

## Pharmacogenetics of Anesthetic and Analgesic Agents: CYP2D6 Genetic Variations

*To the Editor:*—We congratulate Palmer *et al.*<sup>1</sup> for their excellent review on pharmacogenetics of anesthetic and analgesic agents published in the March 2005 issue of ANESTHESIOLOGY. They give a worthwhile introduction into basic molecular concepts and include the latest literature on pharmacogenetic aspects of anesthesia and analgesia.

Because of this very comprehensive and detailed review, we feel the necessity for a brief specification and correction of their comments on the cytochrome P-450 enzyme system CYP2D6 and its influence on efficacy of tramadol analgesia.

Tramadol is a synthetic weak opioid metabolized by CYP2D6. Like codeine, it is a prodrug, considering its  $\mu$ -opioid receptor-mediated analgesia. Hepatic cytochrome P-450 metabolizes tramadol to 11-desmethylated compounds, of which M1 (*O*-desmethyltramadol) predominates and possesses analgesic properties.<sup>2-4</sup> (+)*O*-Desmethyltramadol has been demonstrated to have an affinity to  $\mu$ -opioid receptors that is approximately 200 times greater than that of the parent compound. Therefore, it is largely responsible for opioid receptor-mediated analgesia, whereas (+)-tramadol and (–)-tramadol inhibit reuptake of neurotransmitters serotonin (5-HT) and noradrenaline.<sup>5</sup>

*O*-Desmethylation to M1 requires CYP2D6 for its formation, a highly polymorphic isoenzyme of the cytochrome P-450 system. This enzyme is deficient in approximately 10% of white individuals.<sup>5-7</sup> Several mutations causing a decrease in enzyme activity have been described up to now, the most frequent being single base exchanges or deletions within the 2D6 gene locus.\*

Patients displaying two inactive alleles, so-called poor metabolizers, are characterized by deficient hydroxylation of several classes of commonly used drugs, *e.g.*,  $\beta$ -blockers, antiarrhythmics, tramadol, codeine.

Extensive metabolizers, displaying two functional alleles (*e.g.*, two wild-type alleles: \*1/\*1), present normal enzyme activity and are able to metabolize tramadol sufficiently to *O*-desmethyltramadol. In our study,<sup>7</sup> extensive metabolizers experienced adequate analgesia by tramadol in contrast to poor metabolizers presenting two mutant alleles with deficient enzyme activity. We tested for the seven polymorphisms, \*3, \*4, \*5, \*6, \*7, \*8, and \*14; however, further genetic variations with allele frequencies of less than 0.01 (*e.g.*, \*11, \*12, \*13, \*15, \*16) are known, although they are extremely rare in white individuals. Whether it is worthwhile to test for these rare alleles in a clinical setting remains questionable.

We identified 35 poor metabolizers with the CYP\*3, \*4, \*5, or \*6 alleles. These poor metabolizers were unable to form the analgesic active M1 metabolite of tramadol. This is why poor metabolizers were found to be twice as likely to require additional rescue medication than patients with at least one wild-type allele. The reason for nonresponse in poor metabolizers has to be assumed as a lack of tramadol metabolism.

Therefore, the statement of Palmer *et al.*<sup>1</sup> that nonresponse in patients with one or more functional CYP2D6\*1 alleles require additional postoperative analgesics because of increased tramadol metabolism is incorrect. Correct is that carriers of at least one wild-type allele, CYP2D6\*1, were responsive to tramadol treatment. Nonresponse was clearly associated with carriage of two mutant alleles and poor metabolizing status.

In contrast to tramadol, which has to be considered as a prodrug for  $\mu$ -opioid activity, when administering an active drug such as tricyclic antidepressants<sup>8</sup> or 5-HT<sub>3</sub> receptor antagonists ondansetron or tropisetron,<sup>9</sup> ultrarapid metabolizers with increased CYP2D6 activity require additional medication because of subtherapeutic drug concentrations. As outlined in the same issue of ANESTHESIOLOGY, individuals with multiple functional copies of the CYP2D6 allele and ultrarapid metabolizer status had an increased incidence of ondansetron failure.<sup>9</sup>

The wide interindividual variability of drug concentrations in blood can often be ascribed to variability in drug-metabolizing enzyme activity. This can have an impact on the therapeutic response and toxicity of drugs with a narrow therapeutic index. Phenotypic or genotypic characterization of individuals is an attempt to predict enzyme activity and thus maximize drug safety and efficacy.

