Intrathecal Morphine and Inflammatory Masses

To the Editor:—I read with interest the reports by Yaksh et al.1 and Gradert et al.2 in the July 2003 issue of Anesthesiology describing the association of intrathecal analgesia with catheter-associated masses and the accompanying editorial by Follett.3 Both articles describe a clear dose- and/or concentration-dependent relation between commercially prepared preservative-free morphine sulfate and the production of inflammatory masses in opioid-naive sheep and dogs. The authors are to be commended for their scholarly works and timely nature of the conclusions. Such work is of great interest to patients with intractable pain and the physicians and medical vendors who make this effective therapy available to them. It is now clear that high-dose commercially prepared morphine sulfate delivered by continuous infusion causes inflammatory masses and neurologic injury in a high percentage of at-risk research animals, as well as in an unknown percentage of patients receiving this therapy. Most importantly, the time course and frequency of this complication in laboratory animals provides a much-needed model for further study and development of effective analgesics with a greater safety profile than the only agent currently approved by the U.S. Food and Drug Administration for use in patients.

Catheter-associated masses have the potential to cause devastating permanent neurologic injury in animal models and patients receiving intrathecal therapy.4,5 It has now been shown that occult lesions may be detected in asymptomatic patients using readily available radiographic screening methods and that noninvasive interventions may be undertaken to reverse or arrest the progression of these masses without additional surgery or catheter explantation.6,7 Termination of drug infusion, initiation of saline infusion, or both in asymptomatic or minimally symptomatic patients have been shown to result in spontaneous regression of lesions without the development of neurologic injury, whereas changing to a different analgesic drug may arrest the progression of lesions without interruption of therapy. Although the treatment of individual patients has been greatly improved by these discoveries, the true prevalence and incidence of this complication in the entire at-risk population of patients receiving intrathecal analgesic therapy must now be determined with a greater degree of certainty and urgency than ever before. I cannot recall a situation in which a serious complication directly attributable to or associated with a medical device or therapy was recognized after introduction without immediate large-scale efforts to define the true incidence, prevalence, and morbidity of that complication in all at-risk patients currently receiving the therapy. This is especially important for that group of asymptomatic patients currently harboring occult inflammatory masses who could be spared serious morbidity through noninvasive means. Medtronic Corporation (Minneapolis, MN) is the largest single vendor of implantable intrathecal drug infusion systems and sponsors much of the research regarding intrathecal therapy, including some of the work cited above. It is disappointing that to date, neither company bulletins nor company-sponsored investigators have endorsed such recommendations for immediate large-scale screening of all patients currently receiving continuous intrathecal opioid analgesia. In addition to issues of informed consent and the time or dose-dependent risk of mass development and neurologic injury, I believe that physicians treating these patients and the medical vendors who produce implantable intrathecal systems will be held accountable by patients, our medical colleagues, and society to endorse conservative recommendations for management and to detect and treat occult catheter-associated masses in at-risk patients before the development of symptoms. One wonders how long the Food and Drug Administration will allow the continued use of preservative-free morphine sulfate for intrathecal analgesia without a major change in its labeling regarding the risks of catheter-associated masses and greater understanding of the actual degree of risk involved with its widespread clinical use. In the accompanying editorial,3 Dr. Follett appropriately recommends that, “...physicians who manage patients receiving intrathecal analgesics must be highly aware of the possible development of intrathecal granulomas and must perform regular surveillance of their patients to detect these masses early, before serious complications arise.” I would take this recommendation a step further. I suggest that all patients currently receiving intrathecal analgesic therapy should be offered initial and periodic follow-up radiographic screening by methods with appropriate sensitivity and specificity to detect occult catheter-associated masses while they can be treated conservatively, before the development of symptoms or neurologic injury.7 The only methods currently shown to have appropriate resolution to reliably detect these lesions are computed tomography with myelography and high-resolution magnetic resonance scanning. Only with an accurate assessment of the risks as well as the benefits of long-term intrathecal analgesic therapy can we confidently and safely provide appropriate medical advocacy and treatment for our patients who benefit from this therapy for the treatment of intractable chronic pain.

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To the Editor:—Although intrathecal opioid infusions did bring an innovative approach to the treatment of chronic severe, unrelenting pain, the articles by Yaksh et al.1 and Gradert et al.2 revealed that, as with tachyphylaxis, it is only a matter of time and dosage until granuloma-like formations develop in the tip of the catheter. As with previously reported cases of complications with this system, syrinx formation3 and lymphedema in patients with previous venous stasis,4 the risks of this therapeutic modality are now being recognized, in spite of reports5,6 that have claimed little morbidity in the past.

Both studies1,2 used the trade preparation Infumorph (Elkins-Sinn, Inc., Cherry Hill, NJ) (25 mg/ml) in their studies, but as Yaksh et al.3 noted, higher concentrations of morphine ‘prepared’ by local pharmacies will be more prone to produce granulomas and tachyphylaxis. They also showed that in some cases, inflammatory masses begin to form within 2–4 months after implantation, but there was little mention of the clinical signs and symptoms related to this complication, which include (1) increased resistance to aspirate cerebrospinal fluid through the catheter port; (2) decreased compliance during injection of 0.9% NaCl; (3) unexplained failure to relieve pain; and (4) disparity between the volume of expected morphine as calculated by the computer versus the volume of morphine actually found in the reservoir before refilling.

It is expected that these volumes be recorded every time the pump is refilled; however, not everyone is doing it. It is assumed that as the catheter tip gradually becomes occluded by the granuloma, less of the morphine is infused into the cerebrospinal fluid. The patient’s pain is not relieved, so the tendency is to increase the dosage, which in turn will favor growth of the granuloma.

Either magnetic resonance imaging (with contrast and with the pump shut off) is to be obtained or a ‘pump myelogram’ may be attempted with 50% diluted contrast media after aspirating the catheter contents. The diagnosis of granuloma should be confirmed by either of these imaging tests.

Among the references listed in both articles, there were more than 20 cases reported; however, this number is in all probability just the ‘tip of the iceberg’ because many cases have gone unreported or unrecognized. Manufacturers are obligated to follow each case and produce reliable reports of the pumps’ outcome for all parties involved. Perhaps now they can come forward with their data because it is essential to determine the precise incidence of this complication.

