

Statins Might Contribute to Postoperative Delirium

To the Editor:

In the timely and welcome discussion by Mantz *et al.*¹ of postoperative delirium in an octogenarian, the patient's preoperative use of a statin is mentioned but is not considered in the discussion of the etiology of the delirium. The possibility that the statin might have contributed was set aside on the basis of a single retrospective investigation in which investigators at the University of Toronto, Toronto, Ontario, Canada, observed a lesser incidence of delirium after cardiac surgery, performed with cardiopulmonary bypass, among preprocedure statin takers.² However, we hope that both clinicians and clinical investigators will maintain in mind the possibility that statins might, in at least some circumstances, contribute to postoperative delirium or cognitive dysfunction. We grant quickly that the supporting information is limited. However, in a retrospective review of a large Canadian database, other investigators at the University of Toronto reported an increase in the incidence of delirium after noncardiac surgery among patients older than 65 yr who had been receiving statins.³ Those latter investigators did not offer the hypothesis that prompted their study. However, we speculate that the evidence suggesting long-term preservation of cognitive function and the reduced presence of the pathologic changes associated with Alzheimer disease among elderly statin users might have prompted them to anticipate the opposite result.⁴⁻⁶

There are numerous derivative questions. First, if the observations in both the retrospective studies mentioned above are valid, why the difference? Is it possible that the anti-inflammatory effects of statins have a benefit that is evident in the context of the more intense proinflammatory state created by cardiopulmonary bypass? Is it simultaneously possible that there might also be adverse effects on cognitive function in other situations? Several considerations led us to suspect that there are grounds to suspect that statins might have adverse effects on cognitive function. Among the manifestations of the anti-inflammatory effects of statins are reduced levels of nuclear factor- κ B and tumor necrosis factor. However, nuclear factor- κ B and tumor necrosis factor, in addition to their participation in systemic inflammatory process, are both present in the central nervous system in which they are important participants in synaptic function.⁷⁻¹⁰

Furthermore, cholesterol itself is an important component of cell membranes and, in particular, is an essential element of membrane/lipid rafts (MLRs) that are essential for synaptic function.¹¹ Our own recent investigations (manuscript in preparation) have revealed that genetic ma-

nipulations that increase MLR formation in neurons enhance synaptic signaling cascades and that this effect is blocked by statins or other agents that disrupt MLRs. Evidence obtained by others has shown that disruption or alterations of neuronal MLRs by statins can be neurotoxic, demonstrating the importance of these distinct microdomains for proper neuronal signaling.¹¹⁻¹⁴ Other recent work has shown that the fatty acid content of MLRs isolated from synaptic endings is altered in aged animals.¹⁵ This, in turn, suggests that cognitive processes in the elderly might be more vulnerable to statin-associated changes in neuronal structure and function, of which delirium might be a manifestation.

The inherent paradox is that statins might be beneficial in terms of long-term cognitive well-being⁴⁻⁶ but yet be disadvantageous in the face of certain acute stresses, including anesthesia and surgery.³ This is currently at best a matter of reasonable speculation that requires further investigation. In the interim, our brief message is that we hope that clinicians and clinical investigators will keep their minds open to the possibility that statins might in some circumstances contribute to perioperative delirium or cognitive dysfunction.

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References

- Mantz J, Hemmings HC Jr, Boddaert J: Case scenario: Postoperative delirium in elderly surgical patients. *ANESTHESIOLOGY* 2010; 112:189-95
- Katznelson R, Djaiani GN, Borger MA, Friedman Z, Abbey SE, Fedorko L, Karski J, Mitsakakis N, Carroll J, Beattie WS: Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery. *ANESTHESIOLOGY* 2009; 110:67-73
- Redelmeier DA, Thiruchelvam D, Daneman N: Delirium after elective surgery among elderly patients taking statins. *CMAJ* 2008; 179:645-52
- Etmann M, Gill S, Samii A: The role of lipid-lowering drugs in cognitive function: A meta-analysis of observational studies. *Pharmacotherapy* 2003; 23:726-30
- Li G, Larson EB, Sonnen JA, Shofer JB, Petrie EC, Schantz A, Peskind ER, Raskind MA, Breitner JC, Montine TJ: Statin therapy is associated with reduced neuropathologic changes of Alzheimer disease. *Neurology* 2007; 69:878-85
- Cramer C, Haan MN, Galea S, Langa KM, Kalbfleisch JD: Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. *Neurology* 2008; 71:344-50
- Barger SW, Moerman AM, Mao X: Molecular mechanisms of cytokine-induced neuroprotection: NF κ B and neuroplasticity. *Curr Pharm Des* 2005; 11:985-98
- Beattie EC, Stellwagen D, Morishita W, Bresnahan JC, Ha BK, Von Zastrow M, Beattie MS, Malenka RC: Control of synaptic strength by glial TNF α . *Science* 2002; 295:2282-5
- Pickering M, Cumiskey D, O'Connor JJ: Actions of TNF-alpha on glutamatergic synaptic transmission in the central nervous system. *Exp Physiol* 2005; 90:663-70
- McAfoose J, Koerner H, Baune BT: The effects of TNF deficiency on age-related cognitive performance. *Psychoneuroendocrinology* 2009; 34:615-9
- Hering H, Lin CC, Sheng M: Lipid rafts in the maintenance

