Editorials

Are β -blockers anesthetics?

Homer Yang MD FRCPC, Ashraf Fayad MD FCARCSI

IN this issue of the Journal, the article by Zaugg *et al.*,¹ examines, in a post hoc fashion, anesthetic requirements in patients undergoing abdominal surgery, with or without preoperative and intraoperative atenolol. The authors found that less anesthetics were required in the atenolol group, without an increase in bispectral index scale (BIS) values or intra-operative awareness. Their conclusion was that atenolol "markedly potentiates the hypnosis part of anesthesia".

As they are being used increasingly in the hope of preventing perioperative cardiac complications, could β -blockers mask signs of light anesthesia and thus increase the risk of intraoperative awareness? On the other hand, if the assertion by Zaugg *et al.* is correct, then may β -blockers be anesthetic? Are β -blockers synergistic to anesthetic drugs? In that case, can one use a short-acting β -blocker such as esmolol to reduce anesthetic administration and facilitate fast tracking?

Ginsburg posed a similar question in 1992, "is *iv* esmolol an acceptable substitute for an inadequate anesthetic?"² Since then, there have been reports of reducing anesthetic requirements by esmolol, based mostly on BIS.³⁻⁶ The potential of using esmolol to expedite emergence has also been noted.^{7,8}

There is evidence to suggest that β -blockers have significant effects on the central nervous system. Their effects on sleep and decreased rapid eye movement have been reported.⁹⁻¹² Decreased melatonin secretion has been noted and may be associated with the sleep disturbances noted in some patients on a β -blocker.^{13,14} β -blockers may impair memory¹⁵⁻¹⁷ and affect vigilance.¹⁸ Both propranolol¹⁹⁻²¹ and esmolol²²⁻²⁴ have been noted to have anticonvulsant activities, further evidence that β -blockers may have more central nervous system effects than one might expect. In the case of esmolol, a dose effect relationship has been noted.²⁵ There is evi-

dence in the rat that β -blockers attenuate excitatory neuronal responses in the cingulate cortex²⁶ or epileptiform responses in the limbic system.²⁷ The antinociceptive effects of β -blockers have been noted in rats²⁸ and in humans with allodynia.²⁹ Esmolol, pronethalol, and propranolol have also been noted to have local anesthetic properties in animal models.³⁰⁻³² It certainly seems plausible that β -blockers potentiate the "hypnosis part" of anesthesia.

In contrast, Berkenstadt did not find that esmolol reduced BIS.³³ Others did not find that esmolol reduced movement to command or pupillary response to noxious stimuli under anesthesia.^{34,35} Why the contradictions?

Firstly, BIS predicts the depth of anesthesia based on probability and regression analysis.³⁶ It is not uniformly applicable to all anesthetics and drug combinations.³⁷⁻⁴¹ The use of BIS to predict the depth of anesthesia in the presence of esmolol therefore is not necessarily valid. Secondly, there are different levels of "inadequate" anesthesia, ranging from implicit memory, explicit memory, obeying commands during anesthesia without recall, to actual awareness and recall.⁴² The proper definition of "inadequate anesthesia" is of great importance in this context. The incidence of actual awareness may be in the range of 18/11785 or 0.15%.⁴³ Consequently, a randomized controlled trial to prove one way or another that β -blockers increase the incidence of intraoperative awareness would require a huge sample size and be difficult to conduct.

As is usually the case in research, one answer leads to more questions. Studies in the last decade have shown that β -blockers have a great potential to prevent perioperative cardiac complications. Although they are increasingly being used for that purpose, the hypothesis has not been proven definitely. Trials such as Metoprolol after Vascular Surgery (MaVS) or

From the Department of Anesthesia, McMaster University, Hamilton Health Sciences, Hamilton, Ontario, Canada.

Address correspondence to: Dr. Homer Yang, Department of Anesthesia, McMaster University, HSC-2U1, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada. Phone: 905-521-2100; Fax: 905-523-1224; E-mail: yangh@mcmaster.ca

Perioperative Ischemia Study (POISE) are being conducted to answer that question. The questions raised by Zaugg *et al.* have reminded us that all medical therapies come with side-effects and it is always a balance of risks and benefits. Zaugg *et al.* have given us a glimpse of one of the risks; the definitive answer still eludes us, and awaits further research.

Les β -bloquants sont-ils des anesthésiques ?

