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Opiates, Intracranial Pressure, and Autoregulation

To the Editor:—We read with interest the recent article by de Nadal *et al.*,[1] 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[2] and believe that the work of de Nadal *et al.*[1] 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 ($AVDo_2$) 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 $AVDo_2$ measurements, and not with flow velocity measurements as well? Furthermore, during cerebral autoregulation testing, the authors corrected for change in arterial carbon dioxide tension ($Paco_2$) according to carbon dioxide reactivity, which is appropriate. However, the autoregulatory capacity is influenced by $Paco_2$, with hypocapnia improving it and hypercapnia impairing it. We assume the authors made an effort to control $Paco_2$, but it would be more informative if the authors would also tell us the actual $Paco_2$ 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 advance our understanding of pathophysiology and design better treatment regimens. The criteria of Enevoldsen and Jensen[3] are useful. However, such arbitrary classification can cause problems with interpretation of the current data. Impaired autoregulation is not the same as abolished autoregulation. Therefore, a patient with impaired autoregulation can mount a vasodilatory response to a decrease in blood pressure, albeit not sufficient to restore cerebral blood flow fully. To which group should such a patient be assigned? Therefore, it is not surprising to observe a lack of difference between the two groups with respect to ICP changes in response to opioid administration. When examined as a group (figs. 2A and B), both morphine and fentanyl patients had only a small decrease in MAP (3–4 mmHg) and a similar small increase in ICP. These results differ markedly in magnitude of MAP change (> 10 mmHg) from the observations of Werner *et al.*,[2] who administered 3 μg/kg sufentanil, and, therefore, leave open the question of whether the hypothesis was tested adequately. Given the heterogeneous magnitude of autoregulation preservation present in either group (autoregulating *versus* nonautoregulating patients) and the small effect of the opioids on MAP observed for the doses given, it remains plausible that there was insufficient challenge to discriminate between the two groups on the basis of ICP response. It is possible, however, that de Nadal *et al.*[1] have unmasked a subcomponent of the mechanistic basis of ICP responses to opioid administration. It can be speculated that, although the dose they administered was insufficient to challenge autoregulatory status, a coupled increase in blood flow attributable to cerebral activation by the drugs was seen.

We respectfully submit that the influence of opioids on cerebral hemodynamics is an important issue, and the paper by de Nadal *et al.* has contributed substantively to our understanding of this subject. However, the data presented do not rule out the hypothesis that major opioid effects on ICP are attributable to autoregulatory responses to concurrent reduction in MAP.

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References

1. de Nadal M, Munar F, Poca MA, Sahuquillo J, Garnacho A, Rossello J: Cerebral hemodynamic effects of morphine and fentanyl in patients with severe head injury: Absence of correlation to cerebral autoregulation. ANESTHESIOLOGY 2000; 92:11–9

2. Werner C, Kochs E, Bause H, Hoffman WE, Schulte am Esch J: Effects of sufentanil on cerebral hemodynamics and intracranial pressure in patients with brain injury. ANESTHESIOLOGY 1995; 83:721–6

3. Enevoldsen EM, Jensen FT: Autoregulation and CO_2 responses of cerebral blood flow in patients with acute severe head injury. J Neurosurg 1978; 48:689–707

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In Reply:—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.[1]

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.[2] 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 ($AVDo_2$) 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 ($Paco_2$) are easier to perform with use of this test than with use of TCD.

Focusing on the second issue, we completely agree with Lam and Warner that autoregulation capacity may be influenced by $Paco_2$. 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 $Paco_2$ in the

normoventilation range. The actual $Paco_2$ values during autoregulation testing in our study were (before and after inducing hypertension) 38 ± 4 and 39 ± 3 mmHg in the morphine group and 37 ± 3 and 38 ± 4 mmHg in the fentanyl group (mean ± SD). As shown in table 1, $Paco_2$ values remained unchanged after opiates were administered. The percentage change of $1/AVDo_2$ relative to the resting values was corrected for spontaneous changes in $Paco_2$ with use of the absolute CO_2 reactivity (CO_2R_{abs}), which was calculated as the change in $AVDo_2$ divided by the measured change in $Paco_2$ ($\Delta AVDo_2/\Delta Paco_2$).

