To the Editor—In their recent obstetric anesthesia workforce survey, Bucklin et al. observed that anesthesiologists provided regional anesthesia 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. Hawkins et al. and Lagasse and Santos 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:  

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, 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, 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 other 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-
In Reply:—We appreciate the comments and historical perspective regarding the provision of obstetric anesthesia provided by Robert E. Johnstone II, M.D. In his letter, he outlines the pivotal role of his father, Robert E. Johnstone, M.D., as well as contributions from the American College of Obstetricians and Gynecologists (ACOG) in improving obstetric anesthesia services. Beginning in 1981, Johnstone led the ACOG to new standards of care, i.e., anesthesia provided by anesthesiologists and not by obstetricians. Since that time, surveys have consistently demonstrated dramatic reductions in the number of obstetric anesthetics provided by obstetricians. For example, in 1981, obstetricians performed between 26 and 46% of regional anesthetics for labor in all sizes of hospitals.1 However, in 2001, obstetricians performed only 1–6% of these procedures.2 The most recent Guidelines for Perinatal Care state, “An obstetrician may administer the anesthesia if granted privileges for these procedures. However, having an anesthesiologist or anesthetist provide this care permits the obstetrician to give undivided attention to the delivery.” If obstetric anesthesia is provided by obstetricians, the director of anesthesia services should participate with a representative of the obstetric department in the formulation of procedures designed to ensure the uniform quality of anesthesia services throughout the hospital.3

In addition to these changes that were fundamental to improving patient safety, leaders within the American Society of Anesthesiologists (ASA) have also been instrumental in establishing guidelines and practice parameters to continue these efforts. The ASA published one of the first documents in 1988. Although not guaranteed to provide a specific outcome, the Guidelines for Regional Anesthesia in Obstetrics were designed to provide anesthesia care providers with a framework that allowed them to interpret and establish guidelines for their own practices.4 Other efforts to encourage quality patient care have included publication of Practice Guidelines for Obstetrical Anesthesia in 1999.4 Although these evidence-based, systematically developed recommendations were not intended to serve as standards or absolute requirements, they provide basic recommendations to assist practitioners in decision making. More recently, Optimal Goals for Anesthesia Care in Obstetrics, a joint statement by the ASA and ACOG, was published to further emphasize the importance of collaborative efforts by anesthesiologists and obstetricians in the provision of safe and most effective care for obstetric patients.†

Despite many advancements in the practice of obstetric anesthesia, there has been debate within the specialty resulting from denial of payment for regional labor analgesia by third-party payers.5 In these cases, reimbursement was denied because of a lack of “medical indication.” In response, the ASA and ACOG issued a Statement on Pain Relief during Labor in 2000 with revision in 2004.6 According to this statement, labor results in severe pain for many women. There is no circumstance where it is considered acceptable for a person to experience untreated severe pain, amenable to safe intervention, while under a physician’s care. It is the position of ACOG and ASA that third-party payers who provide reimbursement for obstetric services should not deny reimbursement for regional analgesia/anesthesia because of an absence of other “medical indications.”

Johnstone has provided interesting historical information about early efforts by the ACOG to improve patient safety and care. Since that time, a number of substantial changes have occurred in the practice of obstetric anesthesia, as evidenced by data from the 1981, 1992, and 2001 workforce surveys.7,8 The most recent survey suggested that more parturients used some type of analgesia for labor than ever before and that regional anesthesia for cesarean delivery is the preferred technique. Despite controversy and continued economic pressure, more anesthesiologists are actively involved in the practice of obstetric anesthesia and continue to strive for safe and effective care of obstetric patients.

Brenda A. Bucklin, M.D.,‡ and Joy L. Hawkins, M.D. †University of Colorado School of Medicine, Denver, Colorado. brenda.bucklin@uchsc.edu

References


(Received for publication January 23, 2006.)

© 2006 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Anesthesiology 2006;104:1104–5


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.

John A. W. Wildsmith, M.D., F.R.C.A., F.R.C.P.Ed., Ninewells Hospital and Medical School, Dundee, United Kingdom. j.a.w.wildsmith@dundee.ac.uk

Anesthesiology 2006; 104:1105

In Reply:—We read with interest the comments from Dr. Wildsmith. We agree that many investigators have made important contributions to the mode of epidural infusion. A comparison between continuous infusion versus bolus technique was reported in 1975.1 Drs. Scott, Schweitzer, and Thorn used a pump to administer regular intermittent top-up doses 1982.2 Doses were 6–10 ml local anesthetic every 2 h. Observations with the regimen included "the spread of nerve block was much wider than necessary."