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regular intervals, the risks associated with this study might soon out-
weigh a patient’s risk of granuloma formation. Individual practitioners
should decide whether the costs and risks associated with obtaining
MRI scans or computed tomography scans/myelograms for all patients,
with the expectation of identifying granulomas in a small percentage
of patients, are warranted. A practical compromise between nonselective
radiographic screening of all patients and radiographic evaluation only
when patients become symptomatic might be to offer routine MRI
scanning to patients at increased risk of granuloma formation, e.g.,
those receiving relatively high doses or high concentrations (or both)
of intrathecal opioid or those patients with a history of granuloma who
elect to continue intrathecal opioid therapy after treatment of the
previous granuloma.

A consensus panel convened in 2002 to discuss the clinical evalua-
tion and management of intrathecal granulomas3 specifically consid-
ered the role of “screening” MRI scans for all patients receiving intra-
theal opioid. For a variety of reasons, and recognizing that patients
with granulomas typically present with prodomal symptoms that
should alert the managing physician to the presence of a granuloma
before the onset of frank neurologic deficit (e.g., loss of pain relief,
rapidly escalating dose requirements, neurologic symptoms such as
numbness), the consensus panel did not believe that existing data
supported routine radiographic surveillance of all patients. The panel
emphasized the need for vigilance, regular assessment (including neu-
rologic evaluation), and a high index of suspicion for granulomas to
detect them before the onset of neurologic deficit.

Intrathecal analgesic therapy, despite its seemingly benign nature,
can have serious side effects. Physicians and patients accept these risks
for the benefit derived from the therapy. Dr. McMillan appropriately
expresses concern for the safety of patients receiving intrathecal opi-
oid analgesics. Some physicians may choose, quite reasonably, to offer
screening MRI scans to all patients receiving intrathecal opioid or to
those patients who are at increased risk of granuloma development
(e.g., high daily opioid dose). Other physicians may elect, also quite
reasonably, to monitor patients clinically, with the understanding that
close attention must be paid to symptoms suggestive of granuloma
formation, with expeditious radiographic evaluation of such symptoms
should they arise. Regardless of their approach to monitoring patients
for granuloma formation, physicians who treat patients receiving in-
trathecal opioids will do well to emulate Dr. McMillan’s level of aware-
ness and concern about intrathecal granulomas and exercise due dili-
gence in monitoring patients for the development of these lesions.

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In Reply.—The two letters by Drs. McMillan and Aldrete address the
critical issues raised in the two Laboratory Investigations published in
Anesthesiology1,2 with respect to intrathecal morphine–induced gran-
uloma formation. There is little doubt that the studies reflect the
potential for granuloma formation in the human patient and are in
accord with the literature that is beginning to appear with increasing
frequency since the first reports in 1991 by North et al.3 We would
make three points.

The preclinical studies emphasize the likely role of concentration as
an important contributor to these observed effects. Historic perusal of
the daily morphine doses used since the inception of long-term spinal
morphine as a therapy for chronic pain has typically revealed that it has
been remarkably stable at somewhere between 5 and 10 mg/day (see the
retrospective survey by Yaksh and Onofrio4 and the recent con-
sensus conference proceedings5). Although there are no systematic
data, to the best of our knowledge, the earlier (1980s) use typically
employed concentrations on the order of 10 mg/ml.6 Although these
capacities in excess of 20–25 mg/ml.6

The time course of granuloma development, as evidenced by
changes in behavioral function, clearly occurred by 2–4 weeks and
was corresponded with the development of the granuloma. This raises two
issues. The time course of the human condition “appears” much
longer. Although this may reflect the conditions relevant to the dog
and sheep spinal canals, we suspect that the true time of onset in
humans is not known. Clearly, the temporal development of neuro-
logic signs may reflect the progressive refill-to-refill incrementation of
drug dose/concentration over the early days of the infusion. As empha-
sed in one of Aldrete’s comments, the temporal evolution of neurologic
signs in the animals, as indicated in the articles, are erratic. This would
be expected of any slowly growing mass, where the deficit depends on
the particular locus and degree of compression. In recent work, we
have followed granuloma development in dogs with magnetic reso-
nance imaging and have demonstrated that masses may occur at inter-
vals as short as 7 days and that, as expected, the evolution of the
behavioral deficit corresponded with the growth and spatial disposi-
tion of the mass (e.g., compression of the dorsal midline leading to
alodynia but no motor deficit, encroachment of the mass on the
dorsolateral and ventral aspects leading to caudal spasticity). This
emphasizes the absence of a neurologic sign is no guarantee of the
absence of a mass. This is clearly the message arising from the excel-
 lent report of McMillan.7

Many issues remain. From a practical standpoint, we do not know
the time course versus spinal dose in humans (although concentrations
may be clearly relevant). If a patient undergoes imaging and is negative
for a mass, will there be any mass development over time if there is no
change in infusion parameters? Of equal importance, once a granuloma
is noted, will it resolve if the infusion is turned off or if the catheter
location is altered? What is the pharmacology of the process leading to
the granuloma formation? Preclinical imaging studies should allow
some of these questions to be addressed.

In the meantime, as nonclinical contributors to the conversation, we
would counsel caution. If the benefits of higher concentrations to
permit extended refill intervals are weighed and found advantageous,
care should be exercised in the form of some imaging at an early
interval. Should imaging be repeated if there are no changes? At
the moment, we do not know. One of the interesting aspects of our studies
was that in animals with granulomas, cerebral spinal fluid morphine
concentrations decreased remarkably in the cisterna, although plasma
concentrations were as expected. This suggests that there was an
enhanced clearance of the cerebral spinal fluid morphine, perhaps related
to a redistribution of the infused local anesthetic. Our current work
suggests that epidural fat levels adjacent to the granu-
loba show very high morphine concentrations. Perhaps one telling
indication of something being amiss is the apparent loss of analgesia
with a given dose.

