Japan).<sup>1,2</sup> However, in critically ill and trauma patients who have already undergone intubation with a standard cuffed endotracheal tube, switching the endotracheal tube may not be wise. Although it is easier to place the bronchial blocker coaxially through an endotracheal tube, one of the major drawbacks of this technique is the air leak from the circuit.<sup>3</sup> Solutions suggested include use of bone wax and application of waterproof tape. However, if the blocker must be repositioned, all this needs to be undone. In addition, persistent air leak makes application of continuous positive end-expiratory pressure to the dependent lung impossible. Herein, we describe a simple technique for achieving an airtight seal while instituting one-lung ventilation with a coaxially placed bronchial blocker, a Fogarty occlusion catheter (model 62080814F; Baxter, Irvine, CA), 8/14-French, with a 10-ml balloon.

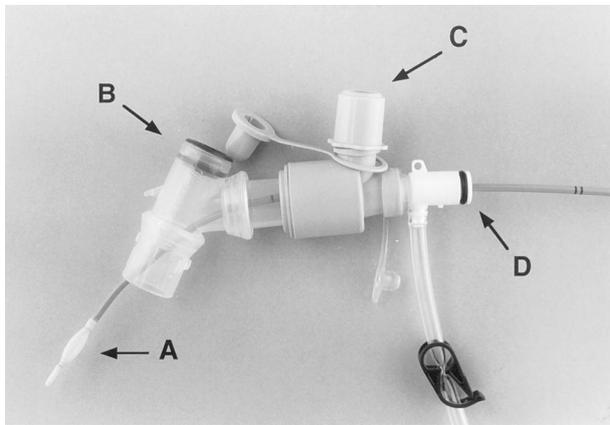
The Fogarty occlusion catheter is available in various sizes; the most commonly used model for adult patients is an 8/14-French catheter with a 10-ml balloon. The technique used is shown in figures 1 and 2. Assembling the various parts in the depicted fashion allows simultaneous use of the fiberoptic bronchoscope for positioning and repositioning of the blocker during the entire procedure. In figure 1, the Fogarty catheter is shown passing through the distal TwistLock assemblies taken out of the Cath-Gard catheter contamination shield (Arrow International Inc., Reading, PA). The proximal TwistLock assemblies can be used also. In figure 2, a 9-French Arrow-Flex sheath (Arrow International Inc., Reading, PA) with an integral hemostasis valve and side port, with the introducer sheath shortened and the side port clamped, is shown accepting the Fogarty catheter. Each Portex swivel adapter (SIMS Portex Inc., Keene, NH) is supplied with two self-sealing diaphragms for use with pediatric and adult bronchoscopes. Both devices make a perfect airtight fit with the pediatric self-sealing diaphragm of the Portex fiberoptic bronchoscope swivel adapter. After thoroughly lubricating the tip of the Fogarty catheter, the catheter is gently advanced through the previously mentioned devices in a rotating motion to prevent damage to the balloon. Use of two swivel



**Fig. 1.** The technique of instituting one-lung ventilation with coaxial placement of the bronchial blocker through the endotracheal tube. (A) Fogarty catheter, 8/14-French, 10-ml balloon to endotracheal tube. (B) Proximal Swivel Elbow (DHD Healthcare, Canastota, NY), port for fiberoptic bronchoscopy. (C) Portex bronchoscope swivel connector, to breathing circuit. (D) The Fogarty catheter passing through the distal TwistLock device, which makes a perfect airtight seal with diaphragm of the Portex bronchoscope swivel connector. (E) Cath-Gard catheter contamination shield with proximal and distal TwistLock devices.

adapters makes simultaneous bronchoscopy and continued uninterrupted ventilation possible. In the case of the TwistLock mechanism, the advantage of the TwistLock mechanism keeps the bronchial blocker securely in position. All the described parts are readily available. In my experience, both the devices are equally efficient. However, it is preferable from the cost-effective standpoint to use the Cath-Gard contamination shield because spares are easy to find, and each shield has two TwistLock devices (proximal and distal); therefore, it is good

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



**Fig. 2.** The parts are assembled in the same fashion as in figure 1 using (D). 9-French Arrow-Flex sheath with integral hemostasis valve and side port clamped off. The introducer sheath has been shortened to just distal to the corrugation near the hub.

for two patients. While using the hemostasis valve, care should be taken to clamp the side port and cut off the tubing distal to the clamp to prevent inadvertent administration of drugs or intravenous fluids.

**Govind R. C. Rajan, M.D.,** Washington University School of Medicine, St. Louis, Missouri. govind\_r@hotmail.com

## References

1. Slinger P: Con: The Univent tube is not the best method of providing one-lung ventilation. *J Cardiothorac Vasc Anesth* 1993; 7:108-12
2. Gayes JM: Pro: One-lung ventilation is best accomplished with the Univent endotracheal tube. *J Cardiothorac Vasc Anesth* 1993; 7:103-7
3. Larson CE, TA Gasior: A device for endobronchial blocker placement during one-lung anesthesia (letter). *Anesth Analg* 1990; 71:311-2

(Accepted for publication July 27, 2000.)

Anesthesiology 2000; 93:1564

© 2000 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

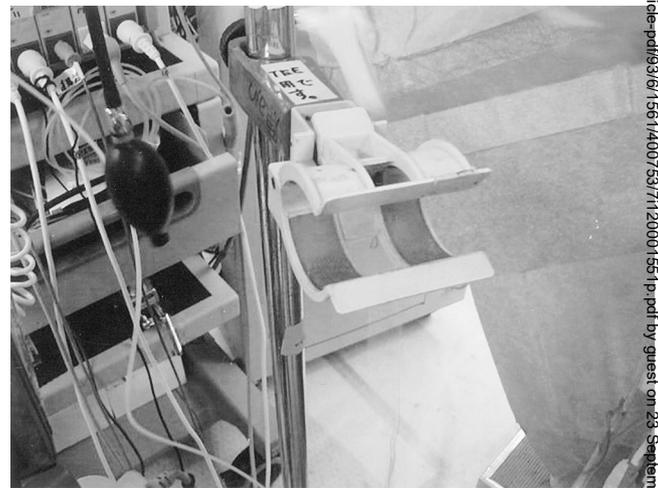
## A Convenient Holder of the Transesophageal Echocardiography Probe

*To the Editor:*—Transesophageal echocardiography (TEE) is a standard monitoring convention for many patients undergoing cardiac surgery. Although several practice guidelines on TEE use have been issued, they provide only brief comments on the actual use of the device in the operating room. For example, the handle of the probe is large and heavy. If rested on the TEE console, it sometimes hides the video screen and can slip off easily and fall to the floor.

We found a simple device for holding the handle. We use the holder of a hollow fiber hemodialysis filter (fig. 1). The dialysis filter is approximately the same size as the handle of the adult-size TEE. Therefore, we can attach the handle of the TEE to the holder and detach it easily for manipulation. We also can change freely the direction of the handle, depending on the patient's position. The cost is minimal.

\***Motoshi Kainuma, M.D., Toshiyuki Miyake, M.D.** \*Fujita Health University, Aichi, Japan. mkainuma@fujita-hu.ac.jp

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



**Fig. 1.** The holder of the dialyzer for hemodialysis.

(Accepted for publication July 27, 2000.)