CORRESPONDENCE

Is the Minimum Local Analgesic Concentration Method Robust Enough?

To the Editor.—We read with interest the articles by Polley et al.1 and Benhamou et al.2 in which they simultaneously published the same study in terms of objective and design performed on different continents. Minimum local analgesic concentration results, including the potency ratios, were surprisingly different from expectations. In a similar study comparing bupivacaine and ropivacaine minimum local analgesic concentrations, Polley et al.3 in the United States and Capogna et al.4 in Italy found different results although the exact same potency ratios. This makes us wonder if the current inconsistencies in results were just intercontinental differences or something else? The possible explanations we propose that were not commented in either study are as follows: 1) No real difference between the drugs. There were no statistical differences in either study, so we should accept the fact as it is. Why did this happen, having in mind all the evidence gathered so far that there is a potency rank? No clue, except for: 2) Chance, which is always a possibility. Here is our greatest concern about the method: When we study subtle differences (i.e., 15 or 20 percent), is the minimum local analgesic concentration method powerful enough to detect these differences without changing the number of subjects to be studied? As this issue is one of the strengths of the up and down sequential allocation method (to detect this clinically small difference), we might need more patients to be included in the design. We encourage the authors to deepen in the interpretation of the “negative” results. We are sure they are as surprised as we are. 3) End point: Is ED50 for pain relief in first-stage labor in the vicinity of the lower part of the dose-response curve for both drugs? Can this be the same kind of effect, but on the opposite part of the curve, when we use supramaximal doses and the potency relationship is lost? Maybe if we analyze another end point, namely motor block, a higher dosage requirement and potency differences will become more apparent.5

Finally, we agree with Benhamou et al. that further studies are required to verify this hypothesis.

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In Reply.—We thank Hector Lacassie et al. for their comments and interest in our recent article1 and are pleased to take this opportunity to reply.

Dr. Lacassie has correctly observed that our study results were different from expectations; we discussed this in our article. It was interesting to note that another minimum local analgesic concentration study authored by Benhamou et al.2 and published in the same issue of the Journal reported a 19 percent difference in potency in favor of levobupivacaine. This, although not statistically significant, is consistent with Dr. Lacassie’s own motor block potency work.

They also raise the interesting question as to whether the minimum local analgesic concentration method is sufficiently powerful to detect small differences in local anesthetic potencies. In general, the reproducibility across the differing modalities of the minimum local analgesic concentration studies to date has been of great interest. For example, not only did the studies comparing the minimum local analgesic concentration of bupivacaine and ropivacaine find identical analgesic potency ratios of 0.6–0.7,4 but Dr. Lacassie’s work using relative motor blocking potencies5 returned similar ratios. In addition, the three studies were conducted on three different continents! The crux of the issue is not whether up-down studies are robust enough to detect differences; they clearly have been. It is rather the reliability of the outcome measure of interest, be it analgesia, sensory level, motor block, or toxicity. Clearly analgesia, and to some extent toxicity, is more subjective and in the particular setting of labor, pain is a dynamic process and therefore subject to greater variability. In contrast, motor block and sensory level should be more independent of, for example, the process of labor and therefore may be more robust measures than analgesia. However, as the primary indication for local anesthetics is analgesia, this has to be directly assessed when considering therapeutic benefit.

The third explanation offered by Lasassie et al. that “the ED50 for pain relief...is in the vicinity of the lower end of the dose-response curves of both drugs” needs some clarification. Binary yes/no outcomes occupy individual dose-response distributions. So it follows that there will be a spectrum of curves for the different measured end points and that the ED50 for each will be in the steep portion of the curve.

In closing, we agree that further studies are required and that up-down ED50 studies have distinct advantages compared with other designs with regard to robustness, whatever the modality being studied. A follow-up study comparing the minimum local analgesic concentrations of bupivacaine, ropivacaine, and levobupivacaine is currently in progress at our institution.

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1. Polley LS, Santos AC: Cardiac arrest following regional anesthesia with ropivacaine: Here we go again! ANESTHESIOLOGY 2003; 99:1253–4
To the Editor:—We read with interest two recent case reports1,2 and an accompanying editorial3 regarding cardiac toxicity associated with ropivacaine administration. Recently, we experienced at our institution a near-miss drug error with ropivacaine that could have resulted in significant patient morbidity and even mortality.

