To the Editor—In their recent obstetric anesthesia workforce survey, Bucklin et al.1 observed that anesthesiologists provided regional analgesia for labor more often in 2001 than in 1992 or 1981. Obstetricians provided correspondingly less, with the main decrease occurring between 1981 and 1992. In 1981, obstetricians provided 26, 31, and 46% of regional analgesia in the three sizes of institutions surveyed, whereas in 1992, they provided 0, 5, and 3%. Similarly obstetricians administered 3, 4, and 9% of anesthetics for cesarean deliveries in 1981 but none in 1992.2 Hawkins et al.2 and Lagasse and Santos3 previously noted these dramatic decreases between 1981 and 1992, relating them in part to concerns about medicolegal liability by obstetricians.

The source of these liability concerns was the publication in 1982 of revised professional standards by the American College of Obstetricians and Gynecologists (ACOG). For the first time, ACOG discouraged the concurrent provision of both an anesthetic and a procedure by an obstetrician, a previously common occurrence, and required the inclusion of anesthesia departments in privileging practitioners for obstetric anesthesia. The fifth edition of the Standards for Obstetric-Gynecologic Services, published in 1982, states,4

An obstetrician trained in the appropriate methods of anesthesia administration may provide the anesthesia if privileges for these procedures have been granted by the obstetric and anesthesia departments. However, it is more desirable for an anesthesiologist or anesthetist to provide this care so the obstetrician may devote undivided attention to the delivery...

Any ambulatory surgical unit that utilizes general, epidural, or spinal anesthesia should do so under the direction of an anesthesiologist.

The fourth edition of the Standards for Obstetric-Gynecologic Services, published in 1974,5 contains no warning about divided attention or inclusion of anesthesiologists in privileging and qualifies anesthesiologist care with the terms “whenever possible.” The 1982 explanation that obstetricians should concentrate on obstetrics while anesthesiologists concentrate on anesthesia appeared in the official ACOG Standards that sought “a high standard of quality care” and were designed “to set forth recommendations and suggested guidelines for agencies, hospitals and individuals to follow.”

This philosophy of care seems obvious today but was controversial in the 1970s. In 1981, 46% of obstetricians agreed with the statement that anesthesiologists are not sufficiently trained in obstetric anesthesia.6 Some insurance plans paid obstetricians for labor anesthesia. Therefore, the outcome of any deliberations by ACOG members in 1981 over obstetric anesthesia care was uncertain. The philosophic shift represented in the 1982 Standards is an obstetric anesthesia milestone.

The obstetrician chairing the ACOG Professional Standards Committee between 1978 and 1981, which developed the fifth edition Standards, was Robert E. Johnstone, M.D. (fig. 1). He was a Professor of Obstetrics and Gynecology at the University of Cincinnati, Ohio, who had organized a group of obstetricians, midwives, and administrators to improve obstetric care within the city. Coleading this group was Richard Schmidt, M.D. (Director, Department of Obstetrics and Gynecology, Good Samaritan Hospital, Cincinnati, Ohio; President, ACOG, 1977–78; retired), Chair of the ACOG committee that published the 1974 standards, who involved Johnstone nationally. Together, they had worked on practices to improve the care of patients with toxemia of pregnancy, using professional education, written policies, and quality assurance programs. They then recognized that the second greatest cause of obstetric mortality in Cincinnati was related to anesthesia care. This was a concern and focus as Johnstone assumed the chair position of the national ACOG committee.

Johnstone had learned to perform regional anesthetics during his obstetric residency training at the Lying-In Hospital in Boston, Massachusetts. When he started his practice in Cincinnati in 1954, he sometimes administered saddle-block anesthetics himself to patients for difficult deliveries. He soon became busy and recruited a nurse anesthetist to anesthetize patients with open-drop ether, paying her salary out of his income. There were few anesthesiologists in Cincinnati during the 1950s and 1960s, and they spent their time in the surgical operating rooms. Women in labor received subcutaneous doses of narcotics, primarily meperidine, and sedatives until the time of delivery, when they would receive either the saddle block or ether anesthesia. Johnstone recognized that having an anesthesia practitioner in the delivery room allowed him to focus on the delivery. In 1970, Johnstone supported the founding of an anesthesiology residency at the University of Cincinnati School of Medicine. As this program grew during the 1970s, he observed lumbar epidural analgesia and other regional techniques that anes-

Fig. 1. Robert E. Johnstone, M.D., in the delivery room, 1967. Figure provided courtesy of author.
obstetricians could provide. He encouraged the participation of
anesthesiologists in obstetric care and supported insurance pay-
ments for their services. Johnstone recognized improvements in
patient outcomes as anesthesiologists provided more care.

The personal experiences by Johnstone with anesthesiology in-
fluenced him to advocate obstetric anesthesia care by anesthesi-
ologists. During the 1970s, his son became an anesthesiologist, train-
ing in Philadelphia, Pennsylvania, and practicing in Alabama, and
provided additional information about what anesthesiologists could
do. They once discussed an unfortunate case in Alabama where an
obstetrician administered a saddle-block anesthetic to a woman,
delivered a baby with forceps, and then looked up to discover that
the patient had arrested. Reinforced with such anecdotes and rely-
ing on personal observations, Johnstone was able in 1981 to lead a
committee of obstetricians to a new standard: anesthesia by anes-
thesiologists.