The fundamental difference we described is a much smaller volume of the local anesthetic and more frequent administration. Our technique delivers a mini-bolus of 1 ml local anesthetic every 20 min.3 Compared with the large-volume, intermittent top-up technique described above, our method is closer to the continuous infusion technique. Like a continuous infusion, the incidence of hypotension or bradycardia is negligible with our technique. However, the quality of analgesia is superior. An analogy is a quiet beach where small waves rapidly degradable HES is not commercially available in the United States. 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

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 hemothostatic competence is critical 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.” 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


Manabe, M.D., Ph.D.,* The University of Iowa Hospitals and Clinics, Iowa City, Iowa. uedak@i6.so-net.ne.jp or kenichi-ueda@uiowa.edu

References


Manabe, M.D., Ph.D.,* The University of Iowa Hospitals and Clinics, Iowa City, Iowa. uedak@i6.so-net.ne.jp or kenichi-ueda@uiowa.edu

References


Manabe, M.D., Ph.D.,* The University of Iowa Hospitals and Clinics, Iowa City, Iowa. uedak@i6.so-net.ne.jp or kenichi-ueda@uiowa.edu

References


Manabe, M.D., Ph.D.,* The University of Iowa Hospitals and Clinics, Iowa City, Iowa. uedak@i6.so-net.ne.jp or kenichi-ueda@uiowa.edu

References


Manabe, M.D., Ph.D.,* The University of Iowa Hospitals and Clinics, Iowa City, Iowa. uedak@i6.so-net.ne.jp or kenichi-ueda@uiowa.edu
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.

To the Editor:—I read with interest the recent report and accompanying editorial regarding package inserts or the label for medications.1,2 This important subject has previously received little attention in the anesthesiology literature.

Anesthesiologists are in an enviable 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.1 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.

In Reply:—I appreciate Drs. Tang, Pittet, and Ganter’s interest in my article on the effects of hydroxyethyl starch (HES) solutions on hemostasis1 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.2 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.

References

2. Gandhi S, Waehlisch D, Weiskopf R, Bepperling F, Baus D, Junghenrich C. Volume substitution therapy with HES 130/0.4 (Voluven®) versus HES 450/0.7 (hetastarch) during major orthopedic surgery. Critical Care 2005; 9:F206

To the Editor.—I read with interest the recent report and accompanying editorial regarding package inserts or the label for medications.1,2 This important subject has previously received little attention in the anesthesiology literature.

Anesthesiologists are in an enviable 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.1 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.

In Reply:—I appreciate Drs. Tang, Pittet, and Ganter’s interest in 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.2 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.

References

2. Gandhi S, Waehlisch D, Weiskopf R, Bepperling F, Baus D, Junghenrich C. Volume substitution therapy with HES 130/0.4 (Voluven®) versus HES 450/0.7 (hetastarch) during major orthopedic surgery. Critical Care 2005; 9:F206

To the Editor.—I read with interest the recent report and accompanying editorial regarding package inserts or the label for medications.1,2 This important subject has previously received little attention in the anesthesiology literature.

Anesthesiologists are in an enviable 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.1 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.

In Reply:—I appreciate Drs. Tang, Pittet, and Ganter’s interest in 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.2 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.

References

2. Gandhi S, Waehlisch D, Weiskopf R, Bepperling F, Baus D, Junghenrich C. Volume substitution therapy with HES 130/0.4 (Voluven®) versus HES 450/0.7 (hetastarch) during major orthopedic surgery. Critical Care 2005; 9:F206
Drug Labels Should Evolve with Medical Knowledge

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 are an excellent example of this regrettable phenomenon.3

When bupivacaine was first brought to market in the United States in 1965, 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.

Richard K. Baumgarten, M.D., Farms Anesthesia and Pain Management, P.C., Grosse Pointe Farms, Michigan. rbaumgarten@comcast.net

(Received for publication January 20, 2006.)

References


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, Center for Drugs and Biologics, Department of Health and Human Services, Public Health Services, Food and Drug Administration, Rockville, Maryland), stated, (1) “Not recommended and contra-indicated 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?

Daniel C. Moore, M.D., Virginia Mason Medical Center, Seattle, Washington. daniel.moore@vmmc.org

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

(*) “Meaning: something interpreted to be the intent, goal or end.” Webster’s II New Riverside University Dictionary. Boston, Riverside, Houghton Mifflin, p 736.
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,3-8 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.9 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 formulation,”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.

Paul S. Tumber, M.D., F.R.C.P.C.,* Ihab Louis, M.B.B.Ch.
“Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada. paul.tumber@uhn.on.ca

References

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 product or excipient, proper education 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

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) also 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®.

Wes Cetnarowski, M.D., Chris Dadas, Pharm.D.* *Allergan, Inc., Irvine, California. dass__christopher@allergan.com

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

(Accepted for publication January 23, 2006.)

