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When Lack of Addition Really Does Add Up

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we cannot assume that approval for epidural administration infers safety for intrathecal administration. To protect the safety of human research subjects, we believe that the requirements for an investigational new drug are appropriate for intrathecal administration if the drug is not approved and not widely recognized as safe, even though the drug may be approved for epidural administration. The requirements for obtaining an investigational new drug are not onerous.

As Dr. Baumgartner's question demonstrates, there are many subtle nuances that we will need to work out as we learn how to implement this new policy.

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When Lack of Addition Really Does Add Up

To the Editor:

Deyhimy et al. recently demonstrated that administration of 2.5% sevoflurane before or after global ischemia and reperfusion reduces infarct size, attenuates creatine kinase release, preserves left ventricular function, and decreases intracellular Na^+ and Ca^{2+} accumulation in Langendorff perfused isolated rat hearts (1). However, combined sevoflurane pre- and postconditioning did not provide additional cardioprotection as compared with either intervention alone. These findings may be anticipated because the concentration of sevoflurane used before or after global ischemia and reperfusion probably caused near maximal protection against ischemic injury, and thus, the combination of sevoflurane pre- and postconditioning failed to produce any further beneficial effect. There is a limited amount of myocardium that may be salvaged by anesthetic or ischemic pre- or postconditioning (2,3). For example, a 30-min exposure to 1 MAC isoflurane or a 5-min ischemic episode before prolonged coronary artery occlusion and reperfusion produced similar reductions in infarct size in dogs, but the combination of these anesthetic and ischemic preconditioning stimuli did not result in further protection (2). In contrast, combined administration of 0.5 MAC isoflurane (a concentration that did not attenuate myocardial necrosis) and a subthreshold ischemic stimulus during early reperfusion caused reductions in infarct size that were equal in magnitude to 1.0 MAC isoflurane or more intense ischemic postconditioning (3). Anesthetic preconditioning has been shown to be dose related between 0.25 and 1.25 MAC (4). In fact, a lower concentration (2%) of sevoflurane was able to decrease the time threshold of classical ischemic preconditioning (5), conferred an additional beneficial effect during delayed ischemic preconditioning (6), and produced more pronounced reductions in infarct size when administered both before and after coronary artery occlusion in rats *in vivo* as compared with pre- or postconditioning alone (7). Thus, it seems very likely that the combination of sevoflurane pre- and postconditioning may also have produced additive cardioprotective effects had a lower concentration of the volatile drug been used in the authors' isolated rat heart model (1).

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In Response:

Dr. Pagel (1) raises an issue worth both discussion and further exploration regarding the actions and possible interactions of lower concentrations of inhalational anesthetic agents with pre- and postconditioning. The studies referenced in his comments differ from ours in many aspects. They combine inhalational anesthetic preconditioning with ischemic postconditioning, delayed preconditioning with postconditioning, or prolonged and multiple episodes of preconditioning. In addition, they are *in vivo* experiments. In contrast, our study uses sevoflurane alone to provide both acute preconditioning and postcondtioning in an *in vitro* model (2).

The studies presented do suggest the possibility of additive effects of combined preconditioning and postcondtioning compared with any of the preconditioning or postconditioning triggers alone. As we discussed in our manuscript, there is no doubt that different results could be due to differences in experimental design. For example, the mechanisms for ischemic preconditioning may be very different from those involved in anesthetic

preconditioning. Sergeev et al. studied the changes in gene expression with anesthetic and ischemic preconditioning and reported only a very small percentage of overlap in the multiple up and down regulated genes (3). It has also been proposed that the mechanisms of acute preconditioning differ from delayed (second window) preconditioning. Acute preconditioning involves primarily posttranslational modifications, whereas delayed precondtioning also involves modified gene expression and synthesis of cardioprotective proteins (4). Even the use of different anesthetic agents could contribute to different results. Isoflurane has been reported not to produce a delayed preconditioning (5).

In our discussion, we suggested that exposure to higher concentrations of sevoflurane could produce different results. We would also agree with Dr. Pagel that lower concentrations of sevoflurane might produce different results. Comprehensive dose response studies of anesthetic pre- and postconditioning in an *in vitro* model would be a constructive addition to this area of research.

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Extended Release Epidural Morphine, Far from Ideal for Postcesarean Delivery Pain Control

To the Editor:

The recent paper by Carvalho et al. (1) describing the use of single dose, extended-release epidural morphine (DepoDur) for postcesarean pain does not support the authors' conclusion that extended release epidural morphine, (DepoDur) seems to be superior to neuraxial morphine sulfate. Two prospective randomized double blind studies have shown that intrathecal morphine sulfate provides excellent postcesarean analgesia (2,3). Furthermore, the advantages of spinal anesthesia for elective cesarean delivery in terms of time management, costs, charges, and complications have been well documented (4). Since extended-release epidural morphine is only approved for epidural injection and can not be co-administered with local anesthetic, it is hard to justify a combined spinal epidural technique versus a single shot spinal for elective cesarean delivery primarily so that extended-release epidural morphine can be utilized. In their study, the authors had one case of accidental dural puncture with an epidural needle in the 70 enrolled patients. Dural puncture with a 17-gauge epidural needle has a substantially higher morbidity when compared with a spinal needle; this will negate the benefit of any marginal improvement with extended-release epidural morphine in postcesarean delivery pain control. Finally, does it really matter if the median verbal rating scale for pain is 3.5 vs 2.2 for morphine versus extended-release epidural morphine at 24–48 h, the only statistically significant pain score of the study, if the patients were equally satisfied with either pain control modalities?

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In Response:

Studies by Dualé et al. (1) and Sarvela et al. (2), as highlighted by Dr. Roboubi (3), found similar analgesic efficacy and duration when comparing equianalgesic doses of intrathecal and epidural morphine for the first 24 h postcesarean. In light of the fact that we found extended-release epidural morphine provided superior analgesia compared with epidural morphine (4), and in keeping with Duale et al. (1) and Sarvela et al.'s. (2) findings, we would expect extended-release epidural morphine to provide superior analgesia over an equianalgesic dose of intrathecal morphine, especially 24–48 h after cesarean delivery when the intrathecal morphine dose is no longer effective and peak pain levels are experienced.

Despite patients using more than twice the amount of postoperative analgesics in the second 24 h postcesarean, serial pain scores at rest and activity were consistently lower (approximately a 50% reduction in pain in the 24–48 h postoperative period) in the extended-release epidural morphine compared with the morphine group (4). As Dr. Roboubi highlights, the overall pain scores during the 24–48 h period were 3.5 in the morphine vs 2.2 in the extended-release epidural morphine group a >33% reduction in pain, a level most clinicians accept as clinically significant pain relief.