Johnstone retired in 1988 but remains proud of his contribution to
improving obstetric care. Personal verbal communications from Rob-
ert E. Johnstone, M.D., Professor, Obstetrics and Gynecology, Uni-
versity of Cincinnati, Cincinnati, Ohio; Director, Department of Obstetrics
and Gynecology, Christ Hospital, Cincinnati, Ohio; retired. His con-
tribution is reported as an explanation for some changes noted in
the obstetric anesthesia workforce surveys and an important step in the
development of anesthesiology.

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References

3. Lagasse RS, Santos AC: Obstetric anesthesia coverage. Anesthesiology
1997; 87:4–5.
4. American College of Obstetricians and Gynecologists: Standards for Obstet-
ric-Gynecologic Services. Washington, D.C., American College of Obstetricians
and Gynecologists, 1982.
5. American College of Obstetricians and Gynecologists: Standards for Obstet-
ric-Gynecologic Services. Chicago, American College of Obstetricians and Gyn-
ecologists, 1974.

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Proper Priority Please

To the Editor:—One always needs to be careful about stating that anything is “new,” and I wonder if I might suggest to Ueda et al.1 that they were incautious in their claim in regard to the use of regular intermittent bolus administration of epidural local anesthetic. This technique was studied in Edinburgh, many years ago, in both open2 and randomized double-blind3 studies in gynecologic patients. I am delighted that others are now studying this method of administration, but priority in this regard belongs properly to Bruce Scott, Stan Schweitzer, and John Thorn.

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References

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Bring Rapidly Degradable Hydroxyethyl Starch to the United States

To the Editor:—We read with great interest the review article of Dr. Kozek-Langenecker on the effects of hydroxyethyl starch (HES) solutions on hemostasis.1 We agree with Dr. Kozek-Langenecker’s conclusion that rapidly degradable HES is favored for relatively beneficial low risk for hemostatic derangements, postoperative blood loss, and reoperation rates. We would like to add some considerations to the article’s recommendations.

First, Dr. Kozek-Langenecker’s practical recommendation that rapidly degradable HES is a suitable volume expander in the routine perioperative setting because of the adequate volume efficacy and the low risk of hemostatic derangement1 may not be useful in the United States because rapidly degradable HES is not commercially available in the United States.

Second, at our level 1 trauma center, we still experience adverse reactions such as exacerbation of coagulopathy among injured patients despite the very restrictive use of slowly degradable HES. Therefore, the article’s recommendation to simply restrict usage of slowly degradable HES types whenever hemostatic competence is critical1 may not be advisable.

Finally, the article admits that “in Europe, a large variety of HES products are commercially available but are dominated by rapidly degradable HES preparations, whereas slowly degradable HES preparations are mainly available in the United States.”1 Notwithstanding the fact that Food and Drug Administration regulations and commercial marketability of HES are beyond the scope of the article, the editor would have significantly contributed to the article’s value if an editorial review has been devoted to

References

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the reasons why the availability and distribution of HES significantly differ between Europe and the United States. More importantly, now that the author has shown that rapidly degradable HES is better suited for trauma centers, the more important question becomes, What does it take to make rapidly degradable HES widely available in the United States? In addition, the publication of this article is worthy of both praise and criticism: praise for its in-depth explanation of HES’s effects on hemostasis, especially for indicating and contraindicating the use of both rapidly degradable and slowly degradable HES; and criticism for leaving the reader frustratingly in search of a rapidly degradable HES counterpart in the United States.

In Reply:—I appreciate Drs. Tang, Pittet, and Ganter’s interest in my article on the effects of hydroxyethyl starch (HES) solutions on hemostasis and their interesting comments. I agree completely with these authors that the availability of HES solutions varies considerably among the continents. In the United States, slowly degradable HES preparations are currently approved for perioperative intravascular volume expansion, whereas in Europe, a variety of new-generation rapidly degradable HESs are approved and widely popular. The reason for the different approaches, however, remains unclear to me.

My article was by no means intended to frustrate American readers of *Anesthesiology*. My aim was to elaborate on the effects of HES preparations on cellular and humoral coagulation and to derive some practical recommendations. In contrast to Dr. Tang et al., I am convinced that these logical conclusions are useful and advisable. The urgent call for rapidly degradable HES as a suitable volume expander with adequate volume efficacy and low risk of hemostatic side effects from overseas colleagues is easy to understand. How to implement supply and availability on the market, however, is beyond the scope of my article. These issues have to be tackled by the national anesthesiologic societies and the respective authorities. Until now, rapidly degradable HES solutions have already been used for scientific purposes in the United States. I strongly believe that such large-scale overseas studies using rapidly degradable HES in connection with our European experience will pave the way to Food and Drug Administration approval.