While preparing to perform a caudal block in a pediatric patient, one of our residents retrieved an ampule of ropivacaine from an anesthesia cart. We routinely stock our anesthesia carts with 20 ml ampules of 0.2% ropivacaine, specifically for use in caudal and epidural blocks in pediatric patients; in addition, we maintain a separate supply of 20 ml ampules of 0.75% ropivacaine in our anesthesia workroom for use in regional anesthesia, primarily in adult patients. As the resident opened the package, it was noted that he had opened a package containing 0.75% ropivacaine, which had inadvertently been placed in the anesthesia cart. On further inspection, it became apparent that the appearance of the two concentrations is very similar (fig. 1): they are identical in size and shape; the lettering and graphics on both the packaging and the ampules themselves are identical (with no color distinction) except for the stated difference in concentrations of the two solutions. Had the potential drug error not been recognized, the patient would have received nearly three and a half times the intended dose of ropivacaine. Although ropivacaine has less cardiotoxicity than does bupivacaine, complications with ropivacaine do occur, as noted in this journal.1,2

One previous report describes the near identical appearance of 0.2% and 0.75% ropivacaine.3 Given the potential for cardiac toxicity of ropivacaine, we have recommended that its manufacturer, AstraZeneca (Wilmington, DE), modify the packaging and ampules of its two concentrations so that the differences are more distinguishable. Since this near-miss event, we have removed these two concentrations of ropivacaine from our anesthesia carts and workroom and have placed them in a Pyxis machine (Cardinal Health, San Diego, CA) to reduce the potential for drug error. This case provides further evidence of the importance of both vigilance and preventive strategies in ensuring safe anesthetic care.

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(Accepted for publication April 18, 2004.)
Ropivacaine-induced Asystole: “Never Again” rather than “Here We Go Again”

To the Editor—The timely editorial by Polley and Santos interpreting two companion Case Reports of ropivacaine-induced asystole merits comment. The explicit “Here We Go Again,” along with the implicit lead-in with bupivacaine-induced cardiac arrests, might leave a hurried reader with the erroneous impression that ropivacaine cardiotoxicity differs but little from bupivacaine cardiotoxicity. Far from it!

I concur that both instances of cardiac asystole reported here were secondary to elevated ropivacaine plasma levels. But I would like to cast a rosier slant on the uneventful resuscitation of ropivacaine-induced asystole, altogether different from the grim lethality of the six bupivacaine- (and etidocaine-) induced cardiac arrests that Albright reported a quarter century ago. The astounding ease of restoration of cardiac rhythm after ropivacaine-induced asystole, as against the notorious resistance to resuscitation after bupivacaine-induced cardiovascular collapse, is a heartening turnaround indeed.

Recall that any local anesthetic, at a plasma concentration sufficient to block cardiac ion channels, slows impulse conduction; witness the use of lidocaine in managing ventricular arrhythmias. When that cardiotherapeutic dose is exceeded, however, asystole may be the ultimate outcome; witness the infamous “Xylocaine Mercy Killer” of the 1980s, linked to some 13 documented murders from overdosing with intravenous lidocaine. At issue here, ever mindful of bupivacaine-induced asystole, is a heartening turnaround indeed.

It should come as no great surprise that high levels of circulating ropivacaine can slow, and ultimately stop, the heart. What does come as a welcome surprise is the ease with which hemodynamic function can be restored by simple therapeutics. Contrast that with the extraordinary measures (up to and including circulatory bypass) that have been attempted in the past to reverse bupivacaine-induced cardiac dysfunction. As postropivacaine resuscitation was both swift and decisive, and can be restored by simple therapeutics. Contrast that with the extraordinary measures that have been attempted in the past to reverse bupivacaine-induced cardiac dysfunction.

The putative cause-effect linkage of hydroxyzine to ropivacaine cardiotoxicity merits a final comment. Not only were both patients premedicated with hydroxyzine (Vistaril®; Pfizer, New York, NY) but both were 66 years old and both were Parisians. To ponder, at some length yet, a speculative link between hydroxyzine and ropivacaine-induced asystole seems as wide off the mark as it would be to caution 66-year-old Parisians against ropivacaine. Hydroxyzine may not be my choice (or yours) for premedication, but that does not warrant giving it an undeserved black eye.

In conclusion, the glad tidings these case reports bring us is that ropivacaine cardiotoxicity, in the hands of vigilant physicians, is readily reversible. The discovery of cardiac ion channel stereoselectivity, and the subsequent synthesis of monomeric ropivacaine (and levobupivacaine), is not a mere laboratory curiosity or yet another marketing ploy but rather a clinically momentous breakthrough that promises to lessen significantly the cardiovascular risk of rapidly rising blood levels when using long-acting local anesthetics. By all appearances, ropivacaine-induced asystole is, in competent hands at the least, a readily reversible event, most unlike the dishearteningly irreversible catastrophe of bupivacaine-induced cardiac arrest.