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### References

- Palmer SN, Giesecke M, Body SC, Sheman SK, Fox AA, Collard CD: Pharmacogenetics of anesthetic and analgesic agents. ANESTHESIOLOGY 2005; 102:663-71
- Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL, Jacoby HI, Selve N: Complimentary and synergistic antinociceptive interaction between the enantiomers of tramadol. J Pharmacol Exp Ther 1993; 267:331-40
- Poulsen L, Arendt-Nielsen L, Brösen K, Sindrup SH: The hypoalgesic effect of tramadol in relation to CYP2D6. Clin Pharmacol Ther 1996; 60:636-44
- Paar WD, Poche S, Gerloff J, Dengler HJ: Polymorphic CYP2D6 mediates *O*-demethylation of the opioid analgesic tramadol. Eur J Clin Pharmacol 1997; 53:235-9
- Stüven T, Griese EU, Kroemer HK, Eichelbaum M, Zanger UM: Rapid detection of CYP2D6 null alleles by long distance- and multiplex-polymerase chain reaction. Pharmacogenetics 1996; 6:417-21
- Sachse C, Brockmüller J, Bauer S, Roots I: Cytochrome P450 2D6 variants in a Caucasian population: Allele frequencies and phenotypic consequences. Am J Hum Gen 1997; 60:284-95
- Stamer UM, Lehnen K, Höthker F, Bayerer B, Wolf S, Hoefl A, Stuber F: Impact of CYP2D6 genotype on postoperative tramadol analgesia. Pain 2003; 105:231-8
- Kirchheiner J, Nickchen K, Bauer M, Wong ML, Licinio J, Roots I, Brockmüller J: Pharmacogenetics of antidepressants and antipsychotics: The contribution of allelic variations to the phenotype of drug response. Mol Psychiatry 2004; 9:442-73
- Candiotti KA, Birnbach DJ, Lubarsky DA, Nhuch F, Kamat A, Koch WH, Nikoloff M, Wu L, Andrews D: The impact of pharmacogenomics on postoperative nausea and vomiting: Do CYP2D6 allele copy number and polymorphisms affect the success or failure of ondansetron prophylaxis? ANESTHESIOLOGY 2005; 102:543-9

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\* For details, see [www.imm.ki.se/CYPalleles/cyp2d6.htm](http://www.imm.ki.se/CYPalleles/cyp2d6.htm). Accessed April 1, 2005.

## The Practicality and Need for Genetic Testing for Malignant Hyperthermia

*To the Editor:*—Recent advances in the pharmacogenetics of anesthetics are relevant to the practice of anesthesia. Therefore, we must address the misstatements and errors in the review article on this subject.<sup>1</sup> We restrict our comments to the section titled Inhalation Anesthetics, in which susceptibility to malignant hyperthermia (MH) is discussed.

In the first paragraph, there is an error. The incidence of MH episodes is not the same as the number of MH-susceptible individuals. We agree that in 1970, the estimated incidence of MH episodes was 1 in 15,000 anesthetics in anesthetized children and 1 in 50,000 anesthetics in anesthetized adults.<sup>2</sup> But the number of individuals who are likely to be susceptible to MH is much, much greater than the number of reports of anesthetic incidents. Monnier *et al.*<sup>3</sup> estimated that the frequency of mutations producing MH susceptibility in the French population could be as great as 1 in 2,000 people.

We do not agree that genetic testing for MH is impractical. The utility of a genetic examination of the *RYR1* has been demonstrated in the Swiss population.<sup>4</sup> Clearly, a genetic test of MH susceptibility can be useful to the anesthesiologist caring for members of a family in which a known MH-causative mutation was identified. A meeting of geneticists and MH researchers concluded that even with a sensitivity of 23% in the small population of North American patients studied, examination of a limited number of *RYR1* exons is practical.<sup>5</sup> Examination of the entire coding region of the *RYR1* will identify a greater number of mutations.<sup>6</sup> In 2005, more than one diagnostic Clinical Laboratory Improvement Act–approved genetic laboratory is preparing to offer a test of *RYR1* to the public.

In 2005, the Web site of the European MH Group listed 23 causative mutations, but examination of the recent literature from North America and Europe records more than 100 mutations in *RYR1*. Some of these have been found in only one family but clearly are associated with lethal MH episodes and positive contracture test results. The number of sequence variants is not as much a problem to the interpretation of the examination of *RYR1* as are the classic requirements that the variant be observed in more than one family and be shown to decrease the threshold for release of calcium from the sarcoplasmic reticulum in an experimental model before it can be acknowledged as causative of MH. Therefore, many of the observable sequence variants will be interpreted as possibly associated with MH susceptibility based on the clinical history of the patient and the potential effect of that sequence variant on the function of the ryanodine receptor channel.

It is important to recognize the pharmacology of the phenotype from which the genetics of MH is described. The *in vitro* contracture test that is used in North America is known as the caffeine-halothane contracture test (CHCT).<sup>7</sup> This test requires a surgical procedure and dissection of a large muscle strip for contractile studies, not extraction of muscle cells. The muscle specimen is separated into bundles of fibers, placed in temperature-controlled chambers, aerated with controlled tensions of oxygen and carbon dioxide, stimulated electrically, and then exposed to halothane, caffeine, or other drugs that affect ryanodine receptor function. It is the reproducible shift in the dose-sensitivity of muscle contraction to these compounds that has led to the use of CHCT as the diagnostic indicator of MH in North America. The *in vitro* contracture test that is used in Europe is known as the

IVCT. The test performed in North America is not identical to the IVCT. Therefore, it is appropriate to state that an *in vitro* contracture test was used to determine the presence or absence of MH. There is more than one such test.