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References

2. Gandhi S, Warthier D, Weiskopf R, Bepperling F, Baus D, Jungheinrich C. Volume substitution therapy with HES 130/0.4 (Voluvén®) versus HES 450/0.7 (hetastarch) during major orthopedic surgery. Critical Care 2005; 9:P206

To the Editor:—I read with interest the recent report and accompanying editorial regarding package inserts or the label for medications. This important subject has previously received little attention in the anesthesiology literature.

Anesthesiologists are in an envious position relative to many other medical specialties because they regularly use only a limited number of medications. This makes it all the easier to be familiar with the package inserts for these drugs. The inserts are free and convenient. They contain a wealth of information such as indications, contraindications, side effects, and drug interactions.

Physicians should be aware of the indications for drugs and realize that they can be criticized for using them in off-label applications if problems arise. A case in point is the intrathecal use of fentanyl. Indeed, armed with the knowledge that this common application is not indicated, clinicians could push for appropriate testing for its approval.

Those medications carrying boxed warnings, the most stringent type, deserve special attention. Some examples are succinylcholine, droperidol, midazolam, and ketorolac.

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References

To the Editor.—The recent article about drug labels and the accompanying editorial1,2 were factual and well written. However, a major flaw in the drug labeling and package insert process is that it is virtually static. Most physicians will not refer to a textbook that is more than 5 yr old. Why spend time reading a package insert that you know has not been updated for 10 or 20 yr? There have been occasional instances of new risks or dangers being amended to the package insert or the label. Adding a new indication, however, is virtually impossible; especially if the medication is near the end of its patent. A pharmaceutical company would prefer to synthesize a congener or concoct a new formulation and market this as a “new” drug before they would add a new indication to an existing drug. The difficulties that we in the United States have encountered with spinal bupivacaine have been updated for 10 or 20 yr? When bupivacaine was first brought to market in the United States in 1963, it bore a bold “Not for Spinal Use” warning on the label. The motivation for this warning is now lost in the fog of time. Although bupivacaine is the most widely used spinal anesthetic in the world, bottles of bupivacaine still bear the “Not for Spinal Use” caveat in the United States. The same bottle in Canada does not have this warning. It is true that a physician may use the drug off-label, but most anesthesia physicians in the United States are reticent to contravene the bold “Not for Spinal” warning as an off-label application. Rather than petition the Food and Drug Administration to remove the “Not for Spinal” warning, the US manufacturers obtained Food and Drug Administration approval to market a “new drug,” Spinal Marcaine, which is simply the same drug packaged in a 2-ml ampule rather than in a 30-ml single-use vial. It probably makes sense for pharmaceutical companies and the Food and Drug Administration to prepare the initial label and package insert for a new drug. For established medications, the US government should amend the regulatory process. At regular intervals after a medication’s initial approval (e.g., 7–10 yr), an independent panel of experts should be convened to update the package insert and label, based on current medical knowledge.

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References

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Labeling (Package Insert): Meaning* by the Food and Drug Administration of Not Recommended, Not Indicated, and Off-label Use

To the Editor.—The article from the Food and Drug Administration (FDA) by Chang et al.1 was erudite. And it stated, “The views . . . do not necessarily reflect those of the Food and Drug Administration.” However, in my opinion, shouldn’t it have alerted anesthesia practitioners to the FDA’s interpretation of these terms?

In 1983, Patricia H. Russell, M.D. (deceased, Acting Director of the Division of Surgical-Dental Drug Products, Office of Drug Research and Review, Rockville, Maryland), stated, (1) “Not recommended and contraindicated as viewed by the FDA are close to being synonymous”; (2) “Not indicated and not recommended is ‘virtually’ saying the same thing”; (3) “. . . not indicated is simply that the drug is not indicated for that particular use because nobody has studied it in that particular use”; and (4) “Not recommended puts the onus squarely back on the practitioner in that we are saying that we (FDA) cannot recommend the use of the drug.”2 In regard to “off-label use,” she stated, (1) “. . . if you feel that you can justify the use of that (not indicated, not recommended) drug by putting a note on the chart and defining why it is you are using the drug in that particular patient, then the responsibility is yours,” and (2) “To study a drug for a new use requires they (anesthesia practitioners) or the pharmaceutical company submits to the FDA an IND (investigational new drug) application.”2 Are these quotes still valid, has the FDA officially restated them, and if so, where?

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References
2. Department of Health and Human Services, Public Health Department, Food and Drug Administration (FDA), Anesthetic and Life Support Drugs Advisory Committee, Fifth Meeting. Vol II. Wednesday, October 5, 1983, transcript page II-14-16

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Botulinum Toxin Type A Therapy and Human Serum Albumin

To the Editor.—This letter is in reference to the recent article on the use of botulinum toxin type A (Botox®; Allergan Inc., Irvine, CA) in the role of chronic myofascial pain and the corresponding editorial.1,2 Although the use of Botox® is regarded as a safe therapy for many patients,3-5 it is our concern that Botox® contains 0.5 mg human serum albumin per 100-U vial and that this is not often discussed in the literature despite increasing usage.6 Other preparations of botulinum toxin used in the world today also contain some amount of human serum albumin (Dysport®; Ipsen Ltd., Berkshire, United Kingdom, and Myobloc®; Elan Pharmaceuticals, Cambridge, MA).6

