

## Are "International" Medical Graduates Second-class Anesthesiologists?

*To the Editor:*—I read with keen interest the article published in the September 2001 issue of ANESTHESIOLOGY entitled "The Anesthesiologist in Critical Care Medicine,"<sup>1</sup> especially since I am currently enrolled in a critical care fellowship after having completed my anesthesiology residency. I agree for the most part with the positions of the authors, especially regarding the profound difference between the situation in the United States, where anesthesiologists have all but abandoned the field of critical care medicine, and that in Europe, where they are at the forefront of it.

However, I was appalled to see that the main criterion used by the authors to evaluate the success of a discipline, such as otorhinolaryngology, is the reduction in the number of "international" medical graduates. This hypocritical denomination aside (what was wrong with "foreign"?), I feel that in a country whose success stems in great part from diversity and in which discrimination is illegal, residency candidates should be evaluated on their abilities and their character, not based on where they attended medical school. Evidence of discrimination in resident recruitment has been found in other specialties.<sup>2,3</sup> I do not think that the education I received in a French medical school is in any way inferior to the one that students get in this country. If there are any objective data that show that "international" medical

graduates are not as good physicians as their American-educated counterparts or that the patients they treat have worse outcomes, more complications, longer lengths of stay, or higher expenditures, I would like to be made aware of it. Until such time, I feel that it is unfairly biased to consider that a specialty fares better or worse based on the number of "international" medical graduates entering residency programs.

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*In Reply:*—Two of the authors of the article are international medical graduates, as are many of the leaders of critical care medicine in the US. The ability or inability of a medical discipline to attract graduates of American medical schools is a well-established indicator of the relative health of that discipline. It is not, in any way, an indictment of the quality of international or foreign medicine or physicians who trained outside of the US.

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## The Distribution of the Probability of Survival and Its Impact on Hypothesis Testing in Randomized Clinical Trials

*To The Editor:*—We read with much interest the article of Riou *et al.*<sup>1</sup> The authors concluded that the bimodal distribution of probability of survival strongly impacts hypothesis testing in randomized trials by overestimating power.

We would like to point out that statistical power depends only on the average probability of survival for each of the groups,<sup>2</sup> not the distribution of the probability of survival (Ps), as the authors claim.

If we have understood the authors' presentation, it appears that the reported results are a direct consequence of the assumptions that are used to construct their models, *i.e.*, "if a drug is thought to increase Ps by 10%, when Ps was below 0.50, it was increased by 10% of Ps, and when Ps was greater or equal to 0.50, it was increased by 10% of 1 - Ps." Their model does not increase the mean Ps by a predictable amount. We illustrate the lack of dependence on a bimodal distribution with a simplified example (table 1) in which there are patients with

probability of survival of only 0.2, 0.6, and 0.8 of differing proportions and the treatment increases survival by 0.05 (*e.g.*, from 0.2 to 0.25).

In the left-hand example of table 1, the distribution has most of the patients with a 0.6 chance of survival, while the right-hand example has a bimodal distribution of patient survival with very few patients in the middle range. Yet, since both examples have the same mean Ps with and without treatment, the power is the same.

We agree that the probabilities of survival would vary greatly in any given sample of trauma patients, between patients who face the greatest probability of mortality or survival regardless of the intervention. The effect size is necessarily minimal at the extremes of the survival probability continuum and can be larger in the middle of the distribution.

Evaluating efficacy in a randomized clinical trial requires the appropriate patient population in which the effect of the intervention can be observed. However, once the appropriate population has been identified, the mean Ps will provide the correct sample size calculations, irrespective of the distribution of probabilities.

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**Table 1. Relationship between the Distribution of the Probability of Survival ( $P_s$ ) and the Mean Probability of Survival**

$P_s$	Proportion of Patients	$P_s'$	$P_s$	Proportion of Patients	$P_s'$
0.2	0.15	0.25	0.2	0.30	0.25
0.6	0.55	0.65	0.6	0.10	0.65
0.8	0.30	0.85	0.8	0.60	0.85
Mean	0.60	0.65	Mean	0.60	0.65

$P_s$  is the probability of survival in the untreated (control) group;  $P_s'$  is the probability of survival in the treated group.

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**In Reply:**—We thank Drs. Halim and McCulloch for their comment. They are correct in their calculation (table 1) but wrong in the use of this calculation. They made the hypothesis that the difference between groups (placebo and treated groups, for example) is a fixed proportion (here +10%), whatever the value of the probability of survival ( $P_s$ ) is. This assumption cannot be correct from a clinical point of view. Indeed, if we look for a group of patients with a very low  $P_s$  (*i.e.*, 0.01), the calculation from Drs. Halim and McCulloch suggests that the  $P_s$  could be 0.16 in the treated group. In the same manner, if the  $P_s$  is very high (*i.e.*, 0.99), what could be the  $P_s$  in the treated group—more than 100%? In these two situations, those are not drug effects, but miracles.

We must recognize that in our study,<sup>1</sup> we tested only one simple hypothesis, concerning the relationship between  $P_s$  in the treated group and  $P_s$  in the placebo group, and that several other types of relationships could be used. For example, one can test the hypothesis that the drug-related increase in  $P_s$  (*i.e.*, the drug effect) is more pronounced in the most severely injured patients (or the contrary). But, whatever the hypothesis used, it must be clinically relevant, and the one proposed by Drs. Halim and McCulloch is not.

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We must remember that several factors influence the number of patients to be included:  $\alpha$  risk,  $\beta$  risk, the difference expected between groups, and last, but not least, the value of mortality in the placebo group. Assuming an  $\alpha$  and  $\beta$  risks of 0.05 and a 50% decrease in mortality in the treatment group, we need more patients if the mortality in the placebo group is 5% ( $n = 3,154$ ) than if it is 50% ( $n = 106$ ). In trauma patients, as we demonstrated in our study,<sup>1</sup> the mean mortality does not represent anything because of the bimodal distribution.