We agree that MH is a complex genetic disease. Nevertheless, the genetic test offered in 2005 can be useful to families and anesthesia providers who wish to secure a diagnosis of MH susceptibility. When there is no *RYR1* sequence variant identified in an individual with a strong clinical history, CHCT should be performed.

Because of these considerations, we disagree with the economic discussion of genetic testing of MH susceptibility. The authors do not seem to know that the cost of the CHCT is \$6,000–10,000, without the necessary added expense of travel to a diagnostic MH center. Because MH susceptibility is relatively rare, it is difficult to develop a screening test for this disorder. The most appropriate testing strategy should be based on the prior probability of the disorder being present before the test is performed.<sup>8</sup> If a mutation causative of MH is identified in an MH-susceptible proband, that *RYR1* mutation can be looked for in first-degree relatives for a cost much less than 10% of the cost of the CHCT.

We hope that clinicians will become sophisticated in the interpretation of genetic test results. But the interpretation of genetic tests must include detailed understanding of the disease that the test was developed to identify. This will not happen in the case of MH susceptibility if the clinical phenomena of this disease, its diagnostic bioassay, and genetic studies to date are misrepresented.

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### References

- Palmer SN, Giesecke NM, Body SC, Shernan SK, Fox AA, Collard CD: Pharmacogenetics of anesthetic and analgesic agents. *ANESTHESIOLOGY* 2005; 102:663–7
- Britt BA, Kalow W: Malignant hyperthermia: A statistical review. *Can Anaesth J* 1970; 17:293–315
- Monnier N, Krivosic-Horber R, Payen J-F, Kozak-Ribbens G, Nivoche Y, Adnet P, Reyford H, Lunardi J: Presence of two different genetic traits in malignant hyperthermia families. *ANESTHESIOLOGY* 2002; 97:1067–74
- Girard T, Treves S, Voronkov E, Siegemund M, Urwyler A: Molecular genetic testing for malignant hyperthermia susceptibility. *ANESTHESIOLOGY* 2004; 100:1076–80
- Nelson TE, Rosenberg H, Muldoon SM: Genetic testing for malignant hyperthermia in North America. *ANESTHESIOLOGY* 2004; 100:212–4
- Sambuughin N, Holley H, Muldoon S, Brandom BW, de Bantel AM, Tobin JR, Nelson TE, Goldfarb LG: Screening of the entire ryanodine receptor type 1 coding region for sequence variants associated with malignant hyperthermia susceptibility in the North American population. *ANESTHESIOLOGY* 2005; 102:515–21
- Larach MG: Standardization of the caffeine halothane muscle contracture test. North American Malignant Hyperthermia Group. *Anesth Analg* 1989; 69:511–5
- Loke J, MacLennan DH: Bayesian modeling of muscle biopsy contracture testing for malignant hyperthermia susceptibility. *ANESTHESIOLOGY* 1998; 88:589–600

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*In Reply:*—We thank the authors of both letters for their thoughtful and insightful comments. Drs. Stamer and Stuber correctly point out that we erred when we stated that “. . . abdominal surgical patients with one or more CYP2D6\*1 alleles were found to be twice as likely to require additional postoperative analgesics if they did not express at least 1 wild-type CYP2D6 allele because of increased tramadol metabolism.”<sup>1</sup> In fact, for the reasons that Drs. Stamer and Stuber so elegantly outline in their letter, we should have stated that abdominal surgical patients without one or more CYP2D6\*1 alleles are twice as likely to require additional postoperative analgesics because of *decreased* tramadol metabolism.<sup>1</sup>

In response to Drs. Brandom and Muldoon, we agree that the incidence of malignant hyperthermia syndrome (MHS) is not the same as the number of MHS-susceptible individuals. Therefore, we should have more accurately stated that the incidence of MHS is approximately 1 in 15,000 anesthetic administrations in children and 1 in 50,000 in adults, with an estimated susceptibility of 1 in 8,500 individuals.<sup>2–4</sup> Although susceptibility may be as high as 1 in 2,000 in France,<sup>5</sup> Dr. Muldoon has also previously demonstrated that the frequencies of many common MHS mutations differ significantly between regions. Notably, the frequency and distribution of RYR1 mutations observed in the North American MHS population are markedly different from that of Europe.<sup>6</sup>