The third issue addressed is our "arbitrary classification of autoregulatory pattern." Our method of interpreting autoregulation is based on experimental models, and we agree that it is arbitrary, as any other classification used before in clinical and experimental studies. However, contrary to Lam and Warner's opinion, we believe that taking ICP into consideration when testing autoregulation may help to clarify our results. If autoregulation is tested only through changes in CBF, some paradoxical observations, such as the false autoregulation phenomenon, can be observed, and patients may be classified wrongly as "preserved autoregulation." In the study referenced by Lam and Warner, Enevoldsen and Jensen[3] described false autoregulation (pseudoautoregulation) as an alteration of autoregulation in which the apparent maintenance on a constant CBF when increasing cerebral perfusion pressure is caused by an increase in brain tissue pressure. In these patients with impaired or abolished vasoconstrictory response to increased cerebral perfusion pressure, increasing MAP induces parallel changes in water filtration through the blood–brain barrier. Because of the compression of the cerebral microcirculation, these changes always induce an ICP increase with an unpredictable change in CBF. This fact makes interpretation of the results with only CBF measurements as a basis difficult, and, consequently, we believe that changes in both CBF and ICP must be taken into consideration when characterizing autoregulatory status. It is puzzling to observe some studies that classify patients with a constant CBF but with 10–15 mmHg increases in ICP (a relatively common phenomenon in the acute phase of severe head injuries) as "intact autoregulation." We agree that impaired autoregulation is not the same as abolished autoregulation, but it would be necessary to test autoregulation in a wide range of MAP (including hypotension) to distinguish one from the other, which 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.[4] 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.

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References

1. de Nadal M, Munar F, Poca MA, Sahuquillo J, Gamacho A, Rossello J: Cerebral hemodynamic effects of morphine and fentanyl in patients with severe head injury: Absence of correlation to cerebral autoregulation. ANESTHESIOLOGY 2000; 92:11–9
2. Mchedlishvili GI: Arterial Behavior and Blood Circulation in the Brain. Edited by Bevan JA. New York, Plenum Press, 1986
3. Enevoldsen EM, Jensen FT: Autoregulation and CO_2 responses of cerebral blood flow in patients with acute severe head injury. J Neurosurg 1978; 48:689–703
4. Armstead WM: Role of opioids in the physiologic and pathophysiologic control of the cerebral circulation. Proc Soc Exp Biol Med 1997; 214:210–21

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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[1] points out, the absolute cost of providing epidural labor analgesia, as detailed by Macario *et al.*[2] and Bell *et al.*,[3] 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 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, one would negotiate and increase the offered reimbursement rate.

Many of my colleagues view the labor-slowing and fever-inducing properties of epidural labor analgesia as trivial problems. I disagree strongly. If we do not fix these problems, a day may come when we are not invited to participate in labor analgesia. We owe it to our patients (and to ourselves) to make sure that that does not happen.

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References

1. Chestnut DH: How do we measure (the cost of) pain relief? ANESTHESIOLOGY 2000; 92:643–5
2. Macario A, Scibetta WC, Navarro J, Riley E: Analgesia for labor pain: A cost model. ANESTHESIOLOGY 2000; 92:841–50
3. Bell ED, Penning DH, Cousineau EF, White WD, Hartle AJ, Gilbert WC, Lubarsky DA: How much labor is in a labor epidural? Manpower cost and reimbursement for an obstetric analgesia service in a teaching institution. ANESTHESIOLOGY 2000; 92:851–8

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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.[1,2] 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 preloads 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 histopatholgic 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.