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## Neurological Complications after Interscalene Brachial Plexus Blockade: What to Make of it?

**To the Editor:**—In the past few years, Dr. Alain Borgeat and his colleagues have acquired a justified reputation by publishing several pivotal studies on interscalene brachial plexus blockade (ISB). We read with great interest the article recently published by Borgeat *et al.*<sup>1</sup> evaluating the incidence of acute and nonacute complications associated with interscalene brachial plexus block for shoulder surgery. In this study, 14% of patients with ISB showed neurologic complications “apparently not related to surgery” on the 10th day after the block. These symptoms were still present in 7.8% of the cases at the 1-month follow-up. This represents an unprecedented high rate of neurologic complications related by “default” to ISB (since no other factors were discussed by the authors). Fanelli *et al.*<sup>2</sup> published a multicenter study (not cited by the authors) evaluating the incidence of neurologic complications following 4,000 peripheral nerve blocks performed with the multiple injection technique. In this study, the incidence of

neurologic complications observed after ISB at the 1-month follow-up visit was 4%, and all symptoms completely resolved within 3 months after surgery.

There is no doubt that minor neurologic complications most likely remain undiagnosed if a proper follow-up is not planned and performed; nonetheless, the definition of neurologic complications “apparently not related to surgery” deserves more consideration. Mitterschiffthaler *et al.*<sup>3</sup> reported two cases of brachial plexus injury caused by wrong positioning during surgery. Postoperative nerve injuries unrelated to regional anesthesia techniques have been reported following shoulder surgery even by our orthopedic colleagues.<sup>4</sup> The lack of details concerning the patient’s rehabilitation protocols also make it difficult to eliminate the role played by physical therapy. Thus, there are great differences in the duration of immobilization and the duration and intensity of the physical therapy protocols according to the type of surgery and for a given type of shoulder surgery among centers, and even more between the United States and Europe.

The unprecedented high number of electroneuromyographic examinations performed by the authors and the associated lack of any significant

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findings confirmed that these studies are mostly unrevealing in this situation. Furthermore, it is unlikely that the use of sensory criteria would be clinically acceptable to justify performing such examinations.

The authors should be congratulated for their efforts. However, the article by Borgeat *et al.*<sup>1</sup> further stresses the need for performing a multicenter and multinational prospective study specifically looking at peripheral nerve blocks and postoperative neurologic complications, taking into consideration the consequences of positioning, surgery, and physical therapy.

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*In Reply:*—We are very flattered by the interest showed by Drs. Casati and Chelly in our study dealing with interscalene block and shoulder surgery.<sup>1</sup> Drs. Casati and Chelly deplored that we did not discuss the various factors that could be responsible for the observed complications. Our title, “. . . Associated with Interscalene Block and Shoulder Surgery,” expresses the aim of the study, which is to assess the incidence of minor and major complications occurring in this clinical context, and not the causal factors. Fanelli *et al.*<sup>2</sup> conducted a remarkable investigation, but their results cannot be extrapolated to ours. Their methodology included different blocks, different approaches (?), different drugs with or without additives, the multiple injections technique (by the way, the supraclavicular nerve is not responsible for shoulder abduction), and different teams, and in their protocol, the complications were only one endpoint among others. On the contrary, in our study, we had a standardized procedure on all aspects, with complications being the only one endpoint. The way Fanelli *et al.*<sup>2</sup> assessed complications led us to believe that the incidence of “minor complications” was underestimated in this study. We noticed that the majority of these minor complications were only revealed by an extensive interview and clinical examination done at different times by one anesthetist and one surgeon separately. For these patients, paresthesias and dysesthesias were mostly trivial as compared to the problems associated with postoperative rehabilitation.

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## Interscalene Block-, Sedation-, Lateral Positioning-, and Hydralazine-induced Hypotension: Is It Really Prudent?

*To the Editor:*—It was with interest that we read the case report presented by Anil S. Ranawat *et al.*<sup>1</sup> in the November issue of ANESTHESIOLOGY. We would like to raise a number of points.

We understand that the author selected this anesthesia technique to decrease blood loss during the procedure and for postoperative pain management.

Although the vast majority of our orthopedic patients also benefit from the use of peripheral nerve blocks for anesthesia supplemented by sedation, we questioned the use of a hypotensive technique (mean arterial pressure of 55 mmHg) without any control of ventilation-perfusion parameters (ETCO<sub>2</sub> not monitored) in a patient with risk of intraoperative loss of a large volume of blood, especially in the lateral position.

In this moderately obese patient (95 kg, 1.70 m), an interscalene block that had induced a phrenic nerve block<sup>2</sup> and consequently an alteration in his respiratory function<sup>3</sup> combined with the lateral position and the use of sedation (100 µg/h fentanyl, 200 mg/h propofol) further increase the risk for perioperative respiratory failure.<sup>4</sup> Further-

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The performance of neurophysiologic examinations (ENMG) should, of course, not be routinely done in daily practice; however, in our study, ENMG has shown that minor complications (paresthesias, dysesthesias, etc.) are not associated with ENMG abnormalities—a point which was to date not clear in the literature—and most importantly that other specific pathologies might occur, which we have to think about after this type of surgery. Finally, we agree that multicenter studies are needed; they will be a good complement to a study like the one we conducted. If we know what we are doing, we may discover what we need.

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more, the patient positioning makes the management of the airway difficult in case of a required intubation.<sup>5</sup> It seems that in this specific situation, a peripheral nerve block combined with general anesthesia would be more appropriate.

It is also important to recognize that an infraclavicular block instead of the reported interscalene would have represented a better alternative because infraclavicular blocks are not associated with a block of the phrenic nerve and consequently do not affect pulmonary function to the same extent as an interscalene block.<sup>6</sup> Finally, it is unfortunate that the authors chose a single injection block and did not consider the placement of a perineural catheter for the management of pain postoperatively, despite numerous demonstrated benefits of such a technique,<sup>7</sup> since most of these patients experience moderate to severe pain well over 24 h.