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Hesitant to Follow the Conclusion Drawn

To the Editor—It is with great interest that we read the two case reports and the accompanying editorial on ropivacaine-induced cardiac arrest after peripheral nerve block in the December 2003 issue of Anesthesiology. First, we would like to congratulate the authors for saving two lives. However, we are hesitant to follow the conclusion drawn that these cases demonstrate the superiority of ropivacaine, compared with bupivacaine, with regard to cardiac safety and resuscitation. Polley and Santos argue in their editorial that patients showing signs of severe systemic toxicity induced by ropivacaine may respond more readily than those intoxicated with bupivacaine to conventional resuscitation. They refer to an animal study published by Groban et al stating that cardiac resuscitation was less difficult and fewer animals died after supernatant doses of ropivacaine as compared with bupivacaine. However, this is not shown in the study. Groban et al explicitly state that too few animals were studied to draw any statistically valid conclusions on any superiority of ropivacaine over bupivacaine with regard to successful resuscitation. Huet et al in their case report also quote the study of Groban et al as well as a study published by Ohmura et al on resuscitation of rats, to make the point that ropivacaine is superior to bupivacaine with regard to cardiac resuscitation. Ohmura et al in their study on systemic toxicity of bupivacaine, levobupivacaine, and ropivacaine clearly show that the number of successful resuscitations did not differ among groups. Furthermore, neither Groban et al nor Ohmura et al corrected for equipotency of bupivacaine and ropivacaine. Even without considering the issue of equipotency neither of the quoted studies demonstrates any significant difference between bupivacaine and ropivacaine in the rate of successful resuscitation.

The case reports2,3 clearly demonstrate that ropivacaine induces cardiac arrest. In this regard it seems not to differ from bupivacaine. However, Huet et al and Chazalon et al suggest that different pathomechanisms underlie cardiac arrest induced by ropivacaine and bupivacaine. We would like to challenge this view, as two case reports do not allow drawing any conclusions regarding the pathomechanisms underlying cardiac arrest induced by ropivacaine or bupivacaine. Ropivacaine is capable of also inducing ventricular arrhythmia.
Local Anesthetic Cardiac Toxicity can Present as Late-onset Hypotension, Bradycardia, and Asystole

To the Editor.—We applaud Dr. Polley and Dr. Santos' for reminding us in their recent editorial of the potential risks of anesthetic toxicity in peripheral nerve block and of the need to employ standard safety methods to reduce the risk of cardiac toxicity in all forms of regional anesthesia. However, we believe their discussion missed another, equally important, lesson to be learned from these interesting case reports of ropivacaine-induced cardiac arrest.

Both cases2,3 presented with hypotension, bradycardia, and asystole. Drs. Polley and Santos state that as bupivacaine would be expected to produce ventricular tachycardia or fibrillation, the arrhythmias produced in humans by ropivacaine and bupivacaine are different. In fact, severe hypotension and bradycardia leading to asystole are commonly seen in animal models of bupivacaine cardiac toxicity,4 and we believe their occurrence during a regional anesthetic should lead to the inclusion, not exclusion, of local anesthetic toxicity from the differential diagnosis.

More importantly, Chalazon et al. report cardiac toxicity 90 min after a ropivacaine-based sciatic block and 30 min after smaller supplementary injections for inadequate sensory anesthesia. Traditionally, the natural history of local anesthetic toxicity is described as occurring immediately after inadvertent intravascular injection of anesthetic. However, as this case indicates, patients can present with delayed onset severe local anesthetic cardiac toxicity. This phenomenon is sufficiently different from the standard textbook presentation that it can be easily overlooked or misdiagnosed. For instance, we recently commented on a case report of cardiac arrest occurring 105 min after a combined bupivacaine-mepivacaine brachial plexus block.5,6 The possibility of anesthetic toxicity was not mentioned in the report and was later dismissed by the authors on the basis of the long interval between injection and the arrest and because the presenting arrhythmia was junctional bradycardia leading to asystole, not ventricular tachycardia or fibrillation.7

We believe that the natural history of local anesthetic toxicity may encompass a much broader clinical phenotype than is indicated in standard textbook descriptions. It is likely that atypical cases of local anesthetic toxicity go unrecognized and are underreported. Given the recent evidence for a possible form of therapy specific for local anesthetic cardiac toxicity,8 it is particularly important to contemplate this diagnosis in patients having signs of cardiac dysfunction in the setting of regional anesthesia, even if the arrhythmias or time course vary from a classic presentation.

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To the Editor—We all learn from the mistakes of others and medicine is no exception. Recently Chalazon et al.1 reported in this journal on their misadventures with ropivacaine in an elderly woman for bun-ionectiony. I have several concerns regarding the quality of anesthetic practice used by the authors, specifically regarding choice of anesthe-sia and resuscitative pharmacology in the face of ropivacaine toxicity.