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References

1. Halpern SH, Leighton BL, Ohlsson A, Barrett JFR, Rice A: Effect of epidural vs parenteral opioid analgesia on the progress of labor: A meta-analysis. JAMA 1999; 280:2105–10
2. Howell CJ: Epidural versus non-epidural analgesia for pain relief in labour (Cochrane Review). The Cochrane Library. Oxford: Update Software, 2000, issue 1
3. American College of Obstetricians and Gynecologists: Vaginal delivery after a previous cesarean birth. ACOG Committee Opinion, October 1994
4. Camann WR, Hortuet LA, Hughes N, Bader AM, Datta S: Maternal temperature regulation during extradural analgesia for labor. Br J Anaesth 1991; 67: 565–8
5. Dashe JS, Rogers BB, McIntire DD, Levenko KJ: Epidural analgesia and intrapartum fever: Placental findings. Obstet Gynecol 1999; 93:341–4
6. Chestnut, DH: Obstetric Anesthesia: Principles and Practice, 2nd edition. St. Louis, Mosby, 1999, p xiii

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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-depending 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 protryptase, 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.[5] 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 anesthetized before.[6] Sensitization may result from exposure to other agents probably of related structure.

Although *in vitro* studies are necessary to understand the molecular— cellular mechanisms, extrapolation of *in vitro* studies to clinical syndromes has led to considerable confusion between nonimmunologic reactions and anaphylaxis. It should be emphasized that nonimmunologic reactions occur with high frequency, are dose-dependent, and may be prevented by slow infusion and premedication. Anaphylactic reactions are rare, are possibly more severe, and do not depend on dose. Premedication is of questionable effectiveness, and prevention requires total avoidance of the responsible agent. Therefore, it is of the utmost importance to differentiate between the two types of reactions to improve patient safety for subsequent procedures.

The current scientific knowledge can be summarized by two clinical studies, which present a very different set of conclusions than do the authors. First, there is the important study of anesthetic reactions by Fisher and Baldo,[7] who demonstrated that 125 of 130 patients with increased plasma tryptase had evidence of immunoglobulin E antibodies, whereas 130 of 137 patients without increased tryptase did not. Second, there is the study of rapid vancomycin infusion in volunteers by Renz *et al.*,[8] which showed marked increases in plasma histamine, without increase of tryptase concentrations. Therefore, in most cases, the measurement of tryptase within the first hours of a severe anesthetic reaction allows differentiation between immunologic and nonimmunologic events.

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References

1. Veien M, Szlam F, Holden JT, Yamagushi K, Denson DD, Levy JH: Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. ANESTHESIOLOGY 2000; 92:1074–81
2. Schwartz LB, Sakai K, Bradford TR, Ren S, Zweiman B, Worobec AS, Metcalfe DD: The a form of human tryptase is the predominant type present in blood at baseline in normal subjects and is elevated in those with systemic mastocytosis. J Clin Invest 1995; 96:2702–10
3. Doenicke A, Moss J, Lorenz W, Hoemecke R, Gottardis M: Are hypotension and rash after atracurium really caused by histamine release? Anesth Analg 1994; 78:967–72
4. Laroche D, Dubois F, Gérard JL, Lefrançois C, André B, Vergnaud MC, Dubus L, Bricard H: Radioimmunoassay for plasma histamine: A study of false positive and false negative values. Br J Anaesth 1995; 74:430–7
5. Laroche D, Aimone-Gastin I, Dubois F, Huet H, Gérard P, Vergnaud MC, Mouton-Faivre C, Guéant JL, Laxenaire MC, Bricard H: Mechanisms of severe, immediate reactions to iodinated contrast material. Radiology 1998; 209:183–90
6. Laxenaire MC, Working Group on Anaphylactoid Reactions during Anesthesia: Epidemiological survey of anaphylactoid reactions occurring during anesthesia: Fourth French Multicenter Survey (July 1994–December 1996) (French). Ann Fr Anesth Reanim 1999; 18:796–809
7. Fisher MM, Baldo BA: Mast cell tryptase in anaesthetic anaphylactoid reactions. Br J Anaesth 1998; 80:26–9
8. Renz CL, Laroche D, Thurn JD, Finn HA, Lynch JP, Thisted R, Moss J: Tryptase levels are not increased during vancomycin-induced anaphylactoid reactions. ANESTHESIOLOGY 1998; 89:620–5