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*In Reply:*— I appreciate the comments from Dr. Sciard *et al.* regarding alternative anesthetic approaches in this case, which deserve consideration. However, the notable aspect of this case and the motivation for reporting it was the fact that this was the first described case of induced hypotension in association with a brachial plexus block. In addition, we were impressed by how easy it was to induce and stabilize the hypotensive state during surgery without resorting to controlled

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ventilation and general anesthesia. This is probably due to a combination of a solid block, careful patient positioning, and intravenous propofol.

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## Anesthesia-induced Alterations in Plasma Tracer Concentrations May Have Relevance for Brain Imaging Studies

*To the Editor:*—We read with great interest the recent report by Gyulai *et al.*<sup>1</sup> regarding the ability of isoflurane to enhance the *in vivo* binding of <sup>11</sup>C-flumazenil to the GABA<sub>A</sub>-benzodiazepine receptors in the human brain. This work demonstrates the feasibility of using brain imaging technology to help bridge the gap in knowledge that exists between the *in vitro* and the *in vivo* worlds of anesthesia research. This effort complements our finding that propofol's *in vivo* regional cerebral metabolic depressant effects correlate well with the reported regional *ex vivo* receptor density data of human benzodiazepine binding sites.<sup>2</sup> In contrast, however, we also found that the regional cerebral metabolic depressant effects of isoflurane did not appear to correlate with the benzodiazepine receptor density data.<sup>2</sup> The present work by Gyulai *et al.* suggests that the regional cerebral metabolic depression caused by isoflurane may indeed involve the GABA receptor, but perhaps in a less regionally specific manner than that of propofol.

However, before accepting this idea, a technical issue relevant to the emerging field of brain imaging applied to anesthesia research needs consideration. An issue that may play a role in the results presented by Gyulai *et al.* is the anesthetic-induced alteration of the arterial plasma drug concentration-*versus*-time relationship in the minutes after rapid intravenous administration of the tracer (the front-end kinetics).<sup>3</sup> The experimental group in the study of Gyulai *et al.* was anesthetized with isoflurane, and the subjects' arterial blood pressures were maintained at control values by infusing phenylephrine. Isoflurane and phenylephrine, by the combined effect of depressing cardiac output, may have increased the fraction of the dose of tracer to which the brain was exposed.<sup>4</sup>

One measure of tissue drug exposure is the area under the arterial plasma concentration-*versus*-time curve (AUC) for the time during which the concentration of the drug remains above some threshold value. We have previously demonstrated that in dogs anesthetized with isoflurane (1.7 MAC), the AUC<sub>0-3min</sub> for antipyrine, a marker of lipophilic drug disposition, more than doubled compared to the same animals while awake.<sup>5</sup> Likewise, when awake dogs were treated with

an infusion of phenylephrine in a dose sufficient to double the baseline calculated systemic vascular resistance, the AUC<sub>0-3min</sub> increased by 75% relative to placebo-treated awake animals.<sup>6</sup> We discovered that the increased arterial concentrations of this lipophilic marker were due to a relative increase in the proportion of cardiac output not involved in the distribution of drug to peripheral tissues. The nondistributive blood flow acts as a "pharmacokinetic shunt." This pharmacokinetic shunt could have significantly increased the amount of tracer delivered to the brain in the isoflurane-phenylephrine condition in the study of Gyulai *et al.*, making it appear as if the isoflurane had done something in the brain to increase tracer binding.

Gyulai *et al.* did, however, report regional differences in apparent binding and that "no significant differences were observed in nonreceptor ligand binding between the two experimental conditions in either experimental group. This would indicate that the observed changes in binding were not confounded by altered ligand delivery."<sup>1</sup> Nevertheless, perhaps the authors could have included a control condition in which a few subjects would have received only a phenylephrine infusion. The increased nondistributive blood flow caused by phenylephrine results in an increase in AUC similar to that seen with isoflurane.<sup>6</sup> Thus, if such an active control experiment were to reveal increased tracer binding relative to the saline-treated controls, then perhaps one might conclude that some of the published isoflurane effect should be attributed to an anesthetic-induced change in tracer kinetics, rather than to a central GABAergic effect of isoflurane itself.

In any event, the work by Gyulai *et al.* provides further evidence that functional brain imaging technology has a role to play in helping us elucidate mechanisms of anesthetic action, and we suggest that some of the work left to be done might involve obtaining a better understanding of how our anesthetic agents interact with the techniques being used to study them.

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*In Reply:*—We appreciate the interest and comments of Alkire *et al.* regarding our human GABA<sub>A</sub>-receptor ligand binding data.<sup>1</sup> We agree that anesthetics, such as isoflurane, have the potential to confound <sup>11</sup>C-flumazenil ligand binding data by various mechanisms, such as alteration of regional cerebral blood flow (rCBF), ligand metabolism, or unmetabolized ligand binding in the plasma.

Although Alkire *et al.* raise only one of these confounders, it is worth discussing all of them to illustrate the systematic strategy employed to preserve the validity of the data in our article.<sup>1</sup> The untoward effect of rCBF changes is adequately addressed in our study by ruling out any correlation between blood flow and ligand binding changes in agreement with previous studies that demonstrated the stability of the binding parameter, distribution volume ratio (DV<sub>RATIO</sub>), under such circumstances.<sup>2</sup> The second potential confounder is related to a change in ligand concentration in the plasma that in turn could result in an error in the calculation of DV<sub>RATIO</sub> if it remains unaccounted for in the computation process. Specifically, as it is raised by Alkire *et al.*, the measure of brain tissue drug exposure, expressed as the area under the arterial plasma concentration-versus-time curve (AUC), could be changed by the combined administration of isoflurane and phenylephrine.<sup>3,4</sup> This would result from a decrease in the early redistribution of the radioligand increasing its plasma concentration and brain tissue exposure, and that in turn would lead to an overestimation of receptor-specific ligand binding. To prevent this, as described in detail in our article,<sup>1</sup> the time course of total <sup>11</sup>C-flumazenil concentration was determined in the plasma in each experimental condition obtaining 20 arterial blood samples during the initial 2 min of the study and 20 more samples over the remainder of the 90-min time frame of the study. Furthermore, to account for potentially altered ligand metabolism during the isoflurane conditions, <sup>11</sup>C-flumazenil metabolism was monitored in the plasma in each experimental condition by quantifying the time course of unmetabolized parent compound concentration in arterial blood samples obtained at 5, 10, 15, 45, and 75 min after injection. Receptor-specific <sup>11</sup>C-flumazenil binding in turn, expressed as DV<sub>RATIO</sub>, was computed using these measured values. Therefore, any change in available ligand concentration, or brain tissue exposure to the ligand, in the presence of isoflurane and phenylephrine was eliminated as a confounder of receptor-specific <sup>11</sup>C-flumazenil binding.