The Datex-Ohmeda M-NMT Module: A Potentially Confusing User Interface

To the Editor.—A recent editorial in this journal has suggested that “…it is time to…introduce objective neuromuscular monitoring in all operating rooms, not just those occupied by researchers and aficionados of muscle relaxants. …objective neuromuscular monitoring is an evidence-based practice and should consequently be used whenever a nondepolarizing neuromuscular blocking agent is administered. …there are strong reasons to believe that its use can improve patient outcome.”

Our department strongly supports this position and recently introduced one such monitor, the S/5 MNMT NeuroMuscular Transmission Module (Datex-Ohmeda, Madison, WI) into all of our operating rooms. Although we are generally pleased with this device, we have identified one aspect of the user interface that delivers a confusing message to the clinician. We think this issue may have clinical ramifications and is important enough that an alert to other users of this module is warranted.

The M-NMT’s transducer (MechanoSensor; Datex-Ohmeda) consists of a strip of piezoelectric polymer that is applied to a boomerang-shaped spring, which is placed between the thumb and the forefinger. Mechanical movement of the thumb results in a redistribution of the electrical charge on the sensor membrane, a change that can be quantitated. The M-NMT is a movement sensor, and the method is not acceleromyography. To differentiate this monitoring approach from acceleromyography, the company refers to their monitor as using kinemyography. The calculated train-of-four (TOF) ratio is displayed numerically (as a percent) on the patient monitor (S/5 Anesthesia Monitor; Datex-Ohmeda). In addition, the unit displays a bar graph of all four responses so that this ratio may be appreciated visually.

Unfortunately, the bar graph and the displayed TOF ratio may appear to disagree (fig. 1). It is a common occurrence during recovery of nondepolarizing neuromuscular block to encounter a numeric TOF

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

Anesthesiology 2006; 104:1109–10

© 2006 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Anesthesiology, V 104, No 5, May 2006

Downloaded From: http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931070/ on 01/13/2019
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 ratio (TOF%) when the MechanoSensor® (kine-myography) 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 recovery1). 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.

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 to 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% value. The result is failure to anticipate 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.

Aaron F. Kopman, M.D., New York Medical College, Valhalla, New York. akopman@nyc.rr.com

References


(Accepted for publication October 24, 2005.)
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.

Markku Paloheimo, M.D., Ph.D., F.E.A.A., GE Healthcare Finland Oy, Finland; Eye Hospital, Helsinki University Hospital, Helsinki, Finland. markku.paloheimo@hus.fi

References

(Accepted for publication October 24, 2005.)

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 undergone 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

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

Anesthesiology 2006; 104:1111–2 © 2006 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

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 undergone 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

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

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 undergone 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

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

Anesthesiology 2006; 104:1111–2 © 2006 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

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 undergone 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

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

Anesthesiology 2006; 104:1111–2 © 2006 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.
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 placement; (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.

Douglas Fetterman, M.D., Anna Dubovoy, M.D., Michael Reay, M.D., F.R.C.A.*
*University Hospital of Michigan, Ann Arbor, Michigan. mreay@umich.edu

References


(Accepted for publication January 4, 2006.)

Anesthesiology 2006; 104:1112–3

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

Fig. 1. The Portex Needle-Pro needle, with needle protection device intact.

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

Fig. 2. The Portex Needle-Pro needle, with needle protection device disassembled.
one needlestick injury. I have stressed to the staff, in educational memos, that it needs to be treated as a sharp needle. The Blunt fill needle has been very well received by the staff. The Blunt-tip needle cannot be used percutaneously, so we also maintain a supply of the Portex needles for that use only.

For infiltration of local anesthesia, we have the Becton Dickinson Integra 3 ml syringe. The plunger of this syringe contains a button on the end. When the button is double clicked, the needle retracts into the syringe. I have found that the cover for the needle does tend to get loose if not capped tightly. There has been one needlestick injury with this needle. Many of the doctors still use the Portex needle, with the safety device detached, for infiltration of local anesthesia before placing an intravenous line.

In conclusion, the introduction of a safety needle, and education on its use, is not a guarantee that it will be used properly, and will in fact reduce needlestick injuries.

Steven Neustein, M.D., The Mount Sinai Medical Center, New York, New York. steve.neustein@msnyuhealth.org

References


(Accepted for publication December 28, 2005.)

Anesthesiology 2006; 104:1113

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 Kastelli 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) injection 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, fever and vomiting persisted. Immediately after the administration of these agents, 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 addictive 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.

Hiroaki Ito, M.D., Kazuya Sobue, M.D., Ph.D., Hiroyuki Hirata, M.D., Takeshi Sugiuwa, M.D., Ph.D., Minlye So, M.D., Takafumi Azami, M.D., Ph.D., Hiroki Sasano, M.D., Ph.D., Hirota Katsuya, M.D., Ph.D. *Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan. hiroiout@sunprom.med.nagoya-cu.ac.jp

References

3. Trujillo KA, Akl H. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science 1991; 251:85–7

(Accepted for publication December 28, 2005.)