Anesthesiology. V 101, No 1, Jul 2004
In Reply.—Despite the lack of large epidemiologic studies to date, increased reporting of the inflammatory mass phenomenon as a consequence of scientific presentations and "Dear Doctor" letters to physicians, as well as the availability of new preclinical data, motivated the organization of a consensus panel. This panel's goal was to formulate hypotheses about the etiology of catheter-tip masses and to provide recommendations for clinicians about the detection and treatment of this complication.1, 2 Together, these papers provide a comprehensive review of the preclinical and clinical data available regarding the incidence, etiology, and clinical features of inflammatory masses associated with intrathecal drug infusion and provide recommendations for screening, detection, diagnosis, treatment, and prevention of these masses. These recommendations emphasize the need for physician awareness, attentive patient follow-up, and maintaining intrathecal opioid dose and concentration as low as possible for as long as possible while still achieving adequate analgesia.

It remains that inadequately treated chronic pain is a serious condition that is associated with its own risks and morbidity. In that context, the risk of catheter-tip mass development as a consequence should remain acceptable provided the treatment is effective. The authors thank Drs. McMillan and Aldrete for their interest and their comments. We share Dr. McMillan’s view on the importance of defining the true incidence and risk of inflammatory mass formation. It is clear that the incidence of granuloma formation is underestimated because of the voluntary nature of reporting and the unknown incidence in asymptomatic patients. The authors believe, however, that imaging of all patients on intrathecal therapy for chronic pain is not supported by the current literature. Given the serious adverse impact of this complication and the likely increase in its incidence with long-term intrathecal opioid administration in noncancer pain populations, the authors believe that the same goals can be reached if physicians maintain a low threshold for ordering imaging studies in patients perceived to be at risk. Even subjective or relatively minor symptoms in a patient receiving long-term or high-dose intrathecal opioid therapy may justify an imaging study to rule out the possibility of a catheter-tip mass. Contrast-enhanced magnetic resonance imaging is the imaging modality of choice, although computed tomography-mycelography is less costly and also effective in confirming the diagnosis.

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More Reasons Why Anesthesiologists Should Administer Preoperative Antibiotics

To the Editor.—Dr. Warters et al.1 provide several good reasons why anesthesia personnel should administer preoperative antibiotics. Based on our experience of doing so, we offer additional reasons.

1. Because of unexpected changes in operating room availability, a patient may have his or her surgery delayed after administration of the antibiotic. This can lead to a delay between antibiotic administration and the start of surgery. This has the potential to decrease the effectiveness of the prophylactic antibiotic.2

2. At my institution, the ordering of prophylactic antibiotics is at the discretion of each individual surgeon; we do not have an institutional protocol. Because we are responsible for administering the antibiotic, if a patient comes to the operating room without an antibiotic for us to administer, it is now our routine to ask the surgeon whether he or she wants an antibiotic administered. This double check helps to prevent errors of omission, which still occur. Errors of omission may be more likely to occur in institutions with surgical training programs.

3. Delays in the patient’s arrival in the operating room because of waiting for the establishment of intravenous access only for the administration of the antibiotic can be eliminated. These delays can lead to wasteful downtime of operating rooms. Overextended floor nurses benefit by having one less task to perform.

4. The previous insertion of an intravenous catheter only for antibiotic administration may use one or more of the few (or only) remaining peripheral veins that are suitable for satisfactory perioperative intravenous access. The intravenous catheter may not be appropriately sized or appropriately located. Additional intravenous access
may need to be established, sometimes before induction of regional or general anesthesia, which is a wasteful of time and supplies, uncomfortable to the patient, and may now be more difficult to accomplish. Patients may then ask, “Why do I need another intravenous? Why can’t you use the one that was just put in?” Scared and nervous patients may lose confidence in the system.

5. Even if the previously established intravenous catheter is of suitable size and location, because at our institution we have been unable to agree on an intravenous tubing design that is satisfactory for both the operating room and the floor, a second intravenous tubing set and bag of crystalloid may be required. Changing the tubing set while leaving the catheter in situ risks infectious contamination, loss of catheterization, and discomfort to the patient from removal of the tape or adhesive dressing.

There may be two exceptions in which it may be preferable to have the antibiotic administered before arrival in the holding area. First, because vancomycin may require up to 1 h to infuse, there may be insufficient time for us to administer the full dose before skin incision.

The second situation is when antibiotics are administered for bacterial endocarditis prophylaxis.

I agree with Dr. Warters et al. that the administration, but not the selection, of prophylactic antibiotics is a responsibility that anesthesiologists should assume. Although there are many tasks required of us to start a case, this responsibility should also be considered a priority so that the full administration is accomplished before skin incision (and tourniquet inflation).

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Anesthesiologists and Perioperative Antibiotic Prophylaxis

To the Editor:—We endorse the viewpoint of Warters et al.1 in their letter “Preoperative Antibiotic Prophylaxis: The Role of the Anesthesiologist.” Various guidelines have been proposed recommending prophylaxis for at-risk patients undergoing at-risk procedures. In spite of the guidelines for antibiotic prophylaxis formulated in the last few years, their prescription pattern still remains inappropriate.2 The seriousness of the potential infection has led the anesthesiologist to play an important role. Adhering to strict aseptic technique in patient preparation, during and after surgery, still remains the best prophylaxis against postoperative infections. Surgical site infections increase total hospital expenses and extend the duration of hospital stay. Antibiotic prophylaxis has been demonstrated to be of greater benefit than risk in procedures with higher infection rates. Various studies have validated the fact that the antimicrobial prophylaxis is not indicated for procedures with low infection rate because the expected benefit of antimicrobial treatment is less than the risk of adverse medication reaction.3–4

Because the data are limited and the problem is complex, decisions must be tailored to the individual patient and the surgical procedure. Anesthesiologists are increasingly involved in perioperative antibiotic administration and postoperative infection control. In a study by Silver et al.,5 it was concluded that by delegating implementation of antibiotic prophylaxis to the anesthesiology team, the incidence of postoperative wound infection may decrease. With this responsibility comes accountability. Antibiotic sensitivity test results before administration should be known because it is of paramount importance to avoid untoward adverse (anaphylactic/anaphylactoid) reactions. To minimize such events, a scratch or puncture test may be performed before more definitive intradermal tests.6 Appropriate skin testing concentrations of medications commonly used in anesthetic practice have been published.7 Patients with positive skin test results to any penicillin reagent should probably not receive cephalosporin antibiotics unless substitutes are clearly less efficacious.