Although the aforementioned approach adequately addresses the concerns of Alkire *et al.*, to eliminate the third potential confounder, however, *i.e.*, altered unmetabolized ligand binding in the plasma, we

also needed to measure nonreceptor binding in our experiments. This was necessary based on the well-established experimental evidence showing that nonreceptor ligand binding sites represent a nonsaturable compartment where the binding of the radioligand is linearly increasing with its plasma concentration.<sup>5</sup> It follows that nonreceptor binding serves as a cumulative index of brain tissue ligand exposure. As shown in table 2 of our article,<sup>1</sup> however, no significant differences were observed in nonreceptor ligand binding during the isoflurane conditions. This clearly indicates that the detected changes in binding were not due to altered unmetabolized ligand binding or altered ligand concentration in the plasma due to any mechanism, including the one proposed by Alkire *et al.*

Taken together, it appears that the employed strategies of measuring total and unmetabolized plasma concentrations of <sup>11</sup>C-flumazenil as well as nonreceptor ligand binding in each experimental condition provide adequate protection against confounders, such as anesthesia-induced alterations in plasma tracer concentrations, in the measurement of <sup>11</sup>C-flumazenil binding, eliminating the need for further validation experiments.

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Taken together, it appears that the employed strategies of measuring total and unmetabolized plasma concentrations of <sup>11</sup>C-flumazenil as well as nonreceptor ligand binding in each experimental condition provide adequate protection against confounders, such as anesthesia-induced alterations in plasma tracer concentrations, in the measurement of <sup>11</sup>C-flumazenil binding, eliminating the need for further validation experiments.

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## Combined Spinal-Epidural *versus* Epidural Labor Analgesia on Progress and Outcome of Labor

*To the Editor:*—We read with interest the article by Norris *et al.*,<sup>1</sup> which compared combined spinal-epidural (CSE) to epidural analgesia. We congratulate the authors in revalidating the safety and low complication rates of these techniques in a large group of mixed-parity parturients; however, we differ in our interpretation of the impact of these techniques on the progress of labor. In our earlier report,<sup>2</sup> we observed significantly faster initial cervical dilation and shorter times from analgesia induction to full cervical dilation in nulliparous women randomized to receive CSE *versus* epidural analgesia. Norris *et al.* interpret our findings as having “arisen by chance alone.” We believe this is unlikely given the statistical analysis we reported. CSE analgesia was associated with significantly faster time from analgesia initiation to full cervical dilation ( $P = 0.02$ ) and rates of initial cervical dilation ( $P = 0.0013$ ); the strength of these associations severely limits the possibility of chance being a major factor.

Instead, we suggest that our conflicting outcomes are the result of subtle but important differences. Parturients in the Norris study had analgesia initiated at a greater cervical dilation ( $4.0-4.5 \pm 2$  cm) than in our study ( $3 \pm 1$  cm), and as noted in a number of investigations, including the seminal work by Friedman,<sup>3</sup> advanced labor alone is associated with faster dilation. This underlying dilation rate may have minimized the impact of analgesic technique. In addition, obstetric management of labor, including using oxytocin for induction and assisting membrane rupture, which were not reported by Norris, may play significant roles in the progress and outcome of labor.<sup>4</sup>

The medications used *via* the techniques also differed in a number of ways. Norris *et al.* allowed clinicians the ability to determine and provide different medication regimens based on a subjective diagnosis of “early” *versus* “advanced” labor, and epidural lidocaine was used, even in the CSE groups, for initiation of the analgesia. Moreover, epidural maintenance infusions were initiated in all groups immediately following the technique placement. By contrast, our groups received a single, standardized regimen based on the technique se-

lected; used bupivacaine as the sole local anesthetic; and in our CSE group, received epidural medications, including the maintenance infusion, only when additional analgesia was requested. We recognize the techniques as employed by Norris *et al.* are popular, but the impact of such variations on progress of labor remains unknown. Since alterations in maternal catecholamines may be an important mechanism by which central neuraxial analgesia modulates uterine activity,<sup>5,6</sup> these variations may play a significant role.

The effect of central neuraxial analgesia on the progress and outcome of labor remains controversial, and we commend Norris *et al.* for adding information to this discussion. However, we stand by the results of our previous study and encourage future investigation into the subtleties of patient selection, obstetric management, and anesthetic technique that may account for these differences.

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*In Reply:*—We are gratified by the interest Drs. Tsen and Segal have shown in our study comparing epidural and combined spinal-epidural labor analgesia.<sup>1</sup> Unlike in their earlier study,<sup>2</sup> we found no shortening of the first stage of labor associated with the combined spinal-epidural technique. In their letter, Drs. Tsen and Segal correctly point out that differences in obstetric and anesthetic management could account for their result. Our study was designed to minimize the differences between these two techniques. Hence, all patients received the same drugs (sufentanil and bupivacaine), all patients received the same dose of sufentanil at induction (10  $\mu$ g), and all patients had an identical epidural infusion started immediately after induction of analgesia. Under these conditions, the durations of the first and second stages of labor and the methods of delivery were identical among both parous and nulliparous women allocated to receive either anesthetic technique. We found the same results when we included only protocol-compliant patients in our analysis.