First, their treatment of the patient’s cardiac asystole comprised repeated doses of ephedrine and a single dose of atropine. If one assumes that this cardiac catastrophe was brought on by ropivacaine toxicity, then it is important to remember that these amide local anesthetics have direct myocardial actions consisting of negative chro-notropic, dromotropic, and inotropic effects. It has been shown in animals that the most effective resuscitative drug in the face of ropivacaine or bupivacaine toxicity is epinephrine, yet the authors used ephedrine, a weaker and indirect-acting alternative.

Second, the authors chose to use a single small dose of intravenous midazolam when their patient exhibited central nervous system signs of ephedrine, a weaker and indirect-acting alternative.

Finally, and perhaps of greatest concern, is whether the authors abided with the patient’s right to ‘self-determine’ her anesthetic care.2 I find it implausible that this patient would agree to another popliteal nerve block after the technique failed for the bunionectiony done on her other foot. In addition, why would the patient be agreeable to repeated injections of ropivacaine after the popliteal block again failed, when a general anesthetic had been administered for her first bunionectiony? The authors need to address this issue of informed consent and the right of their patient to ‘self-determine’ her anesthetic care.

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truly has a greater margin of safety than bupivacaine or whether it is merely less potent. We believe that this is related to the fact that studies comparing the systemic toxicity of ropivacaine and bupivacaine were based on the assumption that although ropivacaine is slightly less potent than bupivacaine, the two drugs would be nonetheless used equieffectively. We know now that, at least in obstetrics, this may not be the case.\(^2\)\(^5\) That also seems to be the clinical impression of many anesthesiologists, as they are using the higher 0.75% concentration rather than 0.5% concentration of ropivacaine for regional anesthesia.\(^2\)\(^5\)

In closing, it almost goes without saying that ropivacaine, like other drugs in its class, is a very potent amide local anesthetic with the potential to cause cardiac arrest. Therefore, when using any of the long-acting potent amide local anesthetics, it is necessary to have heightened vigilance, to adhere to maximum dosage limits and to develop safer practices for drug administration. To profess anything else will condemn us to repeat history.

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In Reply.—We wish to thank our colleagues from Hamburg for their congratulations. However, we continue to believe that the rapid recovery observed in our patient was attributable to the intrinsic properties of ropivacaine rather than to our resuscitation skill. Indeed, it is difficult to perform a controlled study in patients to prove that the S enantiomers of local anesthetics are less cardiotoxic than the racemic mixtures. Nevertheless, there is a large body of arguments that let us consider that ropivacaine is less toxic than bupivacaine, likely because of the lower use-dependent block induced by the S enantiomers as compared with the R enantiomers or with the racemic mixtures. Studies done on cultured cells,\(^1\) isolated cardiomyocytes,\(^2\) papillary muscles,\(^3\) isolated heart preparations,\(^4\) and intact animals\(^5\) have demonstrated such a difference. We agree that the mechanisms of the effects of local anesthetics on cardiac conduction are not that simple\(^6\) and that these differences between enantiomers may be less important in the clinical situation. However, a study done in human volunteers also showed that ropivacaine exhibits less cardiotoxic effects than bupivacaine, at least at low doses.\(^7\) Epinephrine proved to be efficacious for the treatment of bupivacaine overdose, but its intrinsic effects on heart rate are deleterious because epinephrine induces ventricular fibrillation as a result of the use dependence.\(^8\)\(^9\) Accidents related to the cardiotoxic effect of bupivacaine usually need prolonged resuscitation measures because of a refractory ventricular fibrillation. In our case, as in the case reported by Chazalon et al.,\(^10\)\(^11\) the patients recovered very rapidly. We have attributed this rapid recovery to the absence of deleterious effect of epinephrine, as in both cases no arrhythmias were observed after epinephrine injection. These two reports are the first two cases of cardiac arrest following injection of ropivacaine published after more than 10 years of clinical practice with this agent. During the same period of time, at least five cases of cardiac arrest related to bupivacaine have been published, whereas only one case of severe dysrhythmias induced by ropivacaine has been published. Although we do not have full evidence-based proof of the less detrimental effect of ropivacaine on cardiac conduction as compared with bupivacaine, we continue to believe that ropivacaine is safer than bupivacaine.

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To the Editor.—The paper by Angle et al.¹ is a well-designed and carefully conducted study that clearly delineates the effect of epidural needle design and insertion technique on fluid leak through dural tissue after puncture in vitro. The goal of the study was to help define methods that might decrease the incidence of “spinal headache” when the meninges are accidentally punctured during attempted epidural anesthesia/analgesia. Clearly, this is a laudable goal.

