To the Editor—We read with interest the recent article by de Nadal et al., who carefully examined the influence of morphine and fentanyl on cerebral hemodynamics in patients with severe head injury. The authors reported that both opioids cause small and transient increases in intracranial pressure (ICP), regardless of the autoregulatory capacity of the patient.

We agree that this is an important, heretofore considered settled, issue and believe that the work of de Nadal et al. adds to our understanding of the pharmacodynamics of opioids in this population of patients. However, there are methodologic issues in the study that require cautious interpretation.

It is acceptable to use arteriojugular venous oxygen content difference (AVDO₂) changes as a surrogate for cerebral blood flow changes, provided we accept that cerebral metabolic rate stays constant, and no intracerebral steal occurs during the study. However, given that all patients were studied subsequently with transcranial Doppler ultrasonography, why was autoregulation quantified only with AVDO₂ measurements, and not with flow velocity measurements as well? Furthermore, during cerebral autoregulation testing, the authors corrected for change in arterial carbon dioxide tension (Paco₂) according to carbon dioxide reactivity, which is appropriate. However, the autoregulatory capacity is influenced by Paco₂, with hypocapnia improving and hypercapnia impairing it. We assume the authors made an effort to control Paco₂, but it would be more informative if the authors would also tell us the actual Paco₂ present during autoregulation testing and whether this remained unchanged when opiates were administered.

The more difficult issues relate to the arbitrary classification of autoregulatory pattern and the magnitude of mean arterial pressure (MAP) change caused by the doses of opioids given in this study. Cerebral autoregulation is not an all-or-none phenomenon, and there are different magnitudes of impairment. Nevertheless, we agree that it is useful to classify the responses into impaired or preserved to autoregulation when cerebral hemodynamics in patients with severe head injury: Absence of correlation to cerebral autoregulation. ANESTHESIOLOGY 2000; 92:11–9

We are grateful for the comments offered by Drs. Lam and Warner regarding the effect of morphine and fentanyl on intracranial pressure (ICP) in severe head injury patients. They express concern that our methods in autoregulation testing need further interpretation and refer to the possibility that an insufficient mean arterial pressure (MAP) change observed by the doses of opioids administered could have unmasked our results.

The first issue they address is the use of transcranial Doppler ultrasonography (TCD) for the study of autoregulation. Although flow velocity measurements performed with use of TCD would have provided an additional estimation of cerebral blood flow (CBF) during autoregulation studies, it is worth reemphasizing that TCD velocities do not always mirror blood flow. The ability of TCD to assess cerebral vasoreactivity assumes that changes in the diameter of the insolated vessels, usually the middle cerebral artery, are negligible. However, it has been shown that mid-sized arteries, even the internal carotid artery, may be implicated in maintaining a constant CBF when cerebral perfusion pressure is modified. Thus, errors in flow assessment may occur because of changes in middle cerebral artery or internal carotid artery diameter during systemic blood pressure changes. Most of our patients had a diffuse brain injury, and, therefore, global autoregulation measurements such as arteriojugular venous oxygen content difference (AVDO₂) were likely to be more representative of the autoregulatory status than evaluation of bilateral changes in hemispheric middle cerebral artery flow velocities. Furthermore, corrections for changes in arterial carbon dioxide tension (Paco₂) are easier to perform with use of this test than with use of TCD.

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Focusing on the second issue, we completely agree with Lam and Warner that autoregulation capacity may be influenced by Paco₂. However, hypocapnia and hypercapnia do not affect autoregulation per se but may influence the autoregulatory response of cerebral vessels that are already vasoconstricted and vasodilated, respectively. To avoid this known artifact, before testing autoregulation, we always manipulate the ventilator settings to obtain a baseline Paco₂ in the
To Increase Obstetric Reimbursement Rates, We Need to Improve the Product

To the Editor.—Labor is extremely painful for many women. Effective pain relief (i.e., regional labor analgesia) should be available on request to all women in labor. As Chestnut points out, the absolute cost of providing epidural labor analgesia, as detailed by Macario and Bell et al., is not great. I am certain that providing cardiac anesthesia for a mitral valve replacement or neuroanesthesia for a cerebral aneurysm clipping costs more than does providing an epidural labor anesthetic. The problem is the reimbursement rate. I think that the reimbursement rate will not increase until our services are valued more highly, and our services will not be valued more highly until we are viewed as labor facilitators.