Indeed, it is because of such wide ethnic variations in the frequency of MHS-related polymorphisms, as well as the fact that many MHS-susceptible individuals have no known RYR1 polymorphisms, that we stand by our statement that widespread, commercial genetic testing of the population for this disorder currently remains impractical. We did not refer to genetic screening in selected individuals, but rather the wider population. Nor are we alone in questioning the current feasibility of widespread commercial genetic testing for MHS. For example, Hopkins<sup>4</sup> stated that

the complexity of the molecular genetics of MHS precludes DNA-based diagnosis at present, especially when one considers the possibility of one gene defect being associated with susceptibility in only a proportion of individuals and another, as yet unidentified, defect being causative of the condition. This is complicated further by the well-established presence of genetic heterogeneity. The first step in a DNA-based diagnosis, therefore, will rely on initial identification of the abnormality, or abnormalities, causing MHS in individual pedigrees. It is likely that the first reliable DNA-based diagnoses will be carried out in individuals from families that have been extensively investigated by both in-vitro contracture test (IVCT) phenotyping and linkage analysis followed by mutation screening.

More recently, Girard *et al.*<sup>7</sup> stated that

molecular genetic analysis should be used in selected families when possible and appropriate, and it is becoming an important supplement of IVCT. As a prerequisite for genetic testing, mutation frequencies in the geographic region served by the investigation center must be known. Such frequency investigations have already been published for Germany, Italy, North America, Switzerland, and the United Kingdom, but data for other countries are still missing. Screening for MH mutations without this knowledge is costly and is not recommended. The integration of molecular genetic results with pedigree information as well as IVCT data

avoids open muscle biopsies and IVCT in a person whose family is known to have an MH mutation.

In addition, Dr. Muldoon herself has acknowledged problems with genetic testing for MHS:

Although genetic linkage analysis shows that 50–80% of European MHS families are linked to the RYR1 gene, mutations are reported in only 25–40% of MHS families so far. The majority of RYR1 gene mutations are clustered in the N-terminal region with amino acid residues from 35 to 614 and in the central region from 2163 to 2458. Most genetic screening studies target these two regions, which account for only approximately one fourth of the entire coding region of the RYR1 gene. Thus, the absence of RYR1 mutations in the rest of the screened population might be explained either by a mutation located outside the two regions analyzed in the current study or by the involvement of another gene.<sup>6</sup>

Finally, we agree with Drs. Brandom and Muldoon that it is important that clinicians become more sophisticated with respect to the recommended use and interpretation of genetic testing. As such, we point out that the Malignant Hyperthermia Association of the United States currently advises that only the following individuals be considered for genetic testing:<sup>\*</sup>

1. Individuals who have a positive IVCT result.
2. Relatives of individuals who have a positive by IVCT result.
3. Individuals who have been found to have a mutation causative for MHS under a research protocol.
4. Relatives of individuals with a known mutation for MHS.
5. Individuals with a very high likelihood of having experienced an MHS episode.

In addition, despite the high cost of IVCT, the Malignant Hyperthermia Association of the United States does not currently recommend that genetic testing replace IVCT. Finally, genetic testing for MHS susceptibility is currently offered at only three places in the world, one of which is in the United States.† Nonetheless, we are certain that with further advances in the field by experts such as Drs. Muldoon and Brandom, inexpensive genetic testing with reliable positive and negative predictive values will soon become available for population screening. However, that day is not here yet.

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## References

1. Uhl GR, Sora I, Wang Z: The mu opiate receptor as a candidate gene for pain: Polymorphisms, variations in expression, nociception, and opiate responses. *Proc Natl Acad Sci U S A* 1999; 96:7752–5
2. Girard T, Urwyler A, Censier K, Mueller CR, Zorzato F, Treves S: Genotype-phenotype comparison of the Swiss malignant hyperthermia population. *Hum Mutat* 2001; 18:357–8
3. Sambuughin N, Holley H, Muldoon S, Brandom BW, de Bantel AM, Tobin JR, Nelson TE, Goldfarb LG: Screening of the entire ryanodine receptor type 1 coding region for sequence variants associated with malignant hyperthermia susceptibility in the North American population. *ANESTHESIOLOGY* 2005; 102:515–21
4. Hopkins PM: Malignant hyperthermia: Advances in clinical management and diagnosis. *Br J Anaesth* 2000; 85:118–28
5. Monnier N, Krivosic-Horber R, Payen JF, Kozak-Ribbens G, Nivoche Y, Adnet P, Reyford H, Lunardi J: Presence of two different genetic traits in malignant hyperthermia families: implication for genetic analysis, diagnosis, and incidence of malignant hyperthermia susceptibility. *ANESTHESIOLOGY* 2002; 97:1067–74
6. Sambuughin N, Sei Y, Gallagher KL, Wyre HW, Madsen D, Nelson TE, Fletcher JE, Rosenberg H, Muldoon SM: North American malignant hyperthermia population: Screening of the ryanodine receptor gene and identification of novel mutations. *Anesthesiology* 2001; 95:594–9
7. Girard T, Treves S, Voronkov E, Siegmund M, Urwyler A: Molecular genetic testing for malignant hyperthermia susceptibility. *ANESTHESIOLOGY* 2004; 100:1076–80

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David C. Warltier, M.D., Ph.D., acted as Handling Editor for this exchange.