The assumptions that underlie this study design are that persistent cerebrospinal fluid leak through a hole in the meninges is responsible for spinal headache and that the hole in the dura mater is responsible for the persistent cerebrospinal fluid leak. The first assumption is probably correct; however, to my knowledge there are no data to support the idea that the hole in the dura mater, as opposed to the arachnoid mater, is responsible for the persistent cerebrospinal fluid leak. After all, cerebrospinal fluid resides in the subarachnoid space, not the subdural space, and it is entirely possible that it is the nature of the hole in the arachnoid mater that determines whether patients develop spinal headache.

This is certainly not to suggest that the clinical studies demonstrating that parallel insertion of a beveled spinal needle reduces the risk of spinal headache are in error. Clearly, parallel insertion does result in a lower risk of spinal headache. However, the conventional wisdom that ascribes the reduced risk to the nature of the hole in the dura mater has no valid experimental basis. Specifically, because the current study by Angle et al. and similar studies by others failed to address the potential role of the arachnoid mater in persistent cerebrospinal fluid leak, their conclusions as to mechanism are of little or no value, and extrapolation of their findings to the clinical arena are not warranted.

It is hard to conceive of an in vitro study design that would produce a valid model of cerebrospinal fluid leak through the spinal meninges. A more appropriate model would be one in which the spinal meninges of an animal were punctured in vivo and the animals sacrificed at various time points thereafter to determine the nature of the hole in the dura and the arachnoid membranes. In this way, the healing process could be examined and the “rate-limiting” meninx identified. In the absence of experimental data that clearly identify the dura mater as the meninx responsible for persistent cerebrospinal fluid leak, studies like that of Angle et al. should not be considered to provide any insight into the mechanism responsible for spinal headache or the methods that can be used to prevent it.

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Reference


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studies. Tissue was mounted over a window in the model and sealed with a customized gasket containing a matching window through which punctures were performed. Features of our model that add to its clinical relevance include 1) the use of a physiologically pressurized cylindrical model with a diameter closely approximating that of the lumbar dural sac; 2) mounting of dural specimens with in vitro orientation maintained; 3) use of artificial cerebrospinal fluid; and, 4) observed tenting of the dura at the time of puncture. Our model was watertight (as were similar spinal needle models) when pressurized to physiologic pressures with artificial cerebrospinal fluid and, save for isolated leakage from deliberately made needle puncture sites, remained that way. Demonstration of a watertight seal with dural specimens in such models suggests that the lamina arachnoïd membrane (with tight junctions) was not only present but also intact, providing a barrier to fluid passage. It should be noted that authors using similar watertight models for spinal needle studies have described tenting,16 clinical studies examining postdural puncture headache in this setting have not borne the weight of scrutiny when subjected to more powerful imaging techniques such as scanning electron microscopy13 and transmission electron microscopy (our own unpublished data). Given inconsistencies in the results of in vitro studies examining leak rates after parallel bevel orientation during puncture,14–15 and the small number and limited methodological quality of clinical studies examining postdural puncture headache in this setting,16–18 we believe that it would be more reasonable to say that there is little high quality evidence to support a difference in the incidence of postdural puncture headache as a result of needle bevel orientation at the time of puncture.

Our model does not address the process of dural healing. It is implied in Dr. Bernard’s letter that the absence or early resolution of postdural puncture headache in some patients is secondatory to early dural or arachnoid healing. We would consider this to be unclear at best. We would suggest that the weight of the existing, albeit lower quality, evidence in the literature would support that this is not the case, especially for larger gauge punctures.

Few studies have addressed the issue of dural healing. Franksson and Gordh,19 examined the postmortem dura of three patients with documented lumbar punctures at 2 days, 14 days, and 40 days before death. At 2 days, no evidence of haemorrhage was found, and at 14 days, only early signs of healing were evident at the corners of the dural tear made by a bevelled needle. At 40 days a scar was macroscopically visible in the puncture site, with microscopic evidence that the tissue filling the site was of recent origin. Leaking dural defects have also been noted during surgery after “protracted periods of time”20–21 these findings along with a relatively low permanent cure rate of initial epidural blood patches,22–23 and case reports of successful but late (weeks to months) or late repeated use of blood patching for postdural puncture headache are also consistent with a relatively slow process of dural repair.

Given evidence suggesting a slow healing process, that the incidence and severity of postdural puncture headache is likely to be related to the volume and rate of cerebrospinal fluid loss, and that this in turn is related to tissue injury with needles, we maintain that our in vitro model and the models of our counterparts remain relevant to the study of postdural puncture headache.

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References

To the Editor—An oxygen flush valve is a useful feature of most anesthesia machines. Its malfunction is rare but potentially harmful.1-3 In one instance, a fatigued metal spring left a valve wide open during a preoperative machine check. Another valve became slow to release because of inadequate lubrication.2 We report a relatively insidious valve problem.