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Plasma Tryptase in Nonimmunologic Reactions

To the Editor:—I read with interest the elegant study by Veien *et al.*,[1] "Mechanisms of Nonimmunological Histamine and Tryptase Release from Human Cutaneous Mast Cells," 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* studies presented by Veien *et al.*[1] 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,[3] as may be reflected by the somewhat higher than normal doses of releasing agents (10–1,000×) required in the infant foreskin preparation. In our vancomycin infusion studies, the mean peak plasma concentration was 37×10^{-6} M, while the mast cell preparation was exposed to 3×10^{-3} M vancomycin. Another explanation for the difference between results is that plasma concentrations of histamine and tryptase almost certainly reflect overflow from tissues rather than direct release into the circulation. Analogous observations regarding release of norepinephrine and dopamine-β-hydroxylase (DBH) release were made more than two decades ago. Norepinephrine and DBH, which are contained in adrenergic 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 130 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.

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References

1. Veien M, Szlam F, Holden JT, Yamaguchi K, Denson DD, Levy JH: Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. ANESTHESIOLOGY 2000; 92:1074–81
2. Renz C, Laroche D, Thurn J, Finn H, Lynch J, Thisted R, Moss J: Tryptase levels are not increased during vancomycin-induced anaphylactoid reactions. ANESTHESIOLOGY 1998; 89:620–5
3. Barrett KE, Pearce FL: Heterogeneity of mast cells, Histamine and Histamine Antagonists. Edited by Uvnäs B. Berlin, Springer-Verlag, 1991, p 93
4. Lake CR, Ziegler MG: Effect of acute volume alterations on norepinephrine and dopamine-beta-hydroxylase in normotensive and hypertensive subjects. Circulation 1978; 57:774–8
5. Laroche D, Vergnaud MC, Sillard B, Soufarapis H, Bricard H: Biochemical markers of anaphylactoid reactions to drugs. ANESTHESIOLOGY 1991; 75:945–9
6. Fisher MM, Baldo BA: Mast cell tryptase in anaesthetic anaphylactoid reactions. Br J Anaesth 1998; 80:26–9
7. Laroche D, Gastin-Aimone I, Dubois F, Huet H, Gerard P, Vergnaud MC, Mouton-Faivre C, Gueant JL, Laxenaire MC, Bricard H: Mechanism of severe, immediate reactions to iodinated contrast material. Radiology 1998; 209:183–90
8. Levy JH, Davis GK, Dugan J, Szlam F: Determination of the hemodynamics and histamine release of rocuronium (Org 9426) when administered in increased doses under N_2O/O_2-sufentanil anesthesia. Anesth Analg 1994; 78:318–21
9. Levy JH, Pitts M, Thanopoulos A, Szlam F, Bastian R, Kim J: The effects of rapacuronium on histamine release and hemodynamics in adult patients undergoing general anesthesia. Anesth Analg 1999; 89:290–5

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In Reply:—We thank Drs. Renz and Moss[1] 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,[4] a finding that supports our own results.[2] Moreover, even though the results of the Fisher *et al.*[4] 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[5] 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 133 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.*[5] 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 anesthestized 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 at *in vitro* stimulation with contrast material.[6] How do the results from the study of Stellato *et al.*[6] 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 vivo* 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 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.

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References

1. Renz CL, Laroche D, Thurn JD, Finn HA, Lynch JP, Thisted R, Moss J: Tryptase levels are not increased during vancomycin-induced anaphylactoid reactions. ANESTHESIOLOGY 1998; 89:620–5

2. Veien M, Szlam F, Holden JT, Yamaguchi K, Denson DD, Levy JH: Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. ANESTHESIOLOGY 2000; 92:1074–81

3. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T: Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. N Engl J Med 1987; 316:1622–6

4. Fisher MM, Baldo BA: Mast cell tryptase in anesthetic anaphylactoid reactions. Br J Anaesth 1998; 80:26–9

5. Laroche D, Aimone-Gastin I, Dubois F, Huet H, Eng PG, Vergnaud MC, Mouton-Faivre C, Gueant JL, Laxenaire MC, Bricard H: Mechanism of severe, immediate reactions to iodinated contrast material. Radiology 1998; 209:183–90