Dans le présent numéro du Journal, l'article de Zaugg *et coll.*¹ examine, à posteriori, les besoins anesthésiques des patients qui subissent une intervention abdominale avec ou sans aténolol préopératoire et peropératoire. Les auteurs ont découvert que les besoins anesthésiques sont moindres avec l'aténolol, sans que cela augmente les valeurs de l'index bispectral (BIS) ou le réveil peropératoire. Leur conclusion a été que l'aténolol "potentialise de façon nette la composante hypnose de l'anesthésie."

Étant de plus en plus utilisés dans le but de prévenir les complications cardiaques périopératoires, les β -bloquants masquent-ils des signes d'anesthésie insuffisante et, par conséquent, augmentent-ils le risque d'éveil peropératoire ? Par ailleurs, si l'affirmation de Zaugg *et coll.* est exacte, alors les β -bloquants seraient-ils des anesthésiques ? Sont-ils synergiques aux médicaments anesthésiques ? Dans ce cas, peut-on utiliser un β -bloquant comme l'esmolol pour réduire l'administration d'anesthésique et faciliter un mode opératoire rapide ?

Ginsburg a posé une question similaire en 1992 en se demandant "si l'esmolol *in vivo* est un substitut acceptable à un anesthésique inadéquat ?"² Depuis lors, on a rapporté la réduction des besoins anesthésiques avec l'esmolol, principalement mis en évidence avec le BIS.³⁻⁶ La possibilité de hâter le retour à la conscience avec l'esmolol a aussi été notée.^{7,8}

Certaines indications suggèrent que les β -bloquants aient des effets significatifs sur le système nerveux central. Leurs effets sur le sommeil et la diminution des mouvements oculaires rapides ont été cités déjà.⁹⁻¹² Une baisse de la sécrétion de mélatonine a été notée et pourrait être associée à des troubles du sommeil notés chez des patients qui reçoivent des β -bloquants.^{13,14} Les β -bloquants peuvent altérer la mémoire¹⁵⁻¹⁷ et affecter la vigilance.¹⁸ Le propranolol¹⁹⁻²¹ et l'esmolol²²⁻²⁴ présentent des activités anticonvulsivantes

reconnues, autre preuve que les β -bloquants peuvent avoir plus d'effets centraux qu'on ne le croyait. Dans le cas de l'esmolol, une relation dose-effet a été notée.²⁵ Chez le rat, les β -bloquants diminuent les réponses neuronales excitatrices dans le cortex cingulaire²⁶ ou les réponses épileptiformes dans le système limbique.²⁷ Les effets antinociceptifs des β -bloquants ont été démontrés chez les rats²⁸ et chez les humains avec l'allodynie.²⁹ L'esmolol, le pronétholol et le propranolol ont démontré des propriétés anesthésiques locales chez des modèles animaux.³⁰⁻³² Il est certainement plausible que les β -bloquants potentialisent la "composante hypnose" de l'anesthésie.

Par ailleurs, Berkenstadt n'a pas constaté que l'esmolol réduit le BIS.³³ D'autres chercheurs n'ont pu affirmer que l'esmolol réduit le mouvement sur commande ou la réponse pupillaire à des stimuli nociceptifs sous anesthésie.^{34,35} Comment expliquer ces contradictions ?

D'abord, le BIS prédit la profondeur de l'anesthésie à partir d'analyses de probabilité et de régression.³⁶ Ce n'est pas uniformément applicable à tous les anesthésiques et à toutes les combinaisons médicamenteuses.³⁷⁻⁴¹ L'usage du BIS pour prédire la profondeur de l'anesthésie avec l'esmolol n'est donc pas nécessairement valide. Ensuite, il y a différents degrés d'anesthésie "inadéquante", allant de la mémoire implicite, en passant par la mémoire explicite, la réalisation de commandes pendant l'anesthésie, sans souvenir, jusqu'à la conscience et au souvenir réels.⁴² La définition exacte de "l'anesthésie inadéquante" revêt une grande importance dans ce contexte. L'incidence de conscience réelle pourrait être de l'ordre de 18 / 11 785 ou de 0,15 %.⁴³ Par conséquent, un essai randomisé et contrôlé visant à prouver d'une façon ou d'une autre que les β -bloquants augmentent l'incidence de conscience peropératoire exigerait un échantillon imposant et serait difficile à réaliser.

Comme c'est souvent le cas en recherche, une réponse provoque beaucoup d'autres questions. Les études des dix dernières années ont montré que les β -bloquants ont un grand potentiel de prévention périopératoire des complications cardiaques. Même s'ils sont de plus en plus utilisés dans ce but, l'hypothèse n'a pas été prouvée de façon certaine. Des études comme *Metoprolol after Vascular Surgery (MaVS)* ou *Perioperative Ischemia Study (POISE)* sont en cours pour tenter de le faire. Les questions soulevées par Zaugg *et coll.* nous rappellent que tout traitement médical comporte des effets secondaires et représente un équilibre entre des risques et des bénéfices. Zaugg *et coll.* nous ont donné un aperçu des risques ; la réponse finale nous est encore inconnue et demande d'autres recherches.