While the impact of epidural analgesia on the progress and outcome of labor remains the source of controversy,<sup>3</sup> there is no evidence that

choosing between epidural or intrathecal injection of small doses of opioids and local anesthetics for induction of analgesia has any clinically significant impact on the overall duration or outcome of labor.<sup>4</sup>

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## Multiple Estimates of EC<sub>50</sub>

*To the Editor:*—I read with great interest the report by Bergeron *et al.*<sup>1</sup> on the concentration–effect relationship of cisatracurium. One of the findings of the study is the dependence of EC<sub>50</sub> (the concentration of cisatracurium in the effect compartment at half-maximal neuromuscular block) on the bolus dose of cisatracurium. This finding contradicts basic pharmacologic principles. Nondepolarizing muscle relaxants produce neuromuscular block (NMB) by binding to the postsynaptic receptors at the motor end plates. Increasing concentrations of muscle relaxants produce increasing levels of NMB, and there is only one set of concentration–NMB data pairs for a specific muscle and a given muscle relaxant. Therefore, only one concentration corresponds to the half-maximal NMB. However, the authors present several estimates of EC<sub>50</sub>, each as a function of the dose and the method of analysis. Multiple estimates of EC<sub>50</sub> might be due to the experimental design or to the methods of analysis. First, multiple estimates might be due to a complete NMB observed by the investigators with large doses of cisatracurium (1.5 × ED<sub>95</sub> to 6 × ED<sub>95</sub>). A complete NMB is compatible with any concentration of cisatracurium in the effect compartment that is higher than the concentration just sufficient to produce 100% NMB. Since the dependency of NMB on the muscle relaxant concentration is the prerequisite for pharmacodynamic simulations, this prerequisite was not fulfilled in the study. Alternatively, the methods of analysis might not be adequate. Since the pharmacokinetic parameters were dose independent, one has to question the methods of obtaining the estimates of pharmacodynamic parameters. If these provide several

(“statistically different”) estimates for the conceptually single value of EC<sub>50</sub>, then the pharmacodynamic methods might not be appropriate. That multiple estimates of EC<sub>50</sub> were reported previously for vecuronium<sup>2</sup> might be due to the use of identical pharmacodynamic methods; it constitutes neither the proof that the methods are correct nor that the estimates represent real values. To paraphrase, if three methods of determination of sodium in plasma yield three estimates of the sodium concentration, the methods should be questioned before accepting the finding that sodium is present in plasma in three concentrations. Similarly, if the pharmacodynamic methods yield different estimates of EC<sub>50</sub>, the results contradict the accepted pharmacologic principles and need to be reexamined.

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*In Reply:*—We would like to thank Dr. Nigrovic for his interest in our article. We fully agree that the very high doses of muscle relaxant used in dose-ranging studies may not be suitable for deriving EC<sub>50</sub> estimates. This was fully discussed and acknowledged in our report. We are not proposing multiple values for the EC<sub>50</sub> but are reporting a dose dependency of the EC<sub>50</sub> estimates. In our opinion, the example proposed by Dr. Nigrovic does not fully account for the multiplicity of factors involved. Unlike sodium concentrations, effect compartment

concentrations are not measured but derived mathematically by combining the time courses of plasma concentration and effect. This complicates the interpretation and deserves further studies.

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## Pneumatic Compression Boots, Lithotomy Stirrups, and Lower Limb Compartment Syndrome

*To the Editor:*—We thank Pfeffer *et al.*<sup>1</sup> for their excellent article on the effect of leg stirrups and intermittent pneumatic compression boots on calf compartment pressures. We wish to raise some points regarding compartment syndrome in association with the lithotomy position.

The results clearly demonstrate that in awake, young volunteers, the weight of the lower limb in generic knee supports causes a rise in calf compartment pressure. The Allen Medical Stirrup system does appear to distribute the weight of the lower limb away from the calf muscles and limit the rise in compartment pressure and, by implication, would reduce the incidence of compartment syndrome. However, the incidence of compartment syndrome is probably very low, and to demonstrate an actual reduction in the incidence of lower limb compartment syndrome would require large numbers of patients.

The individuals at risk from compartment syndrome are frequently elderly and anesthetized and remain in the lithotomy position with the

addition of Trendelenburg for several hours.<sup>2</sup> The study group was in the lithotomy position for 30 min only. It would be helpful, therefore, to repeat the study in subjects retained in lithotomy for 4 h. However, awake subjects tend to move their legs within the stirrups to prevent discomfort and maintain circulation to the lower limb. Anesthetized patients having surgery in the lithotomy position for several hours are a better model. In a recent study<sup>3</sup> of surgical patients having surgery in which both the Allen stirrups and pneumatic compression boots were used, the authors demonstrated a significant rise in lower limb compartment pressure, at variance to the volunteer group of Pfeffer *et al.*

The addition of the Trendelenburg position has been shown to increase further the compartment pressure compared with the lithotomy position alone.<sup>3</sup> Would Pfeffer *et al.* consider repeating the study and observing the impact of Trendelenburg position in their subjects?

A rise in compartment pressure may not be the only factor that leads to lower limb compartment syndrome. It has been estimated that the

fall in lower limb blood pressure is 2 mmHg for every vertical inch in height of the leg above the heart. The actual fall in blood pressure may be more or less than predicted.<sup>4</sup> The presence of peripheral vascular disease, intraoperative epidural analgesia, general anesthesia, and deliberate hypotension may further compromise the lower limb blood flow. Thus, while Pfeffer *et al.* demonstrated a fall in compartment pressure with the use of pneumatic compression boots, pneumatic compression boots may impair peripheral circulation. If compromise of lower limb blood flow is the initiating event that leads to the development of compartment syndrome, then pneumatic compression boots may only increase the risk of compartment syndrome developing. Repeated cycling of a noninvasive blood pressure cuff has been reported to lead to compartment syndrome of the arm,<sup>5</sup> and other investigators have considered that pneumatic compression boots may have a role in the development of compartment syndrome. Without data from surgical patients measuring lower limb blood pressure and compartment pressure, it would be premature to conclude that pneumatic compression boots minimize the risk of developing lower limb compartment syndrome.