A patient was to undergo percutaneous closure of an atrial septal defect. Because transesophageal sonographic guidance was to be employed, we opted for general anesthesia with the aid of tracheal intubation. After an uneventful check of the machine, anesthesia was induced intravenously. For maintenance, our machine was set to deliver 2% isoflurane in air. However, our gas analyzers indicated delivery of 1% isoflurane and 60% oxygen. A sevoflurane vaporizer also failed to deliver expected concentrations of vapor. Repetition of the machine check revealed a leak of oxygen, approximately 4 l/min, into the breathing circuit. The oxygen flush button superficially appeared to be undamaged, and its spring exhibited the usual force. After the button was pressed a few times, the leak disappeared. The machine was taken to our service area, where routine external checks revealed no problems. However, we found an unstable “orthopedic” condition inside of our 7-yr-old Excel 210 SE machine (Datex-Ohmeda, Madison, WI). The push button for its flush valve was attached to a shaft that transmits the finger pressure to open the valve. Our machine had suffered a spiral fracture of that plastic shaft (fig. 1). As long as the fracture was “reduced,” the assembly functioned normally. However, the two pieces could “displace” upon rotation with respect to each other, and then the shaft was too long and so held the flush valve partially open. With this diagnostic information available, we could deliberately make the leak come and go, and we observed that different operators inadvertently applied various degrees of torque as they pressed the button. The broken part was easily replaced.

Gross trauma to the assembly has been reported to lock open an oxygen flush valve.3 Because of that and other possibilities, federal regulations require the oxygen flush valve to be protectively housed.3 Because of the intermittent character of our valve malfunction, it is not clear if and when our machine suffered a strong impact. The machine does have a sturdy protective rim around the push button, and the fracture may have occurred through routine stress on the plastic shaft. Transient malfunction of a valve should not be dismissed. Our intermittent gremlin was treacherous indeed.

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References


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In Reply—Thank you for allowing us to respond to the article “Oxygen Flush Valve Booby Trap.” The authors describe an intermittent dilution of the breathing circuit gases from a broken flush valve. Although Datex-Ohmeda (Madison, WI) was not advised of this event before notification by Anesthesiology, and our service staff did not have the opportunity to examine the valve in question, we can suppose that the valve fault described would be consistent with the clinical findings observed by the authors. It is important to point out that this type of failure, when the “fracture” is displaced, will fail the Food and Drug Administration Preoperative Checkout Procedure during both the high pressure leak test, recommended once per day, and the low pressure leak test,

Oxygen Flush Valve Booby Trap

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To the Editor:—New extraglottic airway devices have been described at a rate of one per year for the last 25 yr, increasing to two per year since the turn of the century. I would like to propose a classification system for this increasingly complex family of devices. It involves three main criteria. First: whether the device is uncuffed or cuffed. This relates to its suitability as a ventilatory device; those without cuffs require a face or nasal mask (extracorporeal devices) to facilitate ventilation. Second: whether it is inserted through the mouth or nose. Third: the anatomic location of the distal portion in relation to the hypopharynx. This relates to the potential degree of isolation of the respiratory and gastrointestinal tracts. If the distal portion sits above the hypopharynx (oral cavity, nasal cavity, nasopharynx, oropharynx and laryngopharynx†) there is no isolation. If the distal portion sits in the hypopharynx there is some isolation. If the distal portion sits below the hypopharynx (esophagus) there is moderate isolation. In contrast, with a cuffed endotracheal tube there is considerable isolation.

There are four other potential criteria for classification, but these are less suitable. First: the anatomic location of the distal airway aperture. This relates to its efficacy to provide a clear airway and for ease of instrumentation of the respiratory tract; the shorter the distance between the distal airway aperture and the glottic inlet, the greater the efficacy of both—although, the distal airway aperture of most extraglottic airway devices is located in the laryngopharynx. Second: whether the extraglottic airway device is used as an airway intubator; however, most extraglottic airway devices are capable of facilitating intubation. Third: whether the device is disposable or reusable; however, this provides no information about function. Fourth: whether the cuff is in the proximal pharynx (e.g., laryngeal tube aperture) or surrounds the periglottic tissues (e.g., laryngeal mask aperture); however, this only applies to the subset of cuffed extraglottic devices.

Finally, it is worth noting that the term “extraglottic airway device” is more appropriate than “supraglottic airway device,” since many have components that are infraglottic, but all lie outside the glottis. The modern extraglottic airway devices (post-1980) are listed in table 1 according to the proposed classification.

