Isoproterenol-induced elevated bispectral indexes while undergoing radiofrequency ablation: A case report

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The use of bispectral index (BIS) for monitoring neuronal function under general anesthesia has been expanding in practice. However, the meanings of the values are not always clear and have been shown to be altered by such drugs as ketamine, ephedrine, and physostigmine.

Presented here is a case of increasing BIS in response to noradrenergic beta receptor stimulation via the administration of isoproterenol while under general anesthesia. The rise in BIS values appeared to have no correlation to the stimulation produced by the procedure. The patient reported no intraoperative recall despite BIS values in the high 70s. This case reinforces that BIS values require interpretation and can only be relevant to the circumstances of the individual case.

Key words: **Bispectral index, dexmedetomidine, isoproterenol, radiofrequency ablation.**

Presented here is a case of elevated bispectral index (BIS) values associated with the use of isoproterenol during radiofrequency ablation. This rise in the BIS values appeared to have no correlation to the stimulation produced by the procedure.

Case summary

The patient was a 52-year-old, 65-kg female with a 5-year history of recurrent paroxysmal tachycardia. She presented to the electrophysiology suite requiring radiofrequency ablation. The patient's medical history consisted of tachycardic episodes as well as seasonal allergies. Her current medications included sertraline, alprazolam, flecainide, fexofenadine, and calcium. She had known drug allergies to penicillin, nitrofurantoin, and sulfa. Surgical history was significant for partial hysterectomy with general anesthesia. No prior anesthesia complications were noted.

After preoperative assessment and careful consideration of the anticipated length of the procedure, the patient's request, and the cardiologist's needs, all parties agreed to general endotracheal anesthesia. The cardiologist requested that the anesthetic be of the least cardiosuppressive in nature. With this in mind, after establishing a secure airway, total intravenous anesthesia using a propofol infusion was planned.

A standard induction was performed using midazolam, fentanyl, propofol, and rocuronium. A 7.0-mm endotracheal tube was secured after placement was confirmed by bilateral breath sounds and capnography. The patient was ventilated using a gas mixture of 50% nitrous oxide and 50% oxygen. An esophageal stethoscope with temperature probe was placed and the BIS monitor was positioned. Anesthesia was maintained using a propofol infusion that was titrated to a BIS value of 40 to 60.

With induction completed, the patient remained hemodynamically stable for a period lasting 2 hours. During this time the BIS values fluctuated between 30 and 45. This BIS value was achieved with a propofol infusion running at a dose of 50 µg/kg per minute. After 2 hours, the cardiologist requested an isoproterenol infusion and the discontinuation