The human albumin used in Botox® is purchased from a division of the Bayer Corporation (Leverkusen, Germany). Measures taken to prevent disease transmission to humans include screening of donors, plasma testing for human immunodeficiency virus (HIV) and hepatitis B, and pasteurization of the albumin preparation. Therefore, the risk of transmitting viruses such as hepatitis A, B, and C, non-A non-B hepatitis (NANB), and HIV is considered extremely remote. There still exists an extremely remote possibility that some prion causing disease such as Creutzfeldt-Jakob or variant Creutzfeldt-Jakob may be transmitted in the preparation because prions are not inactivated by current sterilization methods.6 Bayer corporation also produces Plasbumin® (human albumin) as a plasma substitute, and there is a clear statement on its product monograph that no case of viral or prion disease transmission has ever been documented with its use.

With the injection of human albumin, there is a possibility of inducing a hypersensitivity reaction resulting in symptoms such as fever, chills, urticaria, malaise, nausea, rash, and asthma. The product monograph for Botox® indicates that the drug is contraindicated if a patient has a “... known hypersensitivity to any ingredient in the formula...,”7 and therefore, patients should be questioned about previous exposure to human albumin or albumin transfusions.

A survey of four other clinicians in our pain clinic indicated that although most knew there was albumin in each vial of Botox®, none knew exactly how much was in each vial, nor were any of the clinicians informing their patients of its presence. Obviously, a Jehovah’s Witness patient would want to know about the human albumin and would likely refuse treatment with this product. Further, we believe that all patients should be informed about the presence of human albumin in botulinum toxin therapy as part of their informed consent. Some non-Jehovah’s Witness patients may have a psychological and emotional reaction to the knowledge they are being injected with a blood product, although it is unlikely to create any adverse effect by its presence. We propose that this concern should be addressed before therapy with botulinum toxin and that medical literature should highlight this issue because dissemination of this information is vital to ethical practice.

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References

2. Abram SE: Does botulinum toxin have a role in the management of myofascial pain? ANESTHESIOLOGY 2005; 103:223–4
7. Botox® (botulinum toxin type A) package insert. Irvine, CA, Allergan Pharmaceuticals, October 2004 (Accepted for publication January 23, 2006.)

Anesthesiology 2006; 104:1108–9

In Reply.—Thank you for the opportunity to provide a response to Dr. Tumber’s letter (Botulinum Toxin Type A Therapy and Human Serum Albumin). Dr. Tumber has correctly identified the continuing need to educate patients on human serum albumin (HSA). As with any drug, the presentation, product monograph, and dissemination of information to patients is the basis for appropriate and ethical clinical practice. This is particularly important in regard to products derived from human tissue, such as HSA. It is for this reason that HSA has undergone intense scrutiny to ensure its safe use in clinical practice.

The concerns of Dr. Tumber focus mainly on two issues: hypersensitivity reactions and viral and prion transmission. Each of these issues will be addressed in this letter.

Each 100-U vial of Botox® (Allergan, Inc Irvine, CA) contains 100 U purified botulinum toxin type A neurotoxin complex, 0.5 mg human albumin, and 0.9 mg sodium chloride in a sterile, vacuum-dried form without a preservative. The HSA used in Botox® is purchased from Talecris Biotherapeutics, Inc. (Research Triangle Park, NC), who acquired the contributed assets of the worldwide plasma business from the Biologic Products Division of Bayer HealthCare AG (Berkeley, CA) and became operational April 1, 2005.

Although it would be difficult to distinguish between hypersensitivity reactions to botulinum toxin and HSA, both Botox® and Plasbumin® (Talecris Biotherapeutics, Inc., Research Triangle Park, NC) product monographs mention the rarity of hypersensitivity reactions.1,2 The Botox® product monograph states, “Serious and/or immediate hypersensitivity reactions have been rarely reported. These reactions include anaphylaxis, urticaria, soft tissue edema, and dyspnea.” The Plasbumin®-25 monograph states, “Adverse reactions to albumin are rare. Such reactions may be allergic in nature or due to high plasma protein levels from excessive albumin administration. Allergic manifestations include urtica-ria, chills, fever, and changes in respiration, pulse and blood pressure.” The expected plasma levels reached after both Plasbumin® and Botox® administration would be quite different. Plasbumin® is packaged as 5%, 20%, and 25% formulations (5-25 g/100 ml) and is administered intravenously. Although no pharmacokinetic information for HSA is included in the product labeling, the expected plasma levels of HSA after Plasbumin® administration would be several orders of magnitude higher than after an intramuscular or intradermal Botox® injection containing 0.5 mg HSA per 100 U. Although any given

The above letter was sent to the authors of the referenced report. The authors did not feel that a response was required. —Michael M. Todd, M.D., Editor-in-Chief


The author thanks Talecris Biotherapeutics, Inc., Research Triangle Park, North Carolina.
patient has the potential to have a hypersensitivity reaction to any drug or excipient, these occurrences, regardless of cause, are rarely reported with Botox®.