Unfortunately, the postgraduate teaching in anesthesiology does not impart extensive training in antibiotic pharmacology. Most of the training programs, especially in developing countries such as ours, have only four to five lectures dealing with antibiotics, their perioperative role, and their potential interaction with the anesthetic drugs. Most of the curriculums and continued medical education programs skip this vital education. Hence, it should be made pertinent that all anesthesiologists are regularly updated regarding the pros and cons of the usual antibiotics used perioperatively.

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To the Editor—We read with a real interest the recent article by Homi et al., published in the October 2003 issue of ANESTHESIOLOGY, on the neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. Briefly, the authors showed that 70 vol% xenon decreased cerebral infarct volume and improved neurologic outcome when compared with 70 vol% nitrous oxide, whereas a mixture of 55 vol% xenon plus 35 vol% nitrous oxide had an intermediate neuroprotective action. Based on the assumption taken from previous data that xenon and nitrous oxide, which both provide N-methyl-D-aspartate (NMDA) receptor antagonism, would have a similar minimum alveolar anesthetic concentration (MAC), Dr. Homi et al. proposed that differences in cerebral infarct volume and neurologic outcome after treatment with xenon, nitrous oxide, or both would not result from variations in MAC between groups but rather from the fact that xenon may be a more potent NMDA receptor antagonist than nitrous oxide.

This work, together with our concomitant article published in the October 2003 issue of the Journal of Cerebral Blood Flow and Metabolism, provides evidence that xenon may have a clinical potential as a neuroprotective agent for stroke treatment. However, it seems to us that some of the possible mechanisms that may explain the more potent neuroprotective action of xenon compared with nitrous oxide might have been overlooked.

To compare gases with “anesthetic” action, it might be important to distinguish between analgiesic potency, as measured by the absence of response to a noxious stimulus, and narcotic (hypnotic) potency, as measured by loss of the righting reflex. Using loss of the righting reflex as a measure of narcotic potency and slow compression rates to avoid response to a noxious stimulus, and narcotic (hypnotic) potency, as suggested by Franks and Dickinson,4,5,24 we found that 75 vol% xenon shows potentially neurotoxic effects when given after transient middle cerebral artery occlusion; interestingly, according to the MAC ratio of nitrous oxide and xenon, xenon at 75 vol% can be considered equipotent to 111 vol% nitrous oxide, a concentration that is not far from that of 117 vol%, at which nitrous oxide exhibits neurotoxic properties related to its NMDA receptor antagonistic action.5 Together, these data provide evidence that the neuroprotective action and NMDA antagonistic properties of nitrous oxide and xenon depend on their MAC ratio. Therefore, the interesting data reported by Dr. Homi et al. on the intermediate neuroprotective effect of 35 vol% xenon plus 35 vol% nitrous oxide, compared to 70 vol% xenon and 70 vol% nitrous oxide, can be easily interpreted on the basis of the MAC ratio and xenon, because 35 vol% xenon plus 35 vol% nitrous oxide can be considered equivalent to 87 vol% nitrous oxide, whereas xenon at 70 vol% can be considered equivalent to 104 vol% nitrous oxide.

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Correspondence

Neuroprotection by Nitrous Oxide and Xenon and Its Relation to Minimum Alveolar Concentration

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In Reply—We are grateful to Drs. Roth and Tewari et al. for their constructive comments. Dr. Roth points out additional compelling reasons for the anesthesiologist to be involved with antibiotic administration. Although some anesthesiologists may resist this involvement, the potential benefit to surgical patients is difficult to ignore.

Dr. Tewari et al. correctly point out, ‘With this responsibility comes accountability.’ By providing our faculty with a protocol developed by our infection control committee, we have attempted to separate the responsibility of drug administration from that of drug selection. We disagree that a concerted effort should be made to educate anesthesiologists on antibiotic selection, because we believe this is beyond the scope of our expertise. We do willingly accept responsibility for appropriate administration, but not selection of the appropriate drug.

The response to our letter in which we described our policy for antibiotic administration has been overwhelming. We have received hundreds of e-mails requesting our protocol, and we have attempted to oblige all requests.

Our experience in formulating a protocol for antibiotic administration with our infection control committee has been very positive. Although our protocol serves as an example, we encourage involvement of institutional infection control experts in the development of institution- and geographic-specific protocols, because their expertise and knowledge of infectious agents, local sensitivities to antibiotics, and the constantly expanding antibiotic choices will enhance appropriate recommendations for perioperative antibiotic prophylaxis.


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To the Editor.—We read with great interest the article titled “Evaluation of Rapid Ischemic Preconditioning in a Rabbit Model of Spinal Cord Ischemia.”1,2 We congratulate Kakimoto et al. on their study of rapid ischemic preconditioning (IPC) to provide ischemic spinal cord protection. This is an interesting study that consists of three experimental groups and evaluates the effect of rapid IPC on spinal cord ischemic injury after a short (24 h) and a relatively long (7-day) recovery period.

Ischemic preconditioning has been found to protect various organs from ischemic injury, and there is experimental evidence that IPC protects the spinal cord after aortic cross clamping. IPC is a biphasic phenomenon, with an early phase and a late phase of protection, and these two phases have been documented in the spinal cord as well.3,4 In this study, Kakimoto et al. evaluated the effect of rapid IPC in a rabbit model of infrarenaal aortic occlusion by using 5 min of brief ischemia, 30 min of reperfusion, and 20 min of aortic cross clamping. They found that rapid IPC reduced spinal cord injury when compared with the controls at 24 h (P < 0.05), but there was no difference in the number of normal neurons between the rapid IPC group and control group at 7 days after reperfusion, suggesting that the efficacy of rapid IPC on the spinal cord may be transient.