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Table 1. Classification of Extraglottic Airway Devices by 1) Presence/Absence of a Cuff, 2) Oral/Nasal Route of Insertion; and 3) Anatomic Location of the Distal Portion

<table>
<thead>
<tr>
<th>Year</th>
<th>Uncuffed, orally-inserted laryngopharyngeal airways</th>
<th>Cuffed, orally-inserted hypopharyngeal airways</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>Williams airway intubator*</td>
<td>Classic LMA‡</td>
</tr>
<tr>
<td>1982</td>
<td>Patil oral airway</td>
<td>Flexible LMA‡</td>
</tr>
<tr>
<td>1987</td>
<td>Ovassapan fiberoptic intubating airway*</td>
<td>Intubating LMA†</td>
</tr>
<tr>
<td>1981</td>
<td>Combined oropharyngeal airway and dental pack</td>
<td>Disposable LMA‡</td>
</tr>
<tr>
<td>2001</td>
<td>Modified Connell airway</td>
<td>ProSeal LMA‡</td>
</tr>
<tr>
<td>1990</td>
<td>Cuffed, orally-inserted laryngopharyngeal airways</td>
<td>Glottic aperture seal airway‡</td>
</tr>
<tr>
<td>1992</td>
<td>Mehta’s cuffed oropharyngeal airway†</td>
<td>Streamlined pharynx airway liner‡</td>
</tr>
<tr>
<td>1998</td>
<td>Cuffed oropharyngeal airway†</td>
<td>Soft Seal laryngeal mask‡</td>
</tr>
<tr>
<td>1999</td>
<td>Uncuffed, nasally-inserted laryngopharyngeal airways</td>
<td>Laryngeal tube airway†</td>
</tr>
<tr>
<td>1988</td>
<td>Variable flange nasopharyngeal airway</td>
<td>Laryngeal tube suction†</td>
</tr>
<tr>
<td>1988</td>
<td>Linder nasopharyngeal airway</td>
<td>Airway management device†</td>
</tr>
<tr>
<td>1990</td>
<td>Cuffed, nasally-inserted laryngopharyngeal airways :</td>
<td>Pharyngeal airway express†</td>
</tr>
<tr>
<td></td>
<td>Boeheimer’s cuffed nasopharyngeal airway</td>
<td>Cobra pharyngeal lumen airway†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uncuffed, orally-inserted esophageal airways</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tracheo-esophageal airway</td>
</tr>
<tr>
<td>1981</td>
<td></td>
<td>Cuffed orally-inserted esophageal airways</td>
</tr>
<tr>
<td>1984</td>
<td></td>
<td>Pharyngeal tracheal lumen airway†</td>
</tr>
<tr>
<td>1987</td>
<td></td>
<td>Esophageal tracheal combitubef†</td>
</tr>
</tbody>
</table>

Many of the names of extraglottic airway devices do not fit with this classification system. For example, the distal ends of the “Patil oral airway” and the “Linder nasopharyngeal airway” are in the laryngopharynx and not in the oral cavity and nasopharynx, respectively. There are no extraglottic airway devices whose distal portion is intended to sit in the oral cavity, nasal cavity or nasopharynx.

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To the Editor—The United States Food and Drug Administration (FDA) recently approved a major change in the labeling of 6% hetastarch in saline, applying specifically to cardiopulmonary bypass surgeries. This synthetic colloid is commonly used in place of 5% human albumin as a plasma volume expander in a variety of surgical and critical care settings.

In August 2003, the following warning statement was added: HESPA N is not recommended for use as a cardiac bypass pump prime, while the patient is on cardiopulmonary bypass, or in the immediate period after the pump has been discontinued because of the risk of increasing coagulation abnormalities and bleeding in patients whose coagulation status is already impaired. The change follows a recommendation of the Blood Products Advisory Committee, Center for Biologics Evaluation and Research, Rockville, Maryland, made to the FDA in June 2002.

The interference by hetastarch with coagulation has been documented repeatedly over the last three decades. These effects were described in the early 1960s when preclinical research on hetastarch demonstrated prolonged bleeding times. Hetastarch infusion mediates a dose-dependent decrease of factor VIII and von Willebrand factor and increased cost.

Although coagulation measures and anecdotal reports of hetastarch-associated hemorrhage have been reviewed extensively, controversy regarding the clinical relevance of these effects has persisted in the absence of adequate data. Because of this controversy a useful approach is to evaluate studies of a well-defined group, such as patients requiring cardiopulmonary bypass. Postoperative bleeding in this group is a very significant complication because the need for surgical reexploration increases the risk to patients with greater mortality, prolonged intensive care unit stay, and increased cost.

Early studies of hetastarch used during cardiac surgery failed to document any difference in postoperative blood loss between hetastarch or albumin given for volume replacement. Three studies showed modestly higher blood loss when patients received hetastarch but none of these reached statistical significance. These reports were limited by small sample sizes (n < 200), and these reports are no longer useful because patient selection, surgical technique, and perioperative management have changed greatly in the years since they were published.