The above letter was sent to the authors of the referenced report. The authors did not wish to reply.—James C. Eisenach, M.D., Editor-in-Chief

- of synapses, dendritic spines, and surface AMPA receptor stability. *J Neurosci* 2003; 23:3262-71
12. Kumar B, Andreatta C, Koustas WT, Cole WC, Edwards-Prasad J, Prasad KN: Mevastatin induces degeneration and decreases viability of cAMP-induced differentiated neuroblastoma cells in culture by inhibiting proteasome activity, and mevalonic acid lactone prevents these effects. *J Neurosci Res* 2002; 68:627-35
 13. Cerezo-Guisado MI, Garcia-Roman N, Garcia-Marin LJ, Alvarez-Barrientos A, Bragado MJ, Lorenzo MJ: Lovastatin inhibits the extracellular-signal-regulated kinase pathway in immortalized rat brain neuroblasts. *Biochem J* 2007; 401:175-83
 14. Kannan M, Steinert JR, Forsythe ID, Smith AG, Chernova T: Mevastatin accelerates loss of synaptic proteins and neurite degeneration in aging cortical neurons in a heme-independent manner. *Neurobiol Aging* 2008 October 23. [Epub ahead of print]
 15. Mateos MV, Salvador GA, Giusto NM: Selective localization of phosphatidylcholine-derived signaling in detergent-resistant membranes from synaptic endings. *Biochim Biophys Acta* 2009; 179:624-36

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The Private Practicing Anesthesiologist and the Four-legged Stool

To the Editor:

As always, I read this month's publication of ANESTHESIOLOGY with my usual enthusiasm and interest. The inclusion of a dedicated section devoted to education is a welcomed addition. As Dr. Schwartz states in his editorial, education is one of anesthesia's "four key activities" with patient care, practice administration, and research the three other legs needed to build a sturdy "four-legged stool" for anesthesiology to use.¹

Unfortunately, these four legs are missing an important joint, the private practicing anesthesiologist. Private practitioners attend to more patients and have more clinical practice administration experience than most other anesthesiologists. Yet, despite comprising a majority of anesthesiologists, this group has been essentially precluded from research because of several situations. They encounter a lack of support from the hospitals in which they practice; they must understand and comply with onerous, yet important, requirements of Investigational Review Boards; they are not provided resources needed for research such as statistical or secretarial assistance; and they are faced with an unacknowledged, yet possibly occurring, discouragement from anesthesia journals by reviewers and editors. (How many articles in journals of anesthesiology are written by anesthesiologists in private practice?)

One example of the exclusion of private practitioners from the "four-legged stool" is The Foundation for Anesthesia Education and Research and its Pediatric Research Council.

* Foundation for Anesthesia Education and Research, Pediatric Research Council letter seeking research funding applications. May 22, 2006. http://www.pedsanesthesia.org/faer_rfp.iphtml. Accessed April 27, 2010.

In order to receive funding for any of their four grant divisions, academic appointments or academic affiliations are required. In addition, a letter sent by the Pediatric Research Council of The Foundation for Anesthesia Education and Research "seeking research funding applications . . ." is only addressed to the Society for Academic Chairs and Academic Anesthesia Program Directors.* There are no invitations for nonacademic private practicing researchers.

As recognized, it is time for education to be a dedicated section of Anesthesiology, but it is also time for the encouragement and support of private practicing anesthesiologists to be more a part of the four key activities encompassing anesthesia. If anesthesia is to have a stable and sturdy stool to stand on, it must be big enough for all anesthesiologists.

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Reference

1. Schwartz AJ: Education: An essential leg for anesthesiology's four-legged stool! *ANESTHESIOLOGY* 2010; 112:3-5

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In Reply:

A gem sparkles because it is multifaceted. Anesthesiology is a gem as it is truly multifaceted, that is, our specialty includes individuals who are facile clinicians, inspiring educators, inquisitive scientists, and practice management experts. Today's reality and complexities of patient care, education, research, and administration make it virtually impossible to be all things that encompass our specialty. The fact that there are many anesthesiologists with great facility in each of these areas tells us to select our strengths and passions and sit on the anesthesiology four-legged stool on equitable and firm footing.¹

Dr. Serlin expresses disappointment about what he describes as being precluded from sitting at the table on a stable stool. He is, however, a rightful and important participant. He is a member of a group of private clinician practitioners. Their contribution to the strength and stability of the anesthesiology stool is quite reassuring as they provide anesthesia patient care and facilitate operating room and hospital clinical practice. Dr. Serlin laments what he perceives as research activity he would like private practitioners to be able to do were it not for lack of support from hospitals, the burdens of Investigational Review Board requirements, and discouragement from anesthesia journals. He calls on our specialty to support private practicing anesthesiologists to be more a part of the research component of our four-legged stool.

I agree with Dr. Serlin's assertion, ". . . it is [always] time for the encouragement and support of private practicing anesthesiologists to be a part of the four key activities encompassing anesthesia." Anesthesiology is a specialty with options. Anesthesiologists are lucky to have choices for how they devote their professional time. Private practitioners are