In a study by Caparrelli et al.,4 in a rabbit model very close that of Kakimoto et al. (5 min of brief ischemia, 30 min of reperfusion, and 20 min of infrarenaal aortic occlusion), when six animals with rapid IPC compared to seven controls, although the IPC group seemed to have a better outcome compared with the control, this difference did not

References
3. Aoust B: Anesthetic potency of xenon and nitrous oxide that we used have similar ability to antagonize N-methyl-D-aspartate receptors and thus produce a neuroprotective effect. We assume that if we administered the gases at the same concentration in rats is greater than previously reported. Anesth Analg 1994; 79:710–21.
In a recent published study, our group demonstrated that rapid IPC without hypotension prevents spinal cord injury in a porcine model of descending thoracic aortic occlusion. We used 20 min of brief ischemia and 80 min of reperfusion, and the duration of the occlusion of the descending thoracic aorta was 35 min. We assessed the neurologic outcome of our animals at the fifth postoperative day after reperfusion, taking into consideration the efficacy of rapid IPC on the spinal cord beyond 2 days after reperfusion. In our study, it was important to maintain arterial systolic blood pressure higher than 100 mmHg during the 80-min reperfusion interval. Two animals had an arterial systolic blood pressure of 80–90 mmHg during the reperfusion period. Although they had a Tarlov score of 4 at 24 h postoperatively, there were no statistical differences in blood pressure among the groups at 24 h.

In addition, Griep et al. mentioned indirect clinical evidence of this kind of protection, and in their study, it was of great importance to maintain mean arterial blood pressure at high normal levels during the sacrifice of intercostals.

In the study of Kakimoto et al., it is mentioned in the published manuscript that proximal arterial blood pressure was monitored continuously during the experimental procedure. Their table 2 illustrates changes in proximal arterial pressure only at baseline, at a half-time point of 17 min of ischemia, and at 10 min after reperfusion. Was there any difference in mean arterial pressure during the 30 min of reperfusion in comparison to baseline mean arterial pressure in the rapid IPC group? That is, did the authors observe any hypotension during this reperfusion interval, and how did they deal with it?

Also, the role of inflammation in ischemic spinal cord injury after temporary aortic occlusion has been demonstrated by several investigators. The authors discussed the beneficial effects of rapid IPC, which may involve an antiinflammatory process. Did the authors have any additional histopathologic data in both the rapid IPC and control groups regarding the grade of inflammation to corroborate the neurologic outcome with the development of inflammation?

In Reply: We thank Drs. Toumpoulis and Anagnostopoulos for their valuable comments regarding our article. As they indicated, hypotension during the reperfusion period after ischemic preconditioning may be an important factor for its neuroprotective efficacy. In our study, transient hypotension was in fact observed in animals with ischemic preconditioning, but this returned spontaneously to the baseline within a few minutes after the reperfusion. Consequently, there were no statistical differences in blood pressure among the groups at baseline before lethal ischemia. We cannot rule out the possibility that this transient hypotension might have affected the neuroprotective efficacy by ischemic preconditioning. However, compared with the method (20 min of brief ischemia) of Toumpoulis et al., we used only 5 min of ischemia as preconditioning. The degree of hypotension observed in our study might be less than that in their study.

As one possible mechanism by which ischemic preconditioning can induce tolerance to subsequent ischemia, it has been suggested that an antiinflammatory process may be involved. However, the data are still limited, especially in a situation of rapid ischemic preconditioning for the spinal cord. Unfortunately, so far, we have not performed further histologic assessments regarding the grade of inflammation. Further study is required.

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References


(Accepted for publication February 20, 2004.)
To the Editor:—We read with great interest the study by Fiege et al.\textsuperscript{1} published in the November 2003 issue of \textit{Anesthesiology}. Although we applaud the authors’ attempt to shed some light on the controversial use of dantrolene in 3,4-methylenedioxymethamphetamine (MDMA)-mediated hyperthermia, several flaws in the design and interpretation of their results cast doubts on their conclusions.

Our strongest criticism of this study is in the authors’ use of a combination therapy (dantrolene, sodium bicarbonate, and hypertension) to determine the role of dantrolene in MDMA-mediated hyperthermia. The positive results attributed to dantrolene in figure 2 of this study, a reduction in partial pressure of carbon dioxide and an increase in pH, can be explained by the use of sodium bicarbonate and hyperventilation alone without any contribution from dantrolene. More notably, we believe that the failure to show a reduction in core body temperature (their fig. 2C) with their treatment suggests the idea that dantrolene has no role in MDMA-mediated hyperthermia. Because malignant hyperthermia—normal swine were similarly affected (although slightly less so), we are curious why the authors did not study their treatment regimen in these animals. Because malignant hyperthermia—normal animals were not genetically susceptible, dantrolene would not have been expected to be beneficial and could have disentangled the effects of dantrolene from the other treatments given.

Also, questions arise with the authors’ sole reliance on clinical criteria in their definition of malignant hyperthermia. Based on their criteria for malignant hyperthermia, any agent that uncouples oxidative phosphorylation, irrespective of its effects on calcium dihydropryridine and ryanodine receptors (RyR), would meet the criteria for mediating malignant hyperthermia. Although we agree that the study by Fiege et al.\textsuperscript{1} suggests an exaggerated hyperthermic response to MDMA in malignant hyperthermia—susceptible swine, the significant alterations in the partial pressure of carbon dioxide, pH, and temperature seen in the malignant hyperthermia—normal swine suggests that the effect is largely not mediated through RyR complexes.

Finally, in the design of their study, Fiege et al.\textsuperscript{1} chose to use sequential dosing of 0.5 mg/kg MDMA every 20 min until a cumulative dose of 12 mg/kg was achieved. MDMA-induced hyperthermia is well established in both humans\textsuperscript{2,3} and rodents\textsuperscript{4} and has been shown to occur after a single dose or intermittent “binge” doses in numerous animal species,\textsuperscript{5} which typically patterns human consumption. Therefore, we question the validity of extrapolating results from the authors’ swine model to that of human ingestions.