\* Available at: <http://www.mhaus.org/index.cfm/fuseaction/Content.Display/PagePK/MolecularGeneticsFAQ.cfm>. Accessed June 20, 2005.

† Available at: [http://www.geneclinics.org/servlet/access?prg=j&db=genetests&site=gt&id=8888891&fcn=c&qry=19725&res=nous&res=nointl&key=jVYz4R2Z2hvNX&show\\_flag=c](http://www.geneclinics.org/servlet/access?prg=j&db=genetests&site=gt&id=8888891&fcn=c&qry=19725&res=nous&res=nointl&key=jVYz4R2Z2hvNX&show_flag=c). Accessed June 20, 2005.



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## Interaction between Anesthetic Molecules and Their Binding Sites Must Be Far More Complex

*To the Editor:*—I read the study by Liu and Eckenhoff<sup>1</sup> with much interest. The authors investigated the binding of isoflurane and enflurane with human serum albumin with isothermal titration calorimetry and calculated the molecular properties of the two anesthetics using molecular analysis software. They concluded that weak polar interactions confer considerable selectivity and that differences in drug action may arise from occupancy of different protein sites. However, I believe that there are some problems drawing these conclusions from this study.

The authors assumed that the different manners of isoflurane and enflurane binding to their binding sites in human serum albumin can be attributed to their different dipole moments. However, this seems untrue. If the selectivity of binding sites to accommodate anesthetic molecules depends on the dipole moments of the drugs, how can we explain the different potencies of optically pure stereoisomers? The size of the dipole moments of the stereoisomers must be the same; however, it is known that the (+) isomer of isoflurane is more potent than the (−) isomer (minimum alveolar concentration =  $1.06 \pm 0.07\%$  vs.  $1.62 \pm 0.02\%$ ).<sup>2</sup> I assume that optical isomers exert their different anesthetic effects *via* different manners of binding to their receptor sites. I hope that the authors can prove that only one of the optical

isomers, presumably not both of them, can bind to the site of human serum albumin using optically pure isoflurane isomers.<sup>3</sup>

Dipole moment is a very useful concept with which to express the asymmetry in the molecular charge distribution; however, it is too simple as an indicator to express the characteristics of chemical substances. I believe that interaction between anesthetic molecules and their binding sites must be far more complex than can be explained by dipole-dipole interactions.

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### References

1. Liu R, Eckenhoff RG: Weak polar interactions confer albumin binding site selectivity for haloether anesthetics. *ANESTHESIOLOGY* 2005; 102:799–805
2. Lysko GS, Robinson JL, Casto R, Ferrone RA: The stereospecific effects of isoflurane isomers in vivo. *Eur J Pharmacol* 1994; 263:25–9
3. Huang CG, Rozov LA, Halpern DF, Vernice GG: Preparation of isoflurane enantiomers: A first step toward understanding the mechanism of anesthesia. *J Org Chem* 1993; 58:7382–7

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*In Reply:*—Professor Ishikawa asks an interesting question: If dipole-dipole interactions explain the selectivity for sites that underlie potency differences between the structural isomers isoflurane and enflurane,<sup>1</sup> how does one explain the potency difference between two compounds with no difference in dipole moment, *e.g.*, the enantiomers of isoflurane?<sup>2</sup> The question, however, implies that differences in potency are always produced *via* occupancy of different binding sites, rather than different occupancy of common sites. It is important to recognize that either case can produce differences in potency. For the *structural* isomers, we found the different physicochemical nature of similar-sized molecules (isoflurane and enflurane) was sufficient to actually select for different sites on albumin.<sup>1</sup> As might be predicted from site selectivity, the clinical differences between these drugs extend beyond that of just potency. Inhaled anesthetic *enantiomers*, however, are, as Dr. Ishikawa points out, identical physicochemically. We would therefore argue that their small differences in potency are due to differing occupancy of common sites. A recent crystallographic study supports this contention.<sup>3</sup> In cocrystallized complexes of apoferritin and the racemic mixture of halothane (1:1), there was a 2:1 occupancy preference of the *S* over the *R* enantiomer in a common binding site. The differences in occupancy result from even weaker interactions than the dipole-dipole ones. For example, subtle differences in the distance of specific halogens from polar atoms on residues such as serine and tyrosine predict slightly improved interactions for *S* as compared with *R* halothane. Relevant data for the isoflurane enan-

tiomers do not yet exist, although we see no reason for them to be different. Certainly, there is a complete absence of evidence that enantiomers of such small molecules can select for unique protein sites.