6. Stellato C, de Crescenzo G, Patella V, Mastronardi P, Mazzarella B, Marone G: Human basophil/mast cell releasability: XI. Heterogeneity of the effects of the contrast media on the mediator release. J Allergy Clin Immunol 1996; 97:838–50

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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.*[5] 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,[5] whereas children accompanied by anxious parents are more anxious themselves.[6] 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[10]—certainly better predictors than anesthetists.[11]

The risks of PPIA are discussed in the editorial. The potential for "serious cardiac dysrhythmias" of the parent is discussed without citation of evidence. PPIA has proved to be exceptionally safe, without major problems for the child or parent, in several studies.[2,3,5,12] In the literature, only one anecdotal report exists of a problem in which no harm resulted.[13] It seems that the editorial overstates the risks. The nurse who accompanies the parent and child can accompany the parent back to the ward after induction of anesthesia. Anxiety levels of anesthetists are not increased by PPIA, as demonstrated by Kain *et al.*[5]

Sedative premedication is effective in reducing child anxiety, but, in unpremedicated children, parental presence has a role and should not be discouraged. Further studies on methods of improving the effectiveness of parental presence are needed in this contentious area.

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References

1. Lerman J: Anxiolysis: By the parent or for the parent? ANESTHESIOLOGY 2000; 92:925–7
2. Schulman JL, Foley JM, Vernon DT, Allan D: A study of the effect of the mother's presence during anesthesia induction. Pediatrics 1967; 39:111–4
3. Hannallah RS, Rosales JK: Experience with parents' presence during anaesthesia induction in children. Can J Anaesth 1983; 30:286–9
4. Cameron JA, Bond MJ, Pointer SC: Reducing the anxiety of children undergoing surgery: Parental presence during anaesthetic induction. J Paed Child Health 1996; 32:51–6
5. Kain ZN, Mayes LC, Caramico LA, Silver D, Spieker M, Nygren MN, Anderson G, Rimar S: Parental presence during induction of anesthesia: A randomized controlled trial. ANESTHESIOLOGY 1996; 84:1060–7
6. Bevan JC, Johnston C, Haig MJ, Toussignant G, Lucy S, Kirnon V, Assimes IK, Carranza R: Preoperative parental anxiety predicts behavioural and emotional responses to induction of anaesthesia in children. Can J Anaesth 1990; 37:177–83
7. Cassady JF, Wysocki TT, Miller KM, Cancel DD, Izenberg N: Use of preanesthetic video for facilitation of parental education and anxiolysis before pediatric ambulatory surgery. Anesth Analg 1999; 88:246–50
8. Vessey JA, Carlson KL, McGill J: Use of distraction with children during an acute pain experience. Nurs Res 1994; 43:369–72
9. Blount RL, Bachanas PJ, Powers SW, Cotter MC, Franklin A, Chaplin W, Mayfield J, Henderson M, Blount SD: Training children to cope and parents to coach them during routine immunizations: Effects on child, parent and staff behaviors. Behavior Therapy 1992; 23:689–705
10. Lumley MA, Melamed BG, Abeles LA: Predicting children's presurgical anxiety and subsequent behavior changes. J Pediatr Psychol 1993; 18:481–97
11. Lyons B, Kirby F, Casey W: Parental or anaesthetist's ability to predict 'stormy' induction in young children (abstract). Br J Anaesth 1996; 76:589P
12. Gauderer MW, Lorig JL, Eastwood DW: Is there a place for parents in the operating room? J Pediatr Surg 1989; 24:705–7
13. Bowie JR: Parents in the operating room (letter)? ANESTHESIOLOGY 1993; 78:1192–3

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Anesthesiology 2001; 94:182–3

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.[1] In contrast, midazolam is uniformly effective without regard to age, temperament, or the child's or parent's anxiety level.[2] 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 dysrhythmias, Kataria *et al.*[3] 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 multilingual 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.