Because MDMA-mediated hyperthermia largely resembles malignant hyperthermia, a pharmacogenetic syndrome triggered by anesthetic agents that manifests itself in skeletal muscle of individuals bearing missense mutations in the gene coding for the RyR,\textsuperscript{6} it has become tempting to speculate and even assume that the molecular underpinnings of anesthetia- and MDMA-induced hyperthermic syndromes are the same.\textsuperscript{6} Although largely unscientific, this assumption has translated into clinical medicine, where patients admitted to the emergency room with MDMA-induced hyperthermia are often given dantrolene, an RyR antagonist, along with other cooling and supportive therapies. Whereas dantrolene is effective in reducing anesthetia-induced hyperthermia,\textsuperscript{7} it seems to be only marginally if at all effective in reducing MDMA-generated hyperthermia.\textsuperscript{8–10} Similar to what Fiege et al.\textsuperscript{1} observed in swine, we observed that dantrolene pretreatment does not prevent or significantly reduce MDMA-induced hyperthermia in rats (fig. 1). The inability of dantrolene to block MDMA-induced hyperthermia suggests that this is not a true “malignant” hyperthermia and that other mechanisms are evoked after MDMA exposure.

Controlled trials have not been performed to determine whether the few purported clinical successes using dantrolene to control MDMA-induced hyperthermia are due to dantrolene alone versus all other supportive, first-line cooling therapies. The inability of dantrolene to block the thermogenic effects of MDMA in both our study and that of Fiege et al.\textsuperscript{1} suggests that RyR-mediated calcium cycling is not the mediator of the thermogenic effects of MDMA. The authors’ recommendation to use dantrolene in all cases of MDMA-induced hyperthermia is not supported by their data or other current scientific literature and may result in overreliance on a drug that may not benefit critically ill patients with MDMA-induced hyperthermia.

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References


*Supported by a Faculty Development Grant from Ohio Northern University, Ada, Ohio.
**In Reply:**—We thank Dr. Rusyniak et al. for their critical comments on our study about the induction of malignant hyperthermia (MH) in susceptible swine by 3,4-methylenedioxymethamphetamine (MDMA) (“ecstasy”).1 However, some of the criticisms of our study must be relativized.

First, to our knowledge, this is the first controlled study investigating the association between MDMA-induced hypermetabolic syndrome and MH. MH crisis is an acute clinical complication; therefore, the experimental setting for this study was following the clinical situation, and diagnosis of MH in our experiment could only be based on clinical parameters. The definition of the clinical cutoff parameters for MH crisis in our study was following the recommendations for clinical diagnosis of human MH crisis and previous animal studies. Increasing doses of MDMA induced a hypermetabolic state in MH-susceptible (MHS) as well as MH-normal (MHN) swine. However, the changes in the MHN swine after receiving a higher dose of MDMA (12 mg/kg) were moderate compared with the changes in MHS swine after 8 mg/kg MDMA, and all MHS swine fulfilled the defined criteria for MH.

The only known differentiation between MHS and MHN swine is the presence of the Arg615-Cys point mutation on chromosome 6 leading to a functional impairment of the skeletal muscle ryanodine receptor (RyR1). We share the opinion of Dr. Rusyniak et al. that MDMA-induced hypermetabolism is not solely mediated through RyR1 complexes. However, the different reactions of MHS and MHN swine in our study are an indirect hint for activation of another skeletal muscle ryanodine receptor (RyR1). We share the opinion of Dr. Rusyniak et al. that MDMA-induced hypermetabolism is not solely mediated through RyR1 complexes. However, the different reactions of MHS and MHN swine in our study are an indirect hint for activation of another skeletal muscle ryanodine receptor (RyR1) that MDMA-

Whether administration of dantrolene is useful in all patients with MDMA-induced hyperthermia could not be answered by our study. However, in a life-threatening clinical situation, “simple hyperthermia” could not be distinguished from “true malignant hyperthermia.” Therefore, in our opinion, dantrolene might be a lifesaving therapy option, and consequently, administration of dantrolene should be considered with respect to patient safety in cases of MDMA-mediated hyperthermic syndrome.

Marko Fiege, M.D.,* Frank Wappler, M.D., Ralf Weisshorn, M.D., Mark U. Gerbershagen, M.D., Melanie Menge, M.S., Jochen Schulte am Esch, M.D. *University Hospital Hamburg-Eppendorf, Hamburg, Germany. fiege@uke.uni-hamburg.de

**Reference**


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**Intracuff Pressure Monitoring during Nitrous Oxide Anesthesia when Using the Soft Seal® Laryngeal Mask**

To the Editor.—We read with interest the recent article by van Zundert et al.1 regarding a new disposable laryngeal mask, the Soft Seal® LM (Smiths Medical International, Portex Ltd., Hythe, Kent, United Kingdom). We believe that the Soft Seal® LM has a good laryngeal seal while demonstrating satisfactory clinical performance. The authors reported that the cuff of the Soft Seal® LM prevented an increase in intracuff pressure, and intracuff pressure increased only from 60 to 62.8 cm H2O.

However, we obtained different results regarding changes in the intracuff pressure during nitrous oxide anesthesia using the Soft Seal® LM. Anesthesia was maintained with 66% N2O in oxygen and 1.5–3% sevoflurane in spontaneously breathing patients. In six patients, the intracuff pressures increased from 60 to 103 cm H2O (mean value) after 120 min. However, the rates of increase regarding the intracuff pressure were significantly lower than with the LMA-Classic™ (Intavent Orthoflux Ltd., Maidenhead, Berkshire, United Kingdom). On the other hand, we measured the aspirated volume from the cuff to maintain the intracuff pressure at 60 cm H2O during nitrous oxide anesthesia. Twenty patients were assigned to use a size 4 LMA-Classic™ (n = 10) or a size 4 Soft Seal® LM (n = 10). After the intracuff pressure was adjusted to 60 cm H2O, anesthesia was also maintained with 66% N2O in oxygen and sevoflurane during spontaneous breathing. The deflated volume to maintain the intracuff pressure at 60 cm H2O was measured. At 120 min after the initiation of anesthesia, the aspirated volume from the cuff to maintain the intracuff pressure at 60 cm H2O was 7.3 ml in the LMA-Classic™ group and 4.5 ml in the Soft Seal® LM group (P < 0.01).

These results suggest that Soft Seal® LM provided a reduction in nitrous oxide diffusion into the cuff; however, cuff deflation was needed to keep intracuff pressure at 60 cm H2O. We therefore still recommend the careful monitoring of the intracuff pressure during nitrous oxide anesthesia, even when using the Soft Seal® LM.