Two studies in cardiac surgery patients and an epidemiological study from the current literature prompted the FDA to ask if hetastarch mediates increased bleeding in patients on cardiopulmonary bypass. Both surgical studies examined the effect of intraoperative hetastarch administration on postoperative blood loss. The studies are significant because their study populations approach or exceed the threshold (200 patients in each arm of a comparative study) suggested by Warren and Durieux to achieve adequate statistical power. Herwalt et al. examined the risk factors associated with increased postoperative bleeding when hetastarch was substituted for albumin in cardiopulmonary bypass pump priming solution. They found an increase in the transfusion of blood products, increased costs, and two risk factors: age greater than 60 yr and the use of more than 5 mL/kg hetastarch were associated with postoperative bleeding in their study of 500 patients.

Cope et al. reviewed 189 consecutive coronary artery bypass graft surgeries. They reported a significant increase in blood loss and use of hemostatic agents when hetastarch was used in the operating room. Increased postoperative chest tube drainage, transfusion requirements, and a greater risk of surgical reexploration were documented in patients who received hetastarch during surgery, and five patients (7.4%) receiving hetastarch intraoperatively required surgical reexploration as opposed to one (1.6%) in the group that did not.

A large review from the Mayo Clinic, Rochester, Minnesota, reported the experience of 444 consecutive cases, all performed by the same surgeon when the routine practice of using hetastarch for volume expansion during surgery was discontinued as a result of the Cope publication. The retrospective study examining postoperative bleeding found the mean blood loss was about 40% higher in patients receiving hetastarch. Like Cope et al., they also noted that it appeared to increase in a dose-dependent manner.

The value of these studies comes from limiting the use of hetastarch to the intraoperative period and examining the postoperative result of that practice. They are retrospective studies but the complete change in hetastarch use minimizes the risk of treatment bias. No important between-group biases were evident and the studies included patient numbers to warrant acceptance of most of the major findings.

The advisory committee also heard the report of Canver and Nichols that supported the use of hetastarch. That study compared crystalloid, albumin, hetastarch, and a combination of albumin and hetastarch for cardiopulmonary bypass pump priming in nearly 900 coronary artery bypass graft patients. The study failed to find any difference in postoperative bleeding or reoperation. The committee did not agree with the conclusion because patients in each arm of the study were dissimilar. Patients given a hetastarch-based priming solution had much shorter cross-clamp times than did those in the other groups. Because the duration of cardiopulmonary bypass influences bleeding, it is noteworthy that even with the shorter cross-clamp time; Canver and Nichols' data shows the highest mean consumption of platelets and fresh frozen plasma was in the hetastarch group.

On a unanimous vote (with two abstentions), the Blood Products Advisory Committee recommended changing the labeling of 6% hetastarch in saline to warn users of the risk of excessive bleeding associated with its use in bypass surgery.

There are additional reports not used by the Blood Products Advisory Committee in reaching their decision that support their action. Wilkes et al. conducted a meta-analysis examining 16 studies encompassing 653 patients in whom hetastarch was used during cardiopulmonary bypass. When compared with albumin administration, patients receiving hetastarch had greater blood loss and the proportion of patients with blood loss greater than 11 was 19% for patients receiving albumin versus 33% for patients receiving hetastarch. Two reports published since the FDA decision provide additional evidence supporting that action. Sedrakyan et al. examined mortality as a clinical outcome in more than 19,000 patients that had coronary artery bypass surgery. Patients receiving albumin or nonprotein colloids (dextran, hetastarch) were compared, and albumin administration was associated with lower mortality (2.47% versus 3.05%). This represents 25% lower odds of mortality compared to nonprotein colloid use. This result is consistent with Knutton et al., who also found a small increase in mortality of 3% in the hetastarch treatment group. Avorn et al. performed a case-controlled study of 238 bypass cases examining patients receiving three or more units of blood products within 72 h of surgery or who returned to the operating room for bleeding. A multi-variate analysis found those receiving one unit of hetastarch had more
than twice the risk of bleeding than control group patients and the risk increased to more than four times that of the control group when patients received 2 or 3 units of hetastarch.

Significant randomized clinical trials of the 6% hetastarch product in lactated electrolyte solution (Hextend®; BioTime, Inc, Berkeley, California) are lacking. The only clinical trial evaluating this material compared the treatment group and a control group that received hetastarch in saline.21 Resuscitation fluids in both arms of the study were given to maintain a target urine output, heart rate, and systolic blood pressure without regard to a maximum dose. As a result, some patients in both the control and treatment groups received up to 5 l of hetastarch. This is far in excess of the recommended dosing guidelines for this product. At the present time there are no robust clinical data to support the manufacturer’s assertion that 6% hetastarch in electrolyte solution is not associated with similar bleeding-related complications in cardiac surgery cases.

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