If one were an insurance company executive, would one volunteer to pay handsomely for an optional service that increases other costs by increasing the duration of labor, causing greater need for oxytocin augmentation, increasing the incidence of neonatal fever, and possibly increasing cesarean delivery rates? Of course not. Now, imagine that epidurals shortened labor and decreased cesarean delivery rates in addition to keeping patients happier. That would be a valuable service. If anesthesiologists threatened to stop providing that service, we believe is not ethically possible in severe head injury patients.

The last issue refers to the magnitude of MAP change caused by the doses of opioids administered in our study. We agree with Lam and Warner that the small decrease in MAP (3–4 mmHg) could not be sufficient to stimulate the vasodilatory cascade. However, the ICP increase seen in patients with preserved and impaired autoregulation suggests that cerebrovascular autoregulation may not be the only probable mechanism responsible for morphine- and fentanyl-induced increases in ICP. As we stated in the discussion, opioids may interact directly with receptors located on brain blood vessels, and μ receptor activation has been proven to cause direct cerebral vasodilation in some experimental models. Although we cannot rule out the hypothesis that greater doses of opioids may increase ICP through an autoregulatory response, we believe that further studies are needed to elucidate the role of opioids on cerebral circulation during brain injury.

We appreciate Lam and Warner’s insights on our work and the chance to clarify some controversial issues about the classification of autoregulation in severe head injury patients.

*Miriam de Nadal, M.D., Ph.D., Juan Sahuquillo, M.D., Ph.D.
Vall d’Hebron University Hospitals, Barcelona, Spain. 27414mdc@comb.cat

References

(Accepted for publication June 20, 2000.)
In Reply.—Dr. Leighton suggests that epidural analgesia for labor is an optional service for which anesthesiologists will not be compensated appropriately until there is some financial benefit to the insurance industry to reimburse for this method of analgesia. These benefits already exist.

Epidural analgesia alleviates labor pain more effectively than do parenteral opioids and results in higher ratings of patient satisfaction.1–3 In the competition for patients, reimbursing for labor epidurals makes insurers attractive to women, the usual healthcare decision makers in the family. The risk of cesarean section does not differ between women who receive epidural analgesia and those who receive parenteral opioid analgesia.1,2 Access to epidural analgesia actually may decrease the cesarean section rate by encouraging women to attempt vaginal delivery after cesarean section.3

Do epidurals increase the duration of labor? In the randomized controlled trials examining this question, most patients were administered fluid preload of 500–1,000 ml and lidocaine test doses, followed by initiation of block with 0.25% bupivacaine,1–2 producing a denser block than many obstetric anesthesiologists today would use in nulliparous women in the first stage of labor. Even if current low-dose epidural analgesia resulted in an increase in duration of labor, it is unlikely to affect cost. Just as recovery room time, decreasing the duration of labor by 1 or even 2 h cannot decrease costs significantly unless nurse staffing is reduced as a result.

Epidural analgesia has been associated with maternal temperature increase.4 The contribution of placental inflammation versus impaired thermoregulation is not clear, with some evidence that fever, in the absence of histopathologic evidence of chorioamnionitis, is not significantly different between patients with or without epidural analgesia.5

As Dr. Chestnut notes in his introduction to the second edition of the textbook Obstetric Anesthesia: Principles and Practice,6 our obstetric colleagues have negotiated equitable reimbursement for their services in some states. Perhaps it is time for anesthesiologists to do the same.

Elizabeth Bell, M.D., M.P.H., Duke University Medical Center, Durham, North Carolina. bell0027@mc.duke.edu

References
3. American College of Obstetricians and Gynecologists: Vaginal delivery after a previous cesarean birth. ACOG Committee Opinion, October 1994

(Accepted for publication August 2, 2000.)

Can In Vitro Studies Be Reliably Extrapolated to In Vivo Behavior?

To the Editor.—Veien et al.1 address the issue of the release of tryptase from dispersed, cultured cutaneous mast cells. The stimulating agents used are known to elicit nonspecific, dose-dependent histamine liberation. The result is a corelease of histamine and tryptase, which the authors interpreted as degranulation.