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**Reference**


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Anesthesiology 2004; 101:265

In Reply:—We thank Drs. Kanazawa and Suzuki for showing interest in our article and their conclusion that the Portex Soft Seal laryngeal mask (LM) (Smiths Medical International, Portex Ltd., Hythe, Kent, United Kingdom) offers good laryngeal seal and clinical performance. We have shown that changes in intracuff pressure in Soft Seal LM during nitrous oxide anesthesia are minimal. The use of new materials in the design of endotracheal tube cuffs has resulted in much lower increases in cuff pressure during nitrous oxide anesthesia. In the Soft Seal LM cuff, the plasticizer added to soften the polyvinyl chloride makes the cuff less permeable to nitrous oxide. We have been informed by the manufacturers of the Soft Seal LM that the material used in manufacturing the cuff of the Soft Seal LM has changed more recently since our study. Our continuing, unpublished work on methods of insertion of the Soft Seal LM has shown results similar to those published. We have no explanation for the pressure changes Drs. Kanazawa and Suzuki describe. The only comment we can make is that the very small numbers of patients studied, six patients, with no information about the laryngeal mask size, position during surgery, the method used to measure the cuff pressure, and the longer duration of anesthesia may have affected the results of their limited study.

André Van Zundert, M.D., Ph.D., F.R.C.A. (Hon),* Baha Al-Shaikh, F.C.A.R.C.S.I., F.R.C.A., Kristine Fonck, M.D., Eric Mortier, M.D., Ph.D. * Catharina Hospital, Eindhoven, The Netherlands. zundert@iae.nl

References


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Anesthesiology 2004; 101:265

To the Editor.—A recent experience served as a vivid reminder that the need for vigilance is not restricted to the intraoperative period.

A male patient with a significant history of inpatient treatment for chemical dependency was scheduled for a urologic procedure as the day’s last case. In the preoperative area, the individual’s unruly behavior prompted the nursing staff to repeatedly phone both the surgeon and the anesthesia team in the operating room. The attending anesthesiologist sent me to the preoperative area to prepare the patient for surgery.

En route, anesthetic drugs were checked out of the pharmacy, including four 5-ml fentanyl vials in a closed self-sealing plastic bag. Entering the preoperative area, I encountered an extremely agitated man continuously writhing and making sudden precipitous movements on a transport cart. The patient was not diaphoretic and denied being in pain, but stated he was very nervous about his surgery. After a review of his otherwise normal anesthesia evaluation, I asked the patient if he was still using drugs. He stated that he had just been through treatment and was “clean.” After placement of an intravenous catheter, 2 mg midazolam was administered. This had no obvious effect, but subsequent administration of an additional 3 mg midazolam and 10 mg morphine seemed to reduce the patient’s movements and agitation. Oxygen saturation measured by pulse oximetry (SpO2) was always greater than 98%, with a heart rate in the 90s.

Just before transport to the operating room, the closed self-sealing bag was put into the plastic supply bucket and placed on the mattress of the cart at the patient’s feet. The patient again became highly agitated, began asking many random questions, and resumed his vigorous movements that seemed to put him at risk for falling off the cart. Even after my repeated warnings, he continued this behavior. On arrival in the operating room, the bucket and closed bag of drugs were given to the attending anesthesiologist, who prepared syringes of thiopental and fentanyl while I secured the patient and placed the monitors. Anesthesia was induced with thiopental, fentanyl, and succinylcholine. After intubation, an end-tidal concentration of 10% desflurane with 70% nitrous oxide and 30% oxygen was required to maintain the patient’s hemodynamic profile within a normal range. A total of 15 ml fentanyl was administered for the hour-long procedure. However, on conducting a review of medications, one 5-ml vial of fentanyl could not be found. At the end of the procedure, with an end-tidal concentration of 3% desflurane in oxygen, the patient suddenly sat upright on the operating room table and extubated himself. Immediately, he clearly asked whether the operation was over and whether he could go home. The patient was encouraged to lie down to permit application of the surgical dressing. When the surgeon lifted the patient’s leg to finish the dressing, the missing, unopened 5 ml vial of fentanyl emerged from the patient’s rectum.

The only time this patient had access to the fentanyl was during the brief period of transport to the operating room. This patient’s agitation and movements were apparently a distraction to permit access to the fentanyl from the closed self-sealing bag. This situation is a reminder of the ends to which an individual will go to obtain drugs to quench their chemical addiction. The hand, motivated by an addicted brain, is truly quicker than the eye.

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To the Editor.—Gastric tube insertion in anesthetized, paralyzed, and intubated patients is routine practice during many surgical operations. Occasionally, this procedure may be difficult. Many techniques have been proposed to aid gastric tube insertion, including anterior displacement of the larynx, lateral neck pressure, use of endotracheal tubes split longitudinally as an introducer, and immersion of the gastric tube in ice water to harden it before use. Most anesthesiologists have developed their own technique of insertion gastric tubes, with variable success rates.

Ozer and Benumof1 viewed the passage of nasogastric and oro gastric tubes in 60 patients via a fiberscope placed through the left naris. They found the most common sites of impaction to be the piriform sinuses and the arytenoid cartilages. They also found that lateral neck pressure converted these impactions to successful passes 85% of the time.

In our experience, the passage of the nasogastric or oro gastric tube with the patient’s head in the lateral position (turned to either the left or the right) often results in a higher success rate than with the patient’s head in the neutral position. We find that by turning the patient’s head laterally, the path taken by the tip of the tube follows the lateral border of the pharynx, and the tube glides smoothly through the esophagus into the stomach, without coiling in the laryngopharynx. It may be that having the patient’s head turned to one side has a similar effect as applying lateral neck pressure, thus aiding the passage of the tube.

We designed a randomized observational study to determine whether insertion of a nasogastric tube in the lateral position results in a higher success rate than in the neutral position. We recruited 30 consecutive patients with normal airways (Mallampati 1 or 2) and normal neck movements undergoing elective surgery who required general anesthesia, intubation, and nasogastric tube insertion as part of the procedure.