We agree however, with Professor Ishikawa's final sentence regarding the complexity of features underlying anesthetic binding sites. Dipole moment is only one feature, but like molecular volume and surface area, it is a fairly strong one—enough to provide for site selectivity, a form of coarse tuning. Within a given site, there are a host of weaker features: steric, electrostatic, and thermodynamic, which combine to provide the fine tuning—the modulation of occupancy. The combination of unique sites and varying occupancy of those sites gives each of our inhaled anesthetics its unique clinical flavor.

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### References

1. Liu R, Eckenhoff RG: Weak polar interactions confer albumin binding site selectivity for the haloether anesthetics. *ANESTHESIOLOGY* 2005; 102:799–805
2. Lysko GS, Robinson JL, Casto R, Ferrone RA: The stereospecific effects of isoflurane isomers in vivo. *Eur J Pharmacol* 1994; 263:25–9
3. Liu R, Loll PJ, Eckenhoff RG: Structural basis for high affinity volatile anesthetic binding in a natural 4-helix bundle protein. *FASEB J* 2005; 19:567–76

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## Let There Be Light! (Preferably on the Inside): Misassembled Laryngoscope Blade as Cause of Failed Intubation

*To the Editor:*—Responding to a code, two experienced endoscopists attempted intubation with what seemed to be a correctly functioning laryngoscope (Welch Allyn fiberoptic Mach 3, Skaneateles Falls, NY). Both examined the laryngoscope before insertion, but at laryngoscopy, illumination of the glottis was not achieved.

Closer examination of the blade revealed a misassembled laryngoscope blade with the fiberoptic light source on the outside of the blade (fig. 1) instead of its correct position (fig. 2). Another laryngoscope was used at this point, and intubation was performed easily, revealing normal anatomy.



**Fig. 1. Misassembled laryngoscopic blade.**



**Fig. 2. Normal laryngoscopic blade.**

The fiberoptic component of this type of laryngoscope blade is removable for cleaning or can spontaneously come loose. Care should be taken during its reassembly.

Laryngoscopy and intubation can be difficult enough. We present one more possible pitfall.

When examining a laryngoscope before use, it is not enough only to “see the light.”

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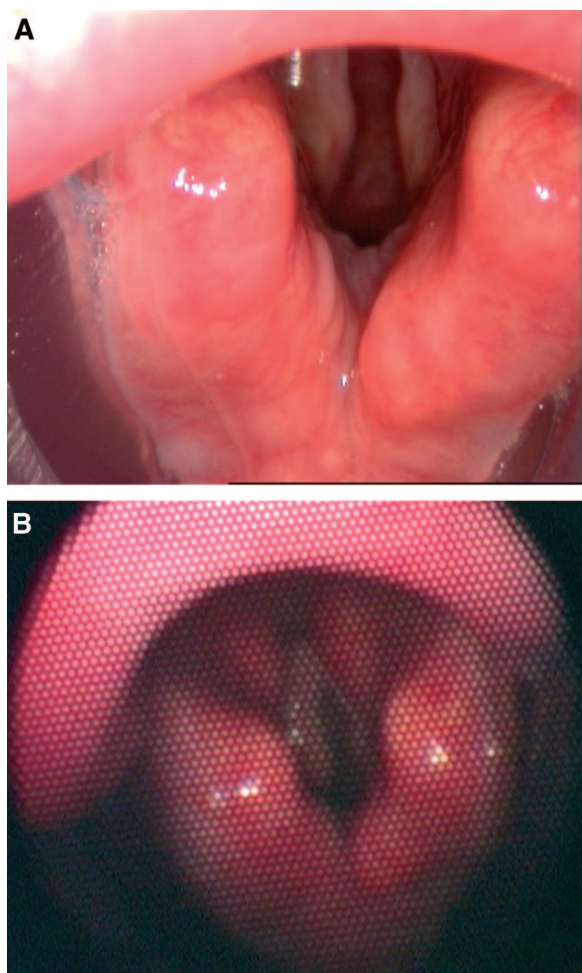
## Rigid Endoscopy for Assessment of Extraglottic Airway Device Position

*To the Editor:*—An established technique for assessing the anatomical position of the laryngeal mask airway is to pass a fiberoptic scope to the distal end of the airway tube.<sup>1</sup> An alternative technique, which has become routine practice at one of our institutes, is to use a rigid endoscope that is usually used for laparoscopic surgery. The technique involves disconnecting the extraglottic device from the anesthesia breathing system, adopting the sniffing position to align<sup>1</sup> the glottis and mouth, and advancing a 30° rigid endoscope (Hopkins II Forward-Oblique Telescope; Karl Storz, Tuttlingen, Germany) to the distal end of the airway tube. The high resolution images are then viewed on an external monitor. The rigid endoscope uses a rod-lens optical system (invented in 1959 by Harold H. Hopkins, Ph.D. [1918–1994; Professor in Physics, University Reading, Reading, United Kingdom]) and fiberoptic light transmission (invented in 1960 by Karl Storz, M.D. [1911–1996; Founder Karl Storz GmbH & Co., Tuttlingen, Germany]).<sup>2</sup> A 6.5-mm-OD rigid endoscope is suitable for adults, and a 3-mm-OD rigid