There are, however, some methodologic issues that cloud the authors’ interpretation of their findings. The tryptase assay they used measures β tryptase, which is stored in the granules, and α prototryptase, which leaks from mast cells in normal subjects and in mastocytosis patients.2 Even then, there is only modest or nonsignificant release versus baseline. Because the total tryptase content of the preparation is not given, it is difficult to evaluate the significance of the work. Although their study may explain the mechanisms leading to false positive intradermal skin testing with concentrated solutions, the suggestion that these results can be extrapolated to patients administered parenteral drug injections does not seem justified by this set of experiments.

During nonimmunologic reactions, increases in plasma histamine concentrations are moderate and transient,3 whereas during anaphylaxis, increases are far larger and sustained.4 It logically follows from the study of Veien et al.1 that plasma tryptase concentration increases would parallel those of histamine and thus be moderate, if detectable at all, in chemically mediated reactions. Therefore, we are puzzled by the criticisms they make of our interpretation of an immunologic basis for severe reactions to contrast media.2 The remark that reactions occurring without previous exposure suggest nonimmunologic release is at odds with the literature because 17% of anaphylactic reactions to muscle-relaxing drugs occur in patients who had never been aneste-

*Dominique Laroche, M.D., Ph.D., Marie-Claire Luxenaire, M.D. *Centre Hospitalier Regional Universitaire, Caen, France. laroche-do@chu-caen.fr

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References


Plasma Tryptase in Nonimmunologic Reactions

To the Editor—We read with interest the elegant study by Veien et al.\(^2\) "Mechanisms of Nonimmunological Histamine and Tryptase Release from Human Cutaneous Mast Cells,"\(^3\) in which the authors examine the release of histamine and tryptase by nonimmunologic stimuli. This in vitro study represents an important addition to our understanding of nonimmunologic histamine release. As the authors noted, some of their findings disagree with those in our clinical study published previously in this journal.\(^2\) In that study, we demonstrated that rapid infusion of vancomycin was accompanied by significant increases in plasma histamine without increases in plasma tryptase concentration. The difference between the two studies is more than academic because clinicians may be able to use plasma tryptase to distinguish between immunologic and nonimmunologic reactions.

There are several possible reasons for the differences between the results of our clinical studies and the in vitro study presented by Veien et al.\(^3\) The most obvious explanation is the difficulty in extrapolating the results from infant foreskin mast cells to measurements in human plasma. As acknowledged by the authors, there is remarkable heterogeneity between mast cells of different tissues, with regard both to their susceptibility to release and to what is released. Cutaneous mast cells may not be a good model for generalized release,\(^5\) as may be mast cells. ANESTHESIOLOGY 2000; 92:1074–81
7. Lake CR, Ziegler MG: Effect of acute volume alterations on norepinephrine and dopamine-beta-hydroxyase (DBH) release were made more than two decades ago. Norepinephrine and DBH, which are contained in adren-ergic vesicles, are released in exocytosis. However, attempts to correlate plasma DBH concentrations with plasma norepinephrine concentrations have been largely unsuccessful.\(^4\) Concentrations of plasma catecholamines often correlate well with acute hemodynamic perturbations, but the plasma half-life of DBH, like tryptase, is several hours, and plasma DBH concentrations often may not be increased in short-term release. Given its long half-life, nonsustained chemically mediated release of tryptase would be expected to generate only small changes in plasma concentrations. On the other hand, sustained release, such as what may occur during anaphylactic reactions, might result in increased plasma tryptase. This explanation seems all the more plausible because increases in tryptase do not always occur, even in documented immunologic anaphylaxis.\(^5\)

Finally, the clinical studies cited as supporting evidence for the in vitro studies support our conclusions. The retrospective study by Fisher and Baldo\(^6\) shows that 125 of 150 patients (96%) with increased tryptase had immunologic evidence (immunoglobulin E antibodies), whereas 130 of 137 patients (95%) without tryptase increases did not. The conclusions of one article that proposes a possible immunologic origin of contrast reactions\(^7\) are reinterpreted by Veien et al.\(^1\) Aside from our study on vancomycin-induced release,\(^2\) the prospective, randomized, clinical trials that we and the authors have used previously to assess nonimmunologic histamine release have not been performed with tryptase.\(^8,9\)

The observations of Veien et al.\(^1\) on human foreskin mast cells contribute greatly to our understanding of the mechanisms of histamine release, but these in vitro observations should be translated into clinical practice with caution.