After obtaining informed consent from the patient, general anesthesia was induced, and the trachea was intubated after administration of an appropriate muscle relaxant. The patient was then randomized into either the neutral group or the lateral group by opening a presealed opaque envelope. A patient assigned to the neutral group had the nasogastric tube inserted with the head in the neutral position. A patient assigned to the lateral group had the tube inserted with the head turned to the right lateral position. When the patient was positioned, a 14-French nasogastric tube was inserted from the ipsilateral (right) nostril, without any further maneuvers of the neck, chin, jaw, or larynx. After two unsuccessful attempts in the intended position, the anesthesiologist was allowed to perform additional maneuvers to aid the successful passage of the nasogastric tube.

The number of attempts required for successful insertion was recorded for each patient. The results are summarized in Table 1.

Fifteen patients were allocated to the lateral group, and 15 were allocated to the neutral group. Passage of the nasogastric tube was successful during the first pass in 12 patients (80%) in the lateral group versus 6 (40%) patients in the neutral group. Three (20%) patients in the lateral group required three or more attempts versus 6 (40%) patients in the neutral group.

These results support our observation that passage of the nasogastric tube with the patient’s head turned to the lateral position is associated with a higher success rate than with the neutral position. This technique avoids some of the messy and time-consuming measures of failed nasogastric tube insertions. We now routinely use this method. We also find that the transesophageal echocardiography probe, in the unlocked position, could easily be inserted orally in the same fashion, without having to perform the jaw thrust maneuver.


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(Accepted for publication February 6, 2004.)

Table 1. Summary of Study Results

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L = lateral; N = neutral.

Support was provided solely from institutional and/or departmental sources.
Grading Scale for Mask Ventilation

To the Editor.—One of the most important aspects of airway management is the ability to mask ventilate a patient. Although there are methods to assess the probability of the difficulty of intubation and grading the view during laryngoscopy, there is, to our knowledge, no recognized scale to grade mask ventilation.

Langeron et al.5 investigated factors predictive of difficult mask ventilation. They found that the incident of difficult mask ventilation was 5% of all cases and was associated with five criteria: age older than 55 yr, body mass index greater than 26 kg/m², lack of teeth, presence of a beard, or history of snoring. In this study, they rated mask ventilation as difficult when the clinician considered it "clinically relevant and could have led to potential problems if mask ventilation had to be maintained for a longer time." They rated mask ventilation as impossible "when it completely failed and an alternative technique of ventilation was required in emergency conditions." This study did not define a grading scale other than ‘difficult’ and ‘impossible.’ In an accompanying editorial, Adnet6 did recommend that a grading scale be developed. The American Society of Anesthesiologists Guidelines for Management of the Difficult Airway defines difficult facemask ventilation as the situation in which ‘it is not possible for the anesthesiologist to provide adequate face mask ventilation due to one or more of the following problems: inadequate mask seal, excessive gas leak, or excessive resistance to ingress or egress of gas.’ The guidelines also describes the signs of an inadequate facemask ventilation, but again, there is no proposed grading system for the ability to facemask ventilate.

During the development of a perioperative information system, we found it useful to devise a grading system similar to that used for grading the view during laryngoscopy. Initially, we chose grades 0–4, defined in table 1. There was also a means by which practitioners could type in a text description of mask ventilation. The incidence of each grade of ease or difficulty was classified as shown in table 1. Institutional review board approval was received for this electronic chart review process. After approximately 3 weeks, we compiled the results of documentation using the selections chosen (table 1). On review of these data, we revised the definitions of the grading as described in table 2, removing the modifiers of "easy" and "difficult" before grades 1 and 2. After another 3 weeks, these data were again compiled with the results in table 2. The second version of the grading system resulted in similar percentages for both grade 3 and grade 4, a reduction in grade 1, and an increase in grade 2 classifications. We also noted a substantial decrease in the number of comments going from 1.4% to 0.3% of cases. We believed that the reduction in comments implied that the second method of defining the grades of mask ventilation was easier to select for the practitioners, although it may have been because individuals were more used to the system, in general. As with the grading of airway evaluation and view of laryngoscopy, grading the ability to mask ventilate is subjective and practitioner dependent. It is interesting to note that Langeron et al.5 reported one case of impossible to ventilate out of the 1,502 patients, whereas we noted three in 2,621 cases. This close agreement in the incidence of being unable to ventilate was probably because being unable to ventilate a patient is a more objective (and memorable) event. We did not find as close an agreement in patients who were defined as “difficult mask ventilation” (grade 5). Langeron et al.5 found this in 5% of their patients, whereas we noted an incidence of 1.3%. This may be because...

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References

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Table 1. Initial Mask Ventilation Classification and Description

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description/Definition</th>
<th>No. of Selections</th>
<th>% of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Did not attempt</td>
<td>272</td>
<td>17.7</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Easy mask</td>
<td>1,079</td>
<td>70.0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Difficult mask requiring an oral airway or other adjuvant</td>
<td>128</td>
<td>8.3</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Very difficult mask ventilation requiring two practitioners</td>
<td>22</td>
<td>1.4</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Unable to mask ventilate</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Comments</td>
<td></td>
<td>22</td>
<td>1.4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,533</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Final Mask Ventilation Classification and Description

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description/Definition</th>
<th>No. of Selections</th>
<th>% of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Ventilation by mask not attempted</td>
<td>449</td>
<td>24.2</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Ventilated by mask</td>
<td>1,010</td>
<td>54.4</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Ventilated by mask with oral airway or other adjuvant</td>
<td>366</td>
<td>20.0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Difficult mask ventilation (inadequate, unstable, or requiring two practitioners)</td>
<td>22</td>
<td>1.2</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Unable to mask ventilate</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Comments</td>
<td></td>
<td>6</td>
<td>0.3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,854</td>
<td></td>
</tr>
</tbody>
</table>

Langeron et al. had a broader definition of difficult mask ventilation. Ultimately, the most important grades to document are the more difficult ones, grades 3 and 4, because those would most likely affect the plan for future anesthetics. We have continued with the classifications and descriptions presented in table 2 and have found this information useful for planning future anesthetics, especially for patients in whom intubation was difficult.

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