The safety of HSA in clinical practice has been well documented. Correctly pasteurized HSA preparations have an excellent safety record in regard to virus and prion protein transmission (Bayer HealthCare written communication, November 2005). Safety and quality of the product are ensured through complete screening and documentation of donors, purification and viral-removal procedures, and extensive pathogen detection assays.

The plasma used by Talecris Biotherapeutics is source plasma from US donors that meets all US license criteria for source plasma, as specified in the US Code of Federal Regulations. Individual donations and plasma pools are screened and must be found nonreactive or negative for numerous viruses and antigens, including the hepatitis B virus antigen, human immunodeficiency virus (HIV)-1 p24 antigen, and antibodies to both HIV and hepatitis C virus. Donated plasma is also screened using viral nucleic acid testing for HIV, hepatitis B and C viruses, and parvovirus B19 genetic material. Each donation is also required to be less than or equal to two times the upper limit of the normal range for alanine aminotransferase levels using Food and Drug Administration–approved test methods.

A high margin of safety from the risk of viral transmission is achieved by using a combination of virus removal by means of the Cohn fractionation process (including cold ethanol precipitation, centrifugation, and/or filtration of human plasma) and inactivation through chemical treatment and pasteurization for 10 h at 60°C. These specific manufacturing steps are reported to be capable of eliminating and inactivating a wide range of viruses and have been demonstrated to remove spiked hamster-adapted scrapie prion protein and transmissible spongiform encephalopathy infectivity. To confirm removal of pathogenic prion proteins during the manufacturing process, a patented Western blot assay was developed that has confirmed the removal of spiked transmissible spongiform encephalopathy infectivity.

On August 17, 1999, the Food and Drug Administration issued a Guidance for Industry regarding precautionary measures to reduce the risk of possible transmission of Creutzfeldt-Jakob disease and new variant Creutzfeldt-Jakob disease to recipients of blood products. The guidance document notes that plasma derivatives are unlikely to transmit disease in humans because of (1) the dilution factor of the infectious agent in a large plasma pool, (2) the less efficient intravenous and intramuscular route of inoculation, and (3) the rigors of the plasma pool manufacturing process. The document also states that no transmission of Creutzfeldt-Jakob or new variant Creutzfeldt-Jakob disease by human blood products or plasma derivatives has been documented to date. We are not aware of any subsequent reports of the transmission of any viral or prion disease associated with the use of HSA. As a precaution, the following warning statement appears on all products containing plasma-derived albumin:

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Bayer first licensed albumin on October 21, 1942. It is estimated that between 1980 and 1991, approximately 20 million individuals received 951 tons of albumin and plasma protein fractions. To date, there has not been a single, confirmed, documented case of viral or prion transmission to any recipient of albumin reported to Talecris.

We appreciate the concern on the part of Dr. Tumber regarding this issue and would like to reiterate that despite the proven safety record of HSA, proper awareness on the part of both physician and patient is necessary for ethical medical treatment with Botox®.

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References
1. BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex, US complete prescribing information. Irvine, CA, Allergan, Inc. Revised July 2004
3. US Department of Health and Human Services (USDHHS), Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products. Rockville, MD. USDHHS. FDA, CBER. August 1999

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correspondence

ratio indicative of inadequate recovery (e.g., < 0.70) at a time when all four responses displayed graphically appear identical. The clinician who merely glances at the bar graph without reading the displayed value may incorrectly assume that neuromuscular recovery is complete when this is clearly not the case. The explanation for this disparity between the displayed graphic and numerical values follows.

In the absence of neuromuscular block, repeated rapid indirect muscle stimulation produces a steady increase in mechanical twitch height. This is a function of altered muscle contractility and is unrelated to changes in neuromuscular transmission. This phenomenon is known as the "staircase effect." Therefore, after 10–15 min of TOF stimulation control, T1 (twitch height) may increase by 50–100%. In the research setting, this is why investigators wait several minutes before doing a final calibration of their baseline values. However, in the clinical setting, anesthesiologists rarely if ever take this effect into account. The usual sequence is (1) induce anesthesia, (2) calibrate the MNMT, and (3) administer muscle relaxant, all within 2 min or less. This failure to establish stable baseline values usually results in T1 values far in excess of 100% when spontaneous or induced recovery is complete. Therefore, at the end of the case, the sensor might record the following values: T1 = 165%, T2 = 145%, T3 = 130%, and T4 = 120% with a calculated TOF ratio of 0.73. This value will be corrected displayed numerically on the monitor screen. However, the bar graph attempts to display the absolute value (relative to control) of all four responses. Unfortunately, all values greater than 120% are truncated or "chopped off" at the top. The result in the above hypothetical case is a bar graph displaying a total absence of fade.

This situation is unsatisfactory for several reasons. Although the T1 value as a percent of control is only displayed in the monitor's display trend mode, values greater than 100% will be confusing to most clinicians. When data that "don't make any sense" are presented to the clinician, there is an understandable tendency to conclude that there must be something wrong with the monitor. If this happens often enough, the offending unit will eventually be destined to occupy a dusty shelf in a back storage room.