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*In Reply:*—We are grateful to Drs. Turnbull and Mills for noting a number of factors to consider when discussing the issue of perioperative compartment syndrome that is not associated with obvious etiologic factors, such as thromboembolic or traumatic arterial or venous occlusions. This problem is indeed quite rare.<sup>1</sup> The combined rarity of the event and the multiple, potential contributing factors make it very difficult to draw conclusions about etiologic factors. Therefore, we believe it is best to perform studies to elucidate isolated factors before drawing any comprehensive conclusions.

Our study specifically focused on the effects of a sequential pneumatic compression device on pressures in the tibialis anterior muscle compartment of awake volunteers in the lithotomy position.<sup>2</sup> We found that the use of the compression device decreased intracompartmental pressures, making no comment about its effects on intracompartmental blood flow. Yes, Chase *et al.*<sup>3</sup> have very nicely shown that anterior leg compartment pressures increase when anesthetized patients are placed in the 45° lithotomy position with consistent use of Allen supports and sequential compression devices, especially for prolonged periods. Their study, however, does not address our question about the effects of the compression device on intracompartmental pressures and is irrelevant to our study.

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Lower extremity arterial and venous blood flow and many other factors likely affect perfusion and oxygenation of the muscles of the leg compartments. Therefore, we agree with Drs. Turnbull and Mills that it would be premature to conclude that sequential pneumatic compression devices minimize the risk of developing lower extremity compartment syndrome. However, these devices appear to decrease pressures in the anterior tibialis muscle compartment, a finding that contrasts with common (and unproved) wisdom.

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## Upon What Is Such a Claim Founded?

*To the Editor:*—I read with interest the report by Hatakorian *et al.*<sup>1</sup> on spinal anesthesia at the cervicothoracic level. I have heard many label this a dangerous practice, along with thoracic epidural anesthesia, because of the danger of spinal cord damage. As yet, I have been unable to find an original reference source upon which such a claim is founded, despite the evidently common practice of thoracic and cervical spinal anesthesia in the early part of the 20th century, as described by Jonnesco,<sup>2</sup> Koster,<sup>3,4</sup> Wright,<sup>5</sup> and others.

In their case report, Hatakorian *et al.*<sup>1</sup> state that spinal anesthesia at the cervicothoracic level "is, and must remain, an exceptional procedure," but fail to reference that claim, and the journal editors let it stand without citation. I would be gratified if the authors would be able to cite original work (*i.e.*, not some expert reviewer's opinion) showing the practice, when carefully performed (as by Hatakorian *et al.*<sup>1</sup>),

to be routinely contraindicated, thus bringing this popular notion up to at least some minimum level of evidenced-based medicine.

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*In Reply:*—We thank Dr. Stemp for his interest and for providing relevant references to an old literature that is not easily accessible. The cautionary statement alluded to by Dr. Stemp was added at the request of the Editor-in-Chief. We were, and still are, in agreement with the statement, even if not supported by a reference. It may well be, however, that high spinal anesthesia combined with modern monitoring tools could prove highly beneficial for selected patients. We cer-

tainly never had any intention of discouraging prudent inquiries on this topic.

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## Arrhythmia Risk of Antiemetic Agents

*To the Editor:*—The recent strengthening of the US Food and Drug Administration (FDA) warning\* on the proarrhythmic effects of droperidol follows 100 or so reported cases of droperidol-related arrhythmias. As clinicians implement the advised restrictions on use of droperidol,† increased use of the 5-HT<sub>3</sub> serotonin antagonists for management of postoperative nausea and vomiting (PONV) can be expected. Practitioners may be unaware that the 5-HT<sub>3</sub> antagonists are among a large group of drugs that can also prolong the QT interval and may theoretically contribute to the development of torsades de pointes.<sup>1</sup>

Although there appear to be no published clinical reports of ventricular tachycardia directly associated with 5-HT<sub>3</sub> antagonists, current prescribing information for dolasetron (Anzemet®; Aventis Pharmaceuticals, Kansas City, MO)<sup>2</sup> includes a specific warning about the potential for QT interval prolongation and serious arrhythmia in at-risk patients. QT prolongation is thought to be due to hydrodolasetron, the active metabolite of dolasetron, and has been observed in healthy volunteers and in controlled clinical trials.<sup>3</sup> The magnitude and frequency of the electrocardiographic changes increases with dose and may last as long as 24 h. The product insert also mentions three reported cardiac events, one fatal, in patients given doses of 100–200 mg, although none was confirmed as torsades.<sup>2</sup>

The prescribing information for ondansetron<sup>3</sup> (Zofran®; GlaxoSmithKline, Research Triangle Park, NC) does not contain a similar warning, although there are case reports of arrhythmias that occurred when ondansetron was combined with metoclopramide.<sup>4</sup>

The electrophysiological mechanisms responsible for drug-induced torsades de pointes are not completely understood. Potent block of the rapid component of the delayed rectifier potassium current by droperidol probably underlies QT prolongation observed in patients treated at therapeutic plasma concentrations (10–400 nM) of the drug.<sup>5</sup> 5-HT<sub>3</sub> antagonists have been shown to block human cardiac Na<sup>+</sup> channels,<sup>6</sup> and this may lead to clinically relevant Na<sup>+</sup> channel blockade, espe-

cially when high heart rates or depolarized/ischemic tissue is present.<sup>6</sup> Na<sup>+</sup> channel blockade is associated with QRS widening. Ondansetron possesses submicromolar affinity for the HERG K<sup>+</sup> channel, which may cause prolongation of repolarization. However, none of the 5-HT<sub>3</sub> antagonists tested produces greater than 30% block of the slow delayed rectifier K<sup>+</sup> channel thought to be particularly important in the genesis of torsades de pointes.<sup>6</sup>