References

- 1 Zaugg M, Tagliente T, Silverstein JH, Lucchinetti E. Atenolol may not modify anesthetic depth indicators in elderly patients – a second look at the data. *Can J Anesth* 2003; 50: 638–42.
- 2 Ginsburg RS, Lippmann M. Is intravenous esmolol an acceptable substitute for an inadequate anesthetic? *Anesth Analg* 1992; 74: 776–7.
- 3 Johansen JW, Flaishon R, Sebel PS. Esmolol reduces anesthetic requirement for skin incision during propofol/nitrous oxide/morphine anesthesia. *Anesthesiology* 1997; 86: 364–71.
- 4 Johansen JW, Schneider G, Windsor AM, Sebel PS. Esmolol potentiates reduction of minimum alveolar isoflurane concentration by alfentanil. *Anesth Analg* 1998; 87: 671–6.
- 5 Johansen JW. Esmolol promotes electroencephalographic burst suppression during propofol/alfentanil anesthesia. *Anesth Analg* 2001; 93: 1526–31.
- 6 Menigaux C, Guignard B, Adam F, Sessler DI, Joly V, Chauvin M. Esmolol prevents movement and attenuates the BIS response to orotracheal intubation. *Br J Anaesth* 2002; 89: 857–62.
- 7 Smith I, Van Hemelrijck J, White PF. Efficacy of esmolol versus alfentanil as a supplement to propofol-nitrous oxide anesthesia. *Anesth Analg* 1991; 73: 540–6.
- 8 Coloma M, Chiu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. *Anesth Analg* 2001; 92: 352–7.
- 9 Betts TA, Alford C. Beta-blockers and sleep: a controlled trial. *Eur J Clin Pharmacol* 1985; 28(Suppl): 65–8.
- 10 Kaye K, Godtliebsen OB. Effects of the beta-adrenoceptor antagonists acebutolol and metoprolol on sleep pattern in normal subjects. *Eur J Clin Pharmacol* 1977; 12: 323–6.
- 11 Thompson DF, Pierce DR. Drug-induced nightmares. *Ann Pharmacother* 1999; 33: 93–8.
- 12 Yamada Y, Shibuya F, Hamada J, Sawada Y, Iga T. Prediction of sleep disorders induced by beta-adrenergic receptor blocking agents based on receptor occupancy. *J Pharmacokinet Biopharm* 1995; 23: 131–45.
- 13 Brismar K, Mogensen L, Wetterberg L. Depressed melatonin secretion in patients with nightmares due to beta-adrenoceptor blocking drugs. *Acta Med Scand* 1987; 221: 155–8.
- 14 Brismar K, Hylander B, Eliasson K, Rossner S, Wetterberg L. Melatonin secretion related to side-effects of beta-blockers from the central nervous system. *Acta Med Scand* 1988; 223: 525–30.
- 15 Przybylski J, Rouillet P, Sara SJ. Attenuation of emotional and nonemotional memories after their reactivation: role of beta adrenergic receptors. *J Neurosci* 1999; 19: 6623–8.
- 16 Cahill L, Prins B, Weber M, McGaugh JL. Beta-adrenergic activation and memory for emotional events. *Nature* 1994; 20: 702–4.
- 17 Cahill L, van Stegeren A. Sex-related impairment of memory for emotional events with beta-adrenergic blockade. *Neurobiol Learn Mem* 2003; 79: 81–8.
- 18 Matousek M, Hjalmarson A, Koch J, Petersen I. The use of the EEG for assessment of vigilance changes caused by beta-blockers. *Neuropsychobiology* 1984; 12: 55–9.
- 19 de Oliveira GG, Borges MA. Propranolol action in chronically unstable generalized epilepsy. *Am J Ther* 1994; 1: 38–41.
- 20 Fischer W. Anticonvulsant profile and mechanism of action of propranolol and its two enantiomers. *Seizure* 2002; 11: 285–302.
- 21 Luchowska E, Luchowski P, Wielosz M, Kleinrok Z, Czuczwar SJ, Urbanska EM. Propranolol and metoprolol enhance the anticonvulsant action of valproate and diazepam against maximal electroshock. *Pharmacol Biochem Behav* 2002; 71: 223–31.
- 22 van den Broek WW, Leentjens AF, Mulder PG, Kusuma A, Bruijn JA. Low-dose esmolol bolus reduces seizure duration during electroconvulsive therapy: a double-blind, placebo-controlled study. *Br J Anaesth* 1999; 83: 271–4.
- 23 McCall WV, Zvara D, Brooker R, Arias L. Effect of esmolol pretreatment on EEG seizure morphology in RUL ECT. *Convuls Ther* 1997; 13: 175–80.
- 24 Howie MB, Black HA, Zvara D, McSweeney TD, Martin DJ, Coffman JA. Esmolol reduces autonomic hypersensitivity and length of seizures induced by electroconvulsive therapy. *Anesth Analg* 1990; 71: 384–8.
- 25 Kovac AL, Goto H, Pardo MP, Arakawa K. Comparison of two esmolol bolus doses on the haemodynamic response and seizure duration during electroconvulsive therapy. *Can J Anaesth* 1991; 38: 204–9.
- 26 Jones RS, Olpe HR. Pharmacological characterization of the receptor mediating the adrenergic inhibition of responses to substance P in the cingulate cortex. *Brain Res* 1986; 367: 151–61.
- 27 Stoop R, Epiney S, Meier E, Pralong E. Modulation of epileptiform discharges in the rat limbic system in vitro by noradrenergic agents. *Neurosci Lett* 2000; 287: 5–8.
- 28 Davidson EM, Doursout MF, Szmuk P, Chelly JE. Antinociceptive and cardiovascular properties of esmolol following formalin injection in rats. *Can J Anesth* 2001; 48: 59–64.
- 29 Ernberg M, Lundberg T, Kopp S. Effect of propranolol and granisetron on experimentally induced pain and allodynia/hyperalgesia by intramuscular injection of