Of greater concern, the conflicting information presented by the monitor may contribute to improper clinical decisions. Some clinicians may opt to believe the bar graph rather than the numerical TOF ratio. The result is failure to antagonize residual block when reversal is clearly indicated. We have found the M-NMT module to be a useful addition to our monitoring armamentarium. However, its current user interface needs to be rethought by the manufacturer.

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References


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The M-NMT development was based on the Datex Relaxograph®, where the default mode of function depended, after the automatic determination of a supramaximal stimulation current, on the determination of an unrelaxed reference value (Tref). During recovery, the relative behavior of the first response (T1%) to this reference value was calculated and displayed in print. It soon became evident that the electromyographic reference baseline shifted to smaller values within the first 15–20 min of anesthesia and usually stayed at this level until full recovery. This was also explained in the Relaxograph User's Guide published in the 1980s. When force transducers were used with the Relaxograph®, the calibrated baseline tended to grow, and the recovered T1% was well over 100% without fade. These phenomena may result from anesthesia-induced increase in muscular blood flow and temperature.\(^1,4\) In addition, the T1% is prone to artifacts, e.g., if the position of the sensor shifts.

Because of ample customer feedback, Datex decided that the TOF% would be the default mode of analysis in the M-NMT. The measurement of TOF% does not require a reference level, because it is the percentage of T4/T1 in each TOF stimulation sequence. During module software development, TOF search for supramaximal current and determination of the mean reference value during Start-up were not separated. I have, when testing the movement sensor in an unrelaxed patient, been able to ascertain a slight increase in the evoked TOF response (1/20 s) and a gradual increase to around 110% during single stimulation at 1 Hz for several minutes, which apparently represents the original "staircase phenomenon."\(^5,6\) If one presses the Start-up button and restricts the sensor movement during the determination of the reference level, one can demonstrate how the responses shoot over 120% during unrestricted hand stimulation. Such manipulation is, however, against the manufacturer's instructions of use for the M-NMT.

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In Reply—We thank Dr. Kopman for the user feedback and appreciate the possibility to comment on his reasonable concern about the possible conflict between the bar graph display and numerically expressed train-of-four (TOF%) when the MechanoSensor® (kinemyography) is used to monitor the degree of neuromuscular block with the Datex-Ohmeda (Helsinki, Finland) NMT module (M-NMT). Dr. Kopman suspects that the phenomenon of increased responses is due to the "staircase effect," a typical feature of the acceleromyographic method (e.g., see page 702 in the October 2005 issue of Anesthesiology; TOF% is > 100% before the block and in full recovery\(^1\)). It is important to note that the technology in the M-NMT module is different than the acceleromyographic method, as Dr. Kopman correctly states. Equally important is to notice that the staircase effect and the fade in the responses are different phenomena.

The measurement of TOF% begins by pressing the Start-up button on the M-NMT module or in the NMT parameter menu. The monitor will start the measurement by automatically setting the stimulus current (maximum 70 mA). With an unrelaxed patient, the TOF% is 100. Nondepolarizing relaxants cause a fade in the responses, indicated by a lower TOF% and a slope in the bar graph. Depolarizing relaxants result in an equal decrease in all responses, without fade. In deep neuromuscular block, the monitor displays the number of detected responses. What Dr. Kopman finds confusing is that in certain situations, the TOF% and the bar graphs seem to give conflicting information. This situation occurs when the reference level is set so that the bar graphs go over the measurement range, i.e., are "chopped off" when the value exceeds 120%. Therefore, the user cannot see the fade. The chopping of the bar graph in the M-NMT is a user interface design inconvenience. Of utmost importance is to note that the TOF% is the primary source of information, and the bar graphs are an additional visual aid.

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Fig. 1. Photograph of a M-NMT module display from the patient monitor. Note that the numeric train-of-four (TOF) ratio is 67%, but the bar graph shows a total absence of fade.
A solution for the user interface disagreement reported by Dr. Kopman would be to access the service pages of the S/5 monitor and adjust the NMT parameter settings so that both the display of T1% and the automatic reference search are set to OFF. This causes the monitor to perform the supramaximal current search automatically and to display the bar graphs on a relative scale (T1 is scaled to a fixed value and T2–T4 are scaled relative to the T1 value). The stimulation current can also always be set manually from the NMT parameter menu. The TOF% trend is available on the trend pages, and, if one intends to do serious research, original response values in bits are available using the S/5 Collect program on a standard personal computer or laptop. This data can be further processed in, for example, Excel.

Regarding Dr. Kopman’s concern of a possibility of the M-NMT to contribute to improper clinical decisions, we disagree. The users should bear in mind that the TOF% is the primary source of information. The reported phenomenon of the bar graphs “chopping off” at values above 120% is clinically not valid if the measurement is used according to manufacturer’s instructions for use.