The potential for serious adverse events during perioperative use of antiemetic agents must be balanced against their benefit. Only two FDA-reported events occurred after administration of low doses (≤1 mg) of droperidol, and although droperidol has definite effects on prolongation of the QTc interval, extensive clinical experience suggests a rather small incidence of serious arrhythmia<sup>7</sup> with prophylaxis or treatment of PONV. Compared to the extensive clinical and laboratory experience with droperidol, relatively little is known about the arrhythmia risk of 5-HT<sub>3</sub> antagonists. There is a lack of comparative data on the frequency of adverse cardiac events for droperidol on the one hand and the 5-HT<sub>3</sub> antagonists on the other. Unfortunately, in the absence of such data, the risk-benefit ratio is hard to assess, and the decision to restrict the prescribing of useful antiemetic agents is a difficult one.

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\* <http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01123.html>. Accessed December 5, 2001

† <http://www.fda.gov/medwatch/SAFETY/2001/inapsine.htm>. Accessed December 6, 2001

## FDA "Black Box" Warning Regarding Use of Droperidol for Postoperative Nausea and Vomiting: Is It Justified?

*To the Editor:*—On December 5, 2001, the US Food and Drug Administration (FDA) issued a new "black box" warning on droperidol (Akorn Pharmaceuticals, Buffalo Grove, IL), a popular antiemetic for the treatment and/or prevention of postoperative nausea and vomiting (PONV).<sup>\*</sup> Droperidol previously carried a warning regarding the potential for sudden cardiac death at high doses (> 25 mg) in psychiatric patients. The revised warning suggests that even low doses of droperidol should only be used when other "first-line" drugs fail. Unfortunately, this situation places the practicing anesthesiologist in a real dilemma<sup>1</sup> as there is now a significant difference between standard clinical practice and the package insert recommendation for this commonly used antiemetic drug.

Droperidol has been used for the management of PONV for over 30 yr. Intravenous doses of 0.625–1.25 mg have been widely accepted as a first-line therapy for the prophylaxis and treatment of PONV.<sup>2,3</sup> In a recent market survey, droperidol constituted over 30% of the antiemetic market share in the US, with over 25 million units sold in 2000. Of the 30 million surgical procedures performed each year in the US, approximately 30% of these patients will develop PONV. Patients would rather experience pain than emesis,<sup>4</sup> and they are willing to pay out of pocket for an effective antiemetic.<sup>5,6</sup>

Several large randomized controlled trials have demonstrated that droperidol is as safe and effective as ondansetron in adults.<sup>6,7</sup> The so-called number-to-treat for prevention of PONV is 5 to 6 for both drugs.<sup>8,9</sup> In a large, prospective, placebo-controlled study sponsored by the manufacturer of ondansetron (Zofran<sup>®</sup>; Glaxo Smith Kline, Research Triangle Park, NC), 2000 patients were randomized to receive 0.625 or 1.25 mg droperidol or 4 mg ondansetron intravenously for antiemetic prophylaxis.<sup>7</sup> There were no differences in the incidences of PONV (although droperidol was more efficacious in preventing nausea). More importantly, there were no significant differences in their side effect profiles. These findings have been confirmed in a meta-analysis of 76 trials, which included 5,351 patients receiving 24 different droperidol regimens.<sup>8</sup> In cost-effectiveness analyses,<sup>6,10</sup> 0.625–1.25 mg droperidol was found to be more cost effective than 4 mg ondansetron for the prevention of PONV (due to droperidol's lower acquisition cost). The costs to gain an additional PONV-free patient were \$149, \$3.4, and \$2.3 for 4 mg ondansetron, 0.625 mg droperidol, and 1.25 mg droperidol, respectively.<sup>10</sup>

The revised black box warning was apparently based on nine case reports in which cardiac arrest was alleged to be caused by low-dose droperidol administration during the perioperative period. However, the details of these cases were not available for us to determine whether there was a direct cause-and-effect relationship. Based on these anecdotal reports, the FDA has recommended that *all* elective surgery patients should undergo 12-lead electrocardiographic monitoring prior to administration of droperidol to determine whether a prolonged QTc interval is present, and to continue electrocardiographic monitoring for 2 to 3 h after its administration. Since low-dose droperidol is most commonly used in outpatients undergoing ambulatory surgery, these recommendations are totally impractical and unnecessarily costly to the patients and the healthcare system.

Of note, there has not been a single case report in a peer-reviewed medical journal in which droperidol in doses used for the management of PONV has been associated with QTc prolongation, arrhythmias, or cardiac

arrest. In fact, a study comparing hyoscine (scopolamine) and droperidol when administered under halothane general anesthesia found that significantly fewer patients in the droperidol group developed arrhythmias.<sup>11</sup>

Following a safety concern raised by the UK Medicines Control Agency (London, United Kingdom) regarding the chronic use of high-dose oral droperidol (Inapsine<sup>®</sup>; Janssen-Cilag Ltd., Beerse, Belgium) in psychiatric patients, the manufacturer decided to withdraw *all* formulations of droperidol.<sup>12</sup> The manufacturer predicted that intravenous droperidol use would decline to such a low level following the agency's new warning that it would not be economically viable to continue production of the parenteral formulation.

Given the extensive use of droperidol for antiemetic prophylaxis where it is routinely administered under anesthesia *with continuous electrocardiographic monitoring*, we believe that the recent black box warning by the FDA is totally unjustified. In light of the enormous economic impact of utilizing the more costly serotonin type 3 antagonist drugs (e.g., ondansetron, dolasetron [Anzemet<sup>®</sup>; Abbott Laboratories, Chicago, IL], granisetron [Kytril<sup>®</sup>; Roche Laboratories, Nutley, NJ]) as replacements for droperidol, we strongly urge the FDA to lift the black box warning regarding low doses of droperidol for the management of PONV. Furthermore, the agency should establish an expert advisory panel to examine these clinical case reports and the recommendations regarding the use of droperidol in the future.