- serotonin into the human masseter muscle. *Pain* 2000; 84: 339–46.
- 30 Gorczynski RJ, Shaffer JE, Lee RJ. Pharmacology of ASL-8052, a novel beta-adrenergic receptor antagonist with an ultrashort duration of action. *J Cardiovasc Pharmacol* 1983; 5: 668–77.
- 31 Morales-Aguilera A, Vaughan Williams EM. The effects on cardiac muscle of β -receptor antagonists in relation to their activity as local anaesthetics. *Br J Pharmacol* 1965; 24: 332–8.
- 32 Vaughan Williams EM. Mode of action of beta receptor antagonists on cardiac muscle. *Am J Cardiol* 1966; 18: 399–405.
- 33 Berkenstadt H, Loebsstein R, Faibishenko I, Halkin H, Keidan I, Perel A. Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia. *Br J Anaesth* 2002; 89: 509–11.
- 34 Orme R, Leslie K, Umranihar A, Ugoni A. Esmolol and anesthetic requirement for loss of responsiveness during propofol anesthesia. *Anesth Analg* 2002; 94: 112–6.
- 35 Larson MD, Sessler DI, Washington DE, Merrifield BR, Hynson JA, McGuire J. Pupillary response to noxious stimulation during isoflurane and propofol anesthesia. *Anesth Analg* 1993; 76: 1072–8.
- 36 Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. *J Clin Monit* 1994; 10: 392–404.
- 37 Barr G, Anderson RE, Owall A, Jakobsson JG. Effects on the bispectral index during medium-high dose fentanyl induction with or without propofol supplement. *Acta Anaesthesiol Scand* 2000; 44: 807–11.
- 38 Barr G, Anderson RE, Owall A, Jakobsson JG. Being awake intermittently during propofol-induced hypnosis: a study of BIS, explicit and implicit memory. *Acta Anaesthesiol Scand* 2001; 45: 834–8.
- 39 Wu CC, Mok MS, Lin CS, Han SR. EEG-bispectral index changes with ketamine versus thiamylal induction of anesthesia. *Acta Anaesthesiol Sin* 2001; 39: 11–5.
- 40 Sakai T, Singh H, Mi WD, Kudo T, Matsuki A. The effect of ketamine on clinical endpoints of hypnosis and EEG variables during propofol infusion. *Acta Anaesthesiol Scand* 1999; 43: 212–6.
- 41 Coste C, Guignard B, Menigaux C, Chauvin M. Nitrous oxide prevents movement during orotracheal intubation without affecting BIS value. *Anesth Analg* 2000; 91: 130–5.
- 42 Russell IF, Wang M. Absence of memory for intra-operative information during surgery with total intravenous anaesthesia. *Br J Anaesth* 2001; 86: 196–202.
- 43 Sandin RH, Enlund G, Samuelsson P, Lennmarken C. Awareness during anaesthesia: a prospective case study. *Lancet* 2000; 355: 707–11.