endoscope is suitable for children. The 30° angle allows a greater field of view by simply rotating the scope around its longitudinal axis. It is useful to apply an antifog solution (Aesculap; B. Braun, Tuttlingen, Germany) before insertion, but lubrication is rarely needed. We have used this technique in 600 patients using laryngeal mask and other extraglottic airway devices. In most situations, it was used to evaluate the anatomical position, but in some, it was used to diagnose glottic pathology. The technique has only failed on six occasions, and all of these were related to limited mouth opening preventing full insertion of the endoscope along the airway tube. A potential advantage is the high resolution images (fig. 1). Potential disadvantages are the risk of dental trauma and displacement of the extraglottic device; however, to date, these problems have not occurred. Finally, the technique is unsuitable for extraglottic devices with rigid or narrow airway tubes, such as the intubating or *ProSeal*<sup>TM</sup> (Laryngeal Mask Company, Ltd., Nicosia, Cyprus) laryngeal mask airways, respectively.

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**Fig. 1.** View of larynx in the same patient taken with (A) a rigid endoscope (see text) and (B) a new flexible fiberoptic scope (Portaview tracheal intubation fiberscope; Olympus, Zoeterwoude, The Netherlands), using the same light source and same capture resolution (728 × 538 pixels).

## References

1. Brimacombe J: Laryngeal mask anesthesia, Principles and Practice, 2nd edition. Philadelphia, Saunders, Elsevier, 2005, pp 93-102
2. Linder TE, Simmen D, Stool SE: Revolutionary inventions in the 20th century: The history of endoscopy. *Arch Otolaryngol Head Neck Surg* 1997; 123:1161-3

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## Effect of Transarterial Axillary Block *versus* General Anesthesia on Paresthesiae 1 Year after Hand Surgery

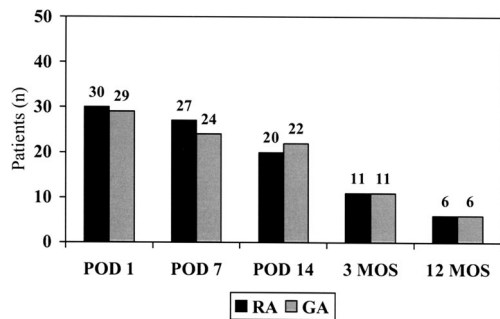
*To the Editor:*—Regional anesthesia (RA) is often implicated as a cause of postoperative neurologic symptoms after upper extremity surgery.<sup>1,2</sup> To date, there are no prospective randomized investigations of long-term postoperative neuropathy in patients receiving RA compared with general anesthesia (GA) for upper extremity surgery. In August 2004, we published a randomized trial that compared RA to GA for ambulatory hand surgery.<sup>3</sup> We found that there was no difference in the incidence of reported paresthesiae up to 2 weeks postoperatively among the 50 patients randomly assigned to RA (axillary brachial plexus block [AXB]) *versus* the 50 patients randomly assigned to GA. It is recognized, however, that the onset of paresthesiae after AXB may be delayed for weeks postoperatively.<sup>4,5</sup> We therefore prospectively

followed up the 100 participants of our previously published trial<sup>3</sup> in an attempt to determine whether RA compared with GA affects the incidence of paresthesiae up to 12 months after ambulatory hand surgery.

After institutional review board approval and informed consent, 100 patients undergoing ambulatory hand surgery were randomly allocated to RA (n = 50) or GA (n = 50).<sup>3</sup> RA comprised transarterial AXB using 10 mg/kg lidocaine, 1.5%, with 1:200,000 epinephrine injected incrementally posterior to the artery, and a standard balanced protocol was administered for GA. A tourniquet was applied to the operative arm for all patients and inflated to 100 mmHg above the systolic blood pressure (minimum 200 mmHg).<sup>3</sup> At the time of discharge from hospital, patients were given a home diary to complete and return by mail. Among various other outcome measures,<sup>3</sup> patients were instructed to document the incidence of paresthesiae (numbness or tingling)<sup>6</sup> in the operative extremity on postoperative days 1, 7, and 14. Telephone calls were placed to all patients at 3 and 12 months postoperatively, at

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**Fig. 1. Incidence of postoperative paresthesiae following regional versus general anesthesia for ambulatory hand surgery. GA = general anesthesia; MOS = months; POD = postoperative day; RA = regional anesthesia (transarterial axillary brachial plexus block).**

which time patients were asked to report whether they experienced paresthesiae in the operative extremity. For patients who reported paresthesiae at 12 months postoperatively, we reviewed the preoperative surgical consultation found in each patient's medical chart for evidence of preoperative paresthesiae.