In conclusion, it is evident that monitoring the level of neuromuscular block has clinical benefits. Quantitative NMT monitoring facilitates optimal and cost-effective administration of neuromuscular blocking agents, enables follow-up and prediction of recovery, and helps in avoiding residual block. As Dr. Kopman states, with some understanding of the principles in NMT monitoring, the M-NMT can be an important addition to the monitored parameters.

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References

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Unforeseen Esophageal Misplacement of Airway Exchange Catheter Leading to Gastric Perforation

To the Editor.—We would like to highlight a case of gastric perforation secondary to the misplacement of an airway exchange catheter (AEC).

An AEC was used as a bridge to full extubation in a patient with a known difficult airway secondary to external radiation to the face for an orbital basal cell carcinoma. Uneventful general anesthesia proceeded with an awake fiberoptic intubation using a 7.0-mm single-lumen endotracheal tube. Placement position was verified by visualizing the carina and secured at 22 cm to the lip. Once fully awake with intact neuromuscular function, the patient was underwent extubation over a 14.0-size Cook AEC (Cook Critical Care, Bloomington, IN) secured with tape at 35 cm at the lips to allow a margin of safety from accidental dislodgment. The patient’s vitals were stable throughout emergence and extubation. Oxygen, 2 l/min, was insufflated through the Cook AEC via a Luer connector for transfer to postanesthesia care unit. The patient was noticed to have an occasional belch during transfer. On arrival, oxygen through the Cook AEC was discontinued, and he was placed on oxygen via facemask. The plan was to leave the AEC in place until it was certain that no residual anesthetic was present and the need for reintubation was unlikely.

During his stay in the postanesthesia care unit, the patient was switched from facemask to oxygen through AEC; the reason for this is unclear. Unfortunately, the flow rate of oxygen insufflation at that time

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was not known. Approximately 1 h into his stay in the postanesthesia care unit, the patient reported pain disproportionate to his surgery. On physical examination, the patient’s abdomen was noted to be remarkably distended, associated with belching. Oxygen through the AEC was discontinued. Portable chest (fig. 1) and abdominal (fig. 2) radiographs were ordered, illustrating free air under the diaphragm and massive gastric distention. A surgical consult highlighted the need for emergent surgery for probable gastric perforation. The patient was scheduled to undergo an emergent laparoscopy. On repeat fiberoptic intubation for the subsequent surgery, the AEC was noted to be in the esophagus. Diagnostic laparoscopy revealed a small perforation on the lesser curvature of the stomach consistent with gastric overdistension, which was subsequently repaired laparoscopically. Whether the perforation was caused directly by the device or gastric distension from oxygen insufflation is unknown. The patient subsequently made a full recovery and was discharged from hospital a week later.

The literature suggests four potential risks associated with the use of AECs: misplacement, bronchial or lung trauma, laryngeal trauma, and barotrauma related to jet ventilation.1,2 This incident illustrates the consequence of unforeseen AEC misplacement. The key issues leading to this complication were as follows: (1) failure to confirm endotracheal placement highlighting the necessity of end-tidal carbon dioxide monitoring (end-tidal monitoring can be facilitated through the Luer lock mechanism provided with the Cook AEC kit; a lateral chest radiograph may be of some benefit to confirm placement; however, the practicality of this investigation could be debated); (2) belching as an early sign of esophageal perforation; (3) the questionable benefit of oxygen insufflation through an AEC (apart from its role as a means for jet ventilation) in a patient able to saturate adequately via facemask; and (4) ensuring appropriate length of placement (in this case, the AEC was inserted too far; the literature recommends 22–25 cm for oral placement and 27–30 cm for nasal placement).1

In summary, we believe that an AEC should be treated as an endotracheal tube, and its placement should never be assumed to be correct until objective data support that conclusion.

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References


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The Use of Safety Needles in Anesthesia

To the Editor—The incidence of needlestick injuries is thought to be higher than reported, which has ranged from 14 to 839 injuries per 1,000 healthcare workers annually.1 In one study, 74% of needlestick injuries were due to incorrect technique.2 In that study, it was concluded that the injuries could have been prevented by the use of safety needles. In 2001, the Occupational Safety and Health Administration mandated the use of safety needles.

I would like to report our experience with safety needles. When the Occupational Safety and Health Administration mandated the use of safety needles, we chose the Portex Needle-Pro needle with needle protection device (Keene, NH). This safety needle contains a plastic cover, which is snapped over the needle after its use, with a one-handed technique (fig. 1). However, it was found that the device was bulky to use, and almost all physicians would simply remove the safety device (fig. 2). This led to multiple needlestick injuries. Despite the availability of the safety needle and knowledge of how to use the device, the safety feature was easily eliminated by the physicians using the device.

We then ordered the 18-gauge Blunt fill needle by Becton Dickinson (Franklin Lakes, NJ). Although the tip of the needle is blunt, it can produce a needlestick injury, but it takes much more force. We have had this needle for approximately 1 yr, and have had only

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Use of Ketamine to Facilitate Opioid Withdrawal in a Child

To the Editor—Advancement of management of critically ill children has resulted in widespread use of opioids for sedation. However, no guidelines for appropriate administration of opioids in pediatric intensive care sedation are yet available. As a result, many children have experienced physical dependence characterized by the emergence of withdrawal symptoms after cessation of opioid administration. It has been demonstrated that N-methyl-D-aspartate (NMDA) receptor antagonists reduce the occurrence of opioid dependence in adult humans and animal models of such dependence.

A 2-yr-old girl (height, 75 cm; weight, 9.5 kg) diagnosed with corrected transposition of the great vessels presented for a Rastelli operation. Anesthesia was provided using air-oxygen (75%/25%), sevoflurane, and fentanyl. Extracorporeal lung and heart assist was administered for heart failure after intracardiac repair. Fentanyl (10 µg/h) and midazolam (2 mg/h) infusion was initiated for sedation in our intensive care unit. Although she was weaned off the extracorporeal lung and heart assist on the 10th postoperative day, further mechanical ventilation was administered because of unstable cardiopulmonary status. Higher doses of fentanyl and midazolam were gradually required and reached 50 µg/h and 10 mg/h, respectively. On the 58th postoperative day, she was weaned from the mechanical ventilator after the analgesics and sedatives had been tapered and eventually discontinued. Three hours after extubation, naloxone (60 µg) and flumazenil (130 µg) were administered because she did not seem fully conscious and had labored respiration. Immediately after the administration of these antagonists, tachypnea recurred, accompanied by severe tremor, hyperreflexia, vomiting, and diarrhea. The trachea was intubated again with restart of infusion of fentanyl and midazolam. Her symptoms, such as tremor, disappeared immediately after these drugs were recommenced. Based on these symptoms and observations, we diagnosed opioid withdrawal syndrome.

Use of the conventional withdrawal technique of tapering fentanyl as slowly as possible to treat this syndrome without additive medication was unsuccessful, and resulted in persistent fever and tachypnea. Therefore, ketamine, a noncompetitive NMDA receptor antagonist, was initiated at 10 mg/h. Fentanyl was successfully discontinued with this technique without any withdrawal symptoms. Ketamine was gradually decreased, with monitoring of signs and symptoms. The patient was weaned from the ventilator after ketamine was discontinued, and she became oriented. Midazolam was then also tapered off. Neither rebound symptoms nor side effects were noted during or after tapering of these drugs.

The rationale for use of ketamine for opioid withdrawal is as follows: (1) it has been demonstrated that NMDA receptor antagonists attenuate the occurrence of opioid physical dependence and withdrawal symptoms in adult humans, and (2) S(+)ketamine has been reported to reduce opioid withdrawal-evoked hyperexcitation in electroencephalographic power spectra in adult humans. Ketamine facilitated opioid withdrawal in our patient, although she was only 2 yr of age. Little is known regarding the effects of NMDA receptor antagonists on opioid withdrawal in young children, although their effects have been demonstrated in adult humans. It has been suggested that NMDA receptor antagonists alone do not block opioid withdrawal syndrome in neonatal rats, because in these rats, NMDA receptors are functionally immature. NMDA receptor antagonists do not attenuate morphine withdrawal in 7-day-old rats, are partially effective in 14-day-old rats, and are fully effective in 21-day-old rats. It has been reported that the pattern of expression of NMDA receptors in the 2-yr-old human brain is almost the same as that in the 21-day-old rat brain. Ketamine might therefore be effective in suppressing opioid withdrawal symptoms in a 2-yr-old child.

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To the Editor—Advancement of management of critically ill children has resulted in widespread use of opioids for sedation. However, no guidelines for appropriate administration of opioids in pediatric intensive care sedation are yet available. As a result, many children have experienced physical dependence characterized by the emergence of withdrawal symptoms after cessation of opioid administration. It has been demonstrated that N-methyl-D-aspartate (NMDA) receptor antagonists reduce the occurrence of opioid dependence in adult humans and animal models of such dependence. A 2-yr-old girl (height, 75 cm; weight, 9.5 kg) diagnosed with corrected transposition of the great vessels presented for a Rastelli operation. Anesthesia was provided using air-oxygen (75%/25%), sevoflurane, and fentanyl. Extracorporeal lung and heart assist was administered for heart failure after intracardiac repair. Fentanyl (10 µg/h) and midazolam (2 mg/h) infusion was initiated for sedation in our intensive care unit. Although she was weaned off the extracorporeal lung and heart assist on the 10th postoperative day, further mechanical ventilation was administered because of unstable cardiopulmonary status. Higher doses of fentanyl and midazolam were gradually required and reached 50 µg/h and 10 mg/h, respectively. On the 58th postoperative day, she was weaned from the mechanical ventilator after the analgesics and sedatives had been tapered and eventually discontinued. Three hours after extubation, naloxone (60 µg) and flumazenil (130 µg) were administered because she did not seem fully conscious and had labored respiration. Immediately after the administration of these antagonists, tachypnea recurred, accompanied by severe tremor, hyperreflexia, vomiting, and diarrhea. The trachea was intubated again with restart of infusion of fentanyl and midazolam. Her symptoms, such as tremor, disappeared immediately after these drugs were recommenced. Based on these symptoms and observations, we diagnosed opioid withdrawal syndrome.

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References


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