*Jonathan Moss, M.D., Ph.D., Cheryl Renz, M.D. *University of Chicago, Chicago, Illinois.

References

4. Lake CR, Ziegler MG: Effect of acute volume alterations on norepinephrine and dopamine-beta-hydroxyase (DBH) release were made more than two decades ago. Norepinephrine and DBH, which are contained in adren-ergic vesicles, are released in exocytosis. However, attempts to correlate plasma DBH concentrations with plasma norepinephrine concentrations have been largely unsuccessful.\(^4\) Concentrations of plasma catecholamines often correlate well with acute hemodynamic perturbations, but the plasma half-life of DBH, like tryptase, is several hours, and plasma DBH concentrations often may not be increased in short-term release. Given its long half-life, nonsustained chemically mediated release of tryptase would be expected to generate only small changes in plasma concentrations. On the other hand, sustained release, such as what may occur during anaphylactic reactions, might result in increased plasma tryptase. This explanation seems all the more plausible because increases in tryptase do not always occur, even in documented immunologic anaphylaxis.\(^5\)

(Accepted for publication August 7, 2000.)
In Reply.—We thank Drs. Renz and Moss for their interest in our manuscript describing the mechanism of nonimmunologic histamine and tryptase release from human cutaneous mast cells.2 They are correct in pointing out the vancomycin concentration differences between our in vitro study and their in vivo study. They should note, however, that when 1 g vancomycin is administered, the concentration “seen” by cutaneous mast cells during peripheral intravenous administration may be different and much higher than the mean plasma concentration measured at the end of the infusion. Additionally, we did not perform vancomycin dose–response studies; the dose we chose corresponded to the highest vancomycin concentration that the mast cells would possibly be exposed to during the intravenous infusion. Whether mast cells exposed to much lower concentrations of vancomycin would still release tryptase along with histamine has not been determined. Because tryptase is a preformed mediator stored along histamine in secretory granules of mast cells, mast cell degranulation, regardless of whether immunologic or nonimmunologic, would cause release of both mediators.3 Further, the reference cited acknowledges that direct histamine release from mast cells in vitro is associated with increased levels of mast cell tryptase, a finding that supports our own results.2 Moreover, even though the results of the Fisher et al.6 study show that there is a significant association between increased levels of tryptase and immunoglobulin E–mediated reactions, the authors conclude that increased levels of tryptase do not always distinguish between anaphylactoid and anaphylactic reactions.4

We also thank Drs. Laroche and Laxenaire for a careful review of our manuscript.2 Regarding their comments about the mast cell degranulation and tryptase assay, we would like to point out that, when mast cells release mediators during direct stimulation, the release reaction is called degranulation and can be observed biochemically and morphologically. The increases in histamine and tryptase concentrations that we measured in our chemically stimulated mast cell preparations resulted from the degranulation process. As for our tryptase determinations, we used a UniCap automated apparatus (UniCap, Pharmacia and Upjohn, Kalamazoo, MI) and the UniCap tryptase fluoroenzyme immunoassay (Pharmacia and Upjohn AB, Uppsala, Sweden), the same equipment and methodology used in a paper published by Laroche et al.1 The average amount of total tryptase released by our mast cell preparations was 135 μg/l, with a baseline release of 9.2 μg/ml. We cannot comment on the tryptase levels observed in patients studied by Laxenaire et al.1 because they used RIACT methodology (Pharmacia and Upjohn AB), and, according to the Pharmacia-Upjohn technical bulletin, tryptase levels differ between the two assays. We are in total agreement with the authors about the importance of being able to differentiate between the nonimmunologic and immunologic reactions, but we are still not sure whether increased levels of tryptase unequivocally confirm an immunologic-mediated event or can occur without immunologic activation. Only by performing more studies, both in vitro and in vivo, will we be able to make that distinction.

We also agree that anaphylaxis to muscle relaxants can occur in patients who have never been anesthetized before because of the complex cross-sensitization. We are confused by this statement and are not sure to what Drs. Laroche and Laxenaire are referring. The fact that one observes increased tryptase levels in radiocontrast reactions does not constitute proof of anaphylaxis. Figure 4 in the manuscript shows the level of specific immunoglobulin E against ioxithalamate or ioxaglate in patients with reactions to these materials compared with the level in control subjects.5 These authors were unable to show immunoglobulin E antibodies against ioxaglate, and, among the ioxithalamate patients, there were five patients with reactions, with one significant outlier in the data. Although the differences between the two groups are significant according to their statistical analysis, because of the small number of patients included in the analysis and a fairly large scatter of the data points, additional patients may have to be studied to show that the differences are real. There is a paucity of data supporting immunologic mechanisms for radiocontrast media reactions. Standard radiocontrast media solutions are extremely hyperosmolar (1,200–1,400 mOsm) and seem to have direct effects on mast cells and basophils. Although true anaphylaxis can occur with any molecule, multiple mechanisms seem to be responsible for radiocontrast media reactions. Finally, they note in their paper that human mast cells with no history of reactions to iodinated contrast materials release tryptase together with histamine in a dose-dependent fashion in vitro stimulation with contrast material.9 How do the results from the study of Stellato et al.10 differ from the results we have observed with our mast cells stimulated with vancomycin? Is it because the reaction caused by vancomycin has been thought of as chemically mediated? We realize that there are many more questions to be answered regarding the in vitro distinction between the nonimmunologically and chemically mediated versus immunoglobulin E–mediated reactions. The main purpose of our in vitro study was to try to elucidate the mechanisms of how molecules can produce direct mast cell activation—mechanisms that we noted to be through cellular signaling mechanisms. We believe our paper represents one more piece of the complex puzzle of anaphylaxis.

Jerrold H. Levy, M.D., Fania Szlam, M.M.S. *Emory University School of Medicine, Atlanta, Georgia.

References

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Anesthesiology 2001; 94:181


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Benefits of Parental Presence Outweigh Risks

To the Editor:—I agree with Professor Lerman in his recent editorial on parental presence at induction of anesthesia (PPIA) \(^1\) when he states that an evidence-based scientific approach is needed in examining this issue, but I disagree with some of the conclusions he draws from current research in this area.

Reviewing the literature on PPIA, three studies show a reduction of child anxiety at anesthesia induction with parental presence. \(^2\)–\(^4\) However, these were not all randomized trials, confounding factors existed, and the measures of anxiety used were not all validated. Two more recent randomized controlled trials show no benefit for children in the PPIA groups compared with controls; however, there was no increase in child anxiety in the PPIA groups. \(^5\)–\(^6\) The study by Kain et al. \(^7\) was randomized, excluded confounding factors, and used a validated measure of child anxiety—the Yale Preoperative Anxiety Scale. No significant difference in child anxiety was seen between the control group and the PPIA group. However, some subgroups of children benefited from PPIA. Anxiety measured by serum cortisol level was reduced in children older than 4 yr, children with calm parents, and shy, inhibited children.

I suggest a more positive view of parental presence is appropriate. It can be effective in alleviating the anxiety of some children. We need to examine how parental presence can be made more effective as an intervention instead of denying this useful resource. Reduced parental anxiety is associated with reduced child anxiety, \(^8\) whereas children accompanied by anxious parents are more anxious themselves. \(^9\) Preparation of parents and providing them with more information is useful in reducing their anxiety. \(^7\) So, studies examining the effect of parental preparation for PPIA on child anxiety would be interesting. Identifying anxious parents and relieving their anxiety may be important.

Study of the interaction between parent and child at anesthesia induction would be useful. Encouraging more involvement of the parent with use of distraction or by teaching coping methods has been shown to be beneficial in other medical settings. \(^8\)–\(^9\)

Distraction may be particularly useful for intravenous induction of anesthesia. Also, we should listen to parents because they are good predictors of their children’s distress at induction—certainly better predictors than anesthetists. \(^10\)

The risks of PPIA are discussed in the editorial. The potential for ‘stormy’ induction in young children (abstract). Br J Anaesth 1996; 76:589P

REFERENCES


In Reply:—I thank Dr. Watson for her comments about parental presence at induction of anesthesia (PPIA). Dr. Watson suggests that “a more positive view of parental presence” should be adopted. I disagree. I believe that all interventions should be evidence-based, and, at the present time, no studies indicate that all children benefit from PPIA. \(^7\) In contrast, midazolam is uniformly effective without regard to age, temperament, or the child’s or parent’s anxiety level. \(^1\) In a busy anesthetic practice, it is easy to understand why midazolam is preferred to PPIA. Dr. Watson also contends that we ought to determine how parental presence “can be made more effective.” I agree. All parents should be required to attend a seminar on induction of anesthesia by responsible physicians, and their role and the limitations of their participation in the induction should be explained. The parents should then be screened: Those who are likely to be positive influences on their children would be permitted to accompany their child, and those who would be negative influences would not be permitted. This is not the standard in most institutions, most likely because of the enormous expense and time that would be needed. It has been my experience that parents request to accompany their child to induction without any preparation for the events that may ensue. Regarding the issue of cardiac dysrythmias, Kataria et al. \(^4\) reported that arrhythmias occurred in 10% of parents during PPIA, with ventricular tachycardia developing in one parent. Finally, cultural, economic, and infrastructure issues are far more complex than alluded to by Dr. Watson. There are few multicultural nurses, few nurses who can leave a child at induction, few induction rooms, and limited resources to address PPIA.
programs in many institutions. I believe PPIA should be approached in the same manner as any new drug: Properly conducted studies must demonstrate its effectiveness and safety before it is released for widespread use by the public. Until that time, it should be a limited resource.

Jerrold Lerman, M.D., F.R.C.P.C., F.A.N.Z.C.A., Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada. lerman@anaes.sickkids.on.ca

References

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Clinical and Experimental Research in Anesthesiology in Europe at the Change of the Millennium

To the Editor—Academic activity in European countries has increased steadily in recent years. However, there is little data about the relative activities in the different nations. To explore this, we analyzed the Medline-indexed publications from 16 European countries appearing between 1965 and September 1999. We searched for all publications (exclusive of letters and case reports) that were attributed to departments of An(a)esthesia, An(a)esthesiology, or Anaesthesiologie. We also defined the total population and the number of medical schools in each of the 16 countries and used these values to construct two indexes. The first was the total number of publications from a country divided by the number of medical schools in that nation. The second was total publications per 10^6 population. The results are shown in table 1.

It can be seen easily that there are large variations in publication rates adjusted for either the total number of medical schools or population. Sweden, Denmark, and Austria lead the list when publications are adjusted for the number of schools, whereas Sweden, Finland, and Denmark lead when adjusted by population.

If publication rates are an accurate representation of the research productivity of the anesthesia community, these numbers indicate that there are major differences between different European countries; differences that are not related to the number of medical faculties or populations. It is tempting to argue that these differences reflect relative political and financial support for research in the specialties. However, a substantial amount of additional data would be needed to permit that hypothesis to be evaluated.

*Roland Hofbauer, M.D., Alan David Kaye, M.D., Ph.D., Bernhard Gmeiner, M.D., Ph.D., Franz X. Lackner, M.D., Michael Frass, M.D.
*University of Vienna, Vienna, Austria. roland.hofbauer@akh-wien.ac.at

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

Table 1. Population Number, Number of Medical Schools, Total Publications, Publications per Medical School, and Publications per 10^6 Population

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*Correspondence* Anesthesiology 2001; 94:183
To the Editor:—Various drugs have been administered inadvertently into the epidural space, sometimes resulting in serious neurologic sequelae. We present a case of inadvertent injection of cefazolin in the epidural space of a child during caudal block.

A 17-month-old, 12.1-kg boy presented for hypospadias repair. General anesthesia was induced. The child, spontaneously breathing through a size 2 laryngeal mask, was placed in the left decubitus position. A 22-gauge angiocatheter was inserted into the caudal space without technical difficulties. A test dose of 1 ml bupivacaine, 0.25%, with epinephrine, 1:200,000, was injected, with no change in heart rate. Then, a 10-ml syringe containing 8 ml cefazolin (100 mg/ml), which had been placed on the anesthesia cart, was used mistakenly in place of the 10-ml syringe containing the local anesthetic to be administered. Three milliliters were injected before it was realized that the label was that of cefazolin. Immediately, the syringe was removed, the local anesthetic syringe containing 0.2% ropivacaine with 2 μg/ml clonidine was connected, and, incrementally, 8 ml of this solution was injected into the epidural space. The patient did not show any change in heart rate or blood pressure during or after the injection. Anesthesia was induced with 0.5% isoflurane in a 1:2 mixture of oxygen-nitrous oxide, respectively. Immediately postoperatively, the patient was comfortable, with no signs of pain or evidence of neurologic dysfunction. The patient was admitted to the hospital for overnight observation. Six and 12 hours later, the patient was examined and found to be relatively comfortable, active, and neurologically intact. One week later, the parents were contacted; they reported no abnormal behavior or changes in the child’s habits.

Neither the cefazolin powder nor the 0.9% normal saline used as solvent had preservatives. A solution similar to that injected was checked and found to have a pH and an osmolarity of 4.77 and 522 mOsm/l, respectively.

Most of our knowledge of inadvertent drug injections in the epidural space comes from case reports. With regard to antibiotics, inadvertent epidural administration of gentamycin has been reported in an adult, with minor sequelae (back pain). As far as we know, cefazolin has not been reported in this context. In this case, after the inadvertent epidural injection of cefazolin, we proceeded with the epidural ropivacaine–clonidine mixture to dilute the concentration of cefazolin in the epidural space. By diluting the cefazolin, we hoped to lessen any potential chemical irritation or damage to nerve tissues the cefazolin may cause; a decision we admit was speculative. We also wanted to provide the patient with adequate postoperative analgesia. However, it is a possibility that the remaining effect of the local anesthetic postoperatively could have confused the diagnosis of potential neurologic injury, if it were to occur. In the absence of clinical trials, the question of what to do in such mishaps is not answered. However, this case report documents good outcome.

**To the Editor:**—The Cochrane Collaboration is an international not-for-profit organization that aims to help people make well-informed decisions about health care by preparing, maintaining, and promoting the accessibility of systematic reviews of the effects of healthcare interventions. The 51 collaborative review groups within the Cochrane Collaboration, each covering a specific area of health care, produce the main work of the collaboration: producing systematic reviews; publishing the results of these systematic reviews in the Cochrane Library and international journals; manually searching the literature for randomized, controlled trials and controlled clinical trials in field-specific journals; and maintaining a specialized register, which includes trials identified through manual searching and electronic searching of databases.

In autumn of 1997, a group of anesthesiologists at Bispebjerg University Hospital in Copenhagen, in cooperation with the Nordic Cochrane Center, began exploring the possibility of forming an anesthesia review group. At that time, anesthesiology was one of the few areas of medical practice not represented within the Cochrane Collaboration. The first preliminary meeting was held during the 6th Annual Meeting of the European Society of Anesthesiologists in 1998, and an international cooperation began. Further informational meetings were held during the Annual Meeting of the American Society of Anesthesiologists in Orlando in 1998 and at the 6th Cochrane Colloquium in Baltimore in 1998. The Cochrane Anaesthesia Review Group was registered within the Cochrane Collaboration in February 2000, with its editorial office based in the Department of Anesthesiology of Bispebjerg University Hospital. The editorial team is composed of anesthesiologists from Australia, Canada, Denmark, France, Hong Kong, New Zealand, Switzerland, the United Kingdom, and the United States. Additionally, there are approximately 300 international physicians and other healthcare providers who produce protocols and reviews, peer referee, and perform manual searches.

The scope of the Cochrane Anaesthesia Review Group encompasses anesthesia, perioperative medicine, postanaesthetic care, intensive care medicine, prehospital medicine, resuscitation, and emergency medicine. The current list of topics for systematic reviews represents clinical practice in relation to current, past, and potential interventions. The purpose of the Cochrane Anaesthesia Review Group is to produce systematic reviews, identify the effects of interventions in anesthesia, and help clinicians and others make well-informed decisions about these interventions. Current reviews and protocols being prepared by members of the Cochrane Anaesthesia Review Group are listed in table 1.
The Cochrane Anaesthesia Review Group welcomes all individuals with an interest in evidence-based medicine. Volunteers are needed to manually search journals, peer referee protocols and reviews before publication, assist with methodology and statistical analysis, and prepare systematic reviews. Further information about the Cochrane Anaesthesia Review Group is available at the Web site, www.cochrane-anaesthesia.suite.dk.

Ann M. Møller, M.D., Lisa W. Bismuth, M.Sc., Tom Pedersen, M.D., Ph.D. The Cochrane Anaesthesia Review Group, University of Copenhagen, Bispebjerg Hospital, Copenhagen, Denmark.
docotp@yahoo.com

References


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### Table 1. Reviews and Protocols

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<tr>
<th>Protocol</th>
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<td>Setrons for control of postoperative nausea and vomiting</td>
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* Protocol. † Review. ‡ Published in the Cochrane Library.