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References

1. Kain ZN, Mayes LC, Caramico LA, Silver D, Spleker M, Nygren MM, Anderson G, Rimar S: Parental presence during induction of anesthesia: A randomized controlled trial. ANESTHESIOLOGY 1996; 84:1060–7
2. Kain ZN, Mayes LC, Wang SM, Caramico LA, Hofstadter MB: Parental presence during induction of anesthesia *versus* sedative premedication: Which intervention is more effective? ANESTHESIOLOGY 1998; 89:1147–56
3. Kataria B, Christenson D, Montana J: (abstract). World Congress of Anesthesiologists, 1996, D820, p 456. Presented at: 11th World Congress of Anaesthesiologists; April 14–20, 1996; Sydney, Australia

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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 specialty. However, a substantial amount of additional data would be needed to permit that hypothesis to be evaluated.

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

Country	Population ($\times 10^6$)	Number of Medical Schools	Total Publications	Publications per Medical School	Publications per 10^6 Population
Germany	82.08	36	1605	45	20
England	58.97	29	248	9	4
Italy	56.78	25	457	18	8
France	58.81	23	617	27	10
Spain	39.13	10	168	17	4
Finland	5.15	8	797	100	155
The Netherlands	15.73	7	736	105	47
Belgium	10.17	7	578	83	57
Norway	4.42	7	245	35	55
Sweden	8.89	6	1491	249	168
Ireland	3.62	6	222	37	61
Poland	38.61	4	28	7	1
Switzerland	7.26	4	466	117	64
Denmark	5.33	4	726	182	136
Greece	10.33	3	79	26	8
Austria	8.13	3	478	159	59

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Inadvertent Caudal Epidural Injection of Cefazolin

To the Editor:—Various drugs have been administered inadvertently into the epidural space, sometimes resulting in serious neurologic sequelae.[1] 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 maintained 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).[2]

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.

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References

1. Shanker KB, Palkar NV, Nishkala R: Paraplegia following epidural potassium chloride. Anesthesia 1985; 40:45–7
2. Sigg TR, Leikin JB: Inadvertent epidural gentamycin administration. Ann Pharmacother 1999; 33:1123

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The Cochrane Anaesthesia Review Group

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.[1] 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, postanesthetic 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 anesthesiology, 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.

Support was provided by Bispebjerg University Hospital, Copenhagen, Denmark, The Copenhagen Hospital Corporation, Copenhagen, Denmark, and the National Board of Health-Danish Institute for Health Technology Assessment, Copenhagen, Denmark.

Table 1. Reviews and Protocols

Anesthesia for cardioversion*
Glutamine supplementation in critically ill adults*
Hydroxyethyl starch, 6%, for intraoperative fluid management in adults*
Inhaled nitric oxide for acute hypoxic respiratory failure in adults and children*†‡
Intraperitoneal local anesthetics for pain after laparoscopic cholecystectomy*
Lidocaine for spinal anesthesia*
Pharmacologic prevention of postoperative nausea and vomiting*‡
Premedication for anxiety in adult day surgery*†‡
Pulse oximetry for perioperative monitoring*‡
Regional anesthesia for prevention of postoperative mortality and major morbidity*
Rocuronium bromide *versus* succinylcholine for rapid sequence induction intubation*
Setrons for control of postoperative nausea and vomiting*

* Protocol. † Review. ‡ Published in the Cochrane Library.

The Cochrane Anaesthesia Review Group welcomes all individuals with an interest in evidence-based medicine.[2–3] 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.

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References

1. The Cochrane Collaboration: The Cochrane manual, The Cochrane Library. Oxford, Update Software, 2000, p 4
2. Greenhalgh T: How to read a paper: The basics of evidence based medicine. London, BMJ Publishing Group, 1997, pp 87–127
3. Sackett DL, Richardson WS, Rosenberg W, Haynes RB: Evidence-based Medicine: How to practice and teach EBM. Edinburgh, Churchill Livingstone, 2000, pp 2–17

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