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\* FDA strengthens warnings for droperidol. Available at: <http://www.fda.gov/bbs/topics/ANSWERS/2001/ANSO1123.html>

## Droperidol "Box Warning" Warrants Scrutiny

*To the Editor:*—The recent addition of a "box warning" to the droperidol label and its recommendation to continue electrocardiographic monitoring for 2 to 3 h after treatment has, in effect, largely eliminated use of the drug. This unfortunate move has deprived both us and our patients of a tremendously effective antiemetic medication and has dealt a severe blow to many already strained hospital budgets. Deprived of droperidol, many practitioners will resort to the possibly no less efficacious but very much more expensive 5-HT<sub>3</sub> antagonists. In our hospital alone, the additional cost is anticipated to run in the hundreds of thousands of dollars per year. Extrapolated nationally, the cost will be astronomical (as will be the windfall to the manufacturers of the 5-HT<sub>3</sub> antagonists—a windfall of such magnitude as to give pause to the more cynical among us).

In our department of more than 30 anesthesiologists whose collective accumulated experience surely includes hundreds of thousands of administered doses of droperidol, there is not one who recalls a case of arrhythmia in association with the drug. This is consistent with the report by Lawrence and Nasraway.<sup>1</sup> Their literature search of the 30 yr from 1966 to 1996 revealed 11 published cases of conduction distur-

bance associated with droperidol or haloperidol. Most of those cases occurred in critically ill patients given high doses of either agent.

It is hard to see how these cases are relevant to common current practice of administering droperidol in the dose range of 0.625–1.25 mg. Moreover, to determine the incidence of any event requires a denominator. It is probably not unreasonable to assume that millions of doses of droperidol are administered annually. Does that not place the few reported arrhythmias (*e.g.*, torsades) in the category of the exceedingly rare? Because of the legal quandary created by the inflammatory label change and the enormous costs to the healthcare system that will ensue, it is important that we insist on a scientifically sound basis (as to actual risk) for the change. We as a specialty and this journal as its most distinguished voice must critically question this label change.

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## The FDA Droperidol Warning: Is It Justified?

*To the Editor:*—In December 2001, the Food and Drug Administration (FDA) issued a "black box" warning that droperidol, even at low doses, could cause QT prolongation and/or torsades de pointes. The warning emphasized that significant cardiac morbidity and mortality was associated with droperidol. The intent and/or the effect of the warning will be to markedly restrict droperidol use. We know of several hospitals that have either removed the drug from its formulary or are considering such an action. We queried the FDA to evaluate the data which led the FDA to make this warning.

Under the Freedom of Information Act, we received information about and analyzed the droperidol cases upon which the FDA warning was based. The cases were reported to the FDA over a period of time from November 1, 1997 until January 2, 2002. Some of the data are described in table 1 below. There were 273 cases reported, and we identified 127 serious adverse outcomes in which the patient experienced death, prolonged hospitalization, or a life-threatening condition. The source of the case was "foreign" in 94 (74%) of these 127 cases. Problems such as alcohol intoxication, suicide attempts, general anesthesia, multiorgan dysfunction or sepsis often were confounding factors. Several of the cases were entered into the database more than once. There were 89 deaths reported, but the dose of droperidol was 2.5 mg or less in just 2 deaths. The majority of deaths involved droperidol doses that ranged from 25 to 250 mg, but the dose of droperidol was not documented in 14 deaths.

Cardiac morbidity possibly played a role in 74 of the 127 cases. Most of these cases (57/74) involved droperidol doses that were either excessive or seemingly inappropriate (*e.g.*, epidural). The droperidol dose was 2.5 mg or less in 17 of these 74 cases. In 12 of these 17 cases,

multiple drugs were administered, including other antiemetics and antipsychotics. In 4 of these 12 cases, patients received 10 or more drugs. In only 3 of the 17 cases was droperidol, 2.5 mg or less, the only drug administered, with 1 case resulting in hospitalization and 2 resulting in life-threatening problems. A total of five patients receiving droperidol, 2.5 mg or less, experienced either ventricular tachycardia ( $n = 2$ ) or torsades ( $n = 3$ ) but not prolonged QT. Three of these cases were considered life threatening or required prolonged hospitalization, and only one case was fatal (table 1).

If one considers only the cases contained in the FDA database in which the droperidol dose used was 2.5 mg or less *and* the outcome was death, the reported incidence of such cases is less than one per year. While this is almost certainly an underestimate (since it is based on anecdotal reporting) and considering the millions of doses given each year, it suggests that droperidol used in low doses is actually quite safe.

Droperidol is a cost-effective antiemetic. Many hospitals, in light of the FDA's warning, may remove droperidol from their formulary.

**Table 1. Summary of Cases on Which the Droperidol Warning by the Food and Drug Administration Was Based**

Factor	N
Total cases reported	273
Foreign source of case report	94
Serious adverse event (AE)	127
Total deaths reported	89
Deaths with droperidol dose 2.5 mg or less	2
Possible cardiac event	74
Torsade or prolonged QT	17/127
Excessive/inappropriate droperidol dose	57/74
Droperidol (2.5 mg or less) likely cause of AE	5

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

Substituting newer drugs for droperidol will significantly increase costs, and the use of newer drugs might be less safe. For example, consider if a single dose of ondansetron costs about \$10.50 and the cost of droperidol is \$0.50: Substituting ondansetron for droperidol will increase costs \$10,000.00 for every 1,000 doses. Applying this same cost analysis to one third of surgical candidates in the United States (~10,000,000), the cost impact of the FDA warning could easily be \$100 million or more. In addition, there is an unproven assumption that alternatives to droperidol are actually safer.

The FDA warning does not appear justified. Since other FDA warnings have been modified or retracted, perhaps a review of how such warnings are generated is in order.

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