Results of our primary and short-term (up to 2 weeks) secondary outcome measures were published previously.<sup>3</sup> A total of 3 patients were lost to follow-up in the current study: 50 (100%) RA and 48 (96%) GA patients were successfully contacted by telephone at 3 months postoperatively, whereas 50 (100%) RA and 47 (94%) GA patients were successfully contacted by telephone at 12 months postoperatively. All contacted patients agreed to participate in the current study. The incidences of reported paresthesiae in the operative extremity were similar between groups at each measured time interval postoperatively (fig. 1) and nearly indistinguishable between the two groups at 3 months (11 RA patients, 11 GA patients;  $P = 0.358$ ) and 12 months (6 RA patients, 6 GA patients;  $P = 0.212$ ) after surgery. For all patients in aggregate, the incidence of paresthesiae in the operative extremity at 12 months postoperatively was not related to age ( $P = 0.493$ ), sex ( $P = 0.381$ ), surgeon ( $P = 0.160$ ), type of hand surgery performed ( $P = 0.563$ ), tourniquet inflation pressure ( $P = 0.596$ ), or duration of tourniquet inflation ( $P = 0.188$ ). However, patients who reported paresthesiae at 12 months postoperatively weighed significantly less at the time of surgery than those who had no paresthesiae at 12 months ( $67.1 \pm 14.8$  vs.  $78.5 \pm 16.2$  kg;  $P = 0.023$ ). For RA patients, the incidence of paresthesiae at 12 months postoperatively was not statistically associated with the amount of needle-skin punctures ( $P = 0.804$ ), duration of needle-skin penetration ( $P = 0.274$ ), or occurrence of incidental transient paresthesiae ( $P = 0.339$ ) during AXB administration. Finally, among the 6 patients in the RA group and the 6 patients in the GA group who reported paresthesiae at 12 months postoperatively, there was no difference between groups in the number of patients who had preoperative paresthesiae (3 RA patients, 2 GA patients;  $P = 0.558$ ) as documented in their preoperative surgical consultations.

Our results suggest that neurologic symptoms are common after

either RA or GA for ambulatory hand surgery, such that all potential patient-, surgical-, and anesthetic-related causes of paresthesiae should be explored before apportioning blame to RA. Indeed, Horlocker *et al.*<sup>7</sup> determined that only 7 (11%) of the 62 nerve injuries that followed 1,614 AXBs were related to the block itself. Although our data reveal little about the cause of neurologic symptoms, there exists an association between decreased body mass and postoperative paresthesiae at 12 months. It is arguable that increased body mass may be protective and/or the tourniquet inflation pressure was set too high for leaner patients.

One important limitation of our study is that we did not examine for paresthesiae preoperatively. Our randomized study design nonetheless limits the introduction of bias from preexisting neuropathy. A second limitation is that we cannot exclude a type II error from our current findings. Our sample of 100 patients (50 per group) stemmed directly from our previously published trial,<sup>3</sup> in which we had defined our primary outcome measure as pain intensity on postoperative day 14. In the current study, we found that 6% and 8% of patients in the RA and GA groups, respectively, reported new-onset paresthesiae at 12 months postoperatively relative to their preoperative surgical consultations. *Post hoc* power analysis using these findings reveals that we would require 5,108 patients (2,554 per group) to detect a 2% greater incidence of new-onset paresthesiae at 12 months postoperatively in the GA group compared with the RA group, with 5% significance and 80% power. Nonetheless, we believe that our current findings are, however underpowered, useful and worthy of dissemination.

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## References

1. Cheney FW, Domino KB, Caplan RA, Posner KL: Nerve injury associated with anesthesia: A closed claims analysis. *ANESTHESIOLOGY* 1999; 90:1062-9
2. Lee LA, Posner KL, Domino KB, Caplan RA, Cheney FW: Injuries associated with regional anesthesia in the 1980s and 1990s: A closed claims analysis. *ANESTHESIOLOGY* 2004; 101:143-52
3. McCartney CJ, Brull R, Chan VW, Katz J, Abbas S, Graham B, Nova H, Rawson R, Anastakis DJ, von Schroeder H: Early but no long-term benefit of regional compared with general anesthesia for ambulatory hand surgery. *ANESTHESIOLOGY* 2004; 101:461-7
4. Lofstrom B, Wennberg A, Wien L: Late disturbances in nerve function after block with local anaesthetic agents: An electroneurographic study. *Acta Anaesthesiol Scand* 1966; 10:111-22
5. Selander D, Edshage S, Wolff T: Paresthesiae or no paresthesiae? Nerve lesions after axillary blocks. *Acta Anaesthesiol Scand* 1979; 23:27-33
6. Urban MK, Urquhart B: Evaluation of brachial plexus anesthesia for upper extremity surgery. *Reg Anesth* 1994; 19:175-82
7. Horlocker TT, Kufner RP, Bishop AT, Maxson PM, Schroeder DR: The risk of persistent paresthesia is not increased with repeated axillary block. *Anesth Analg* 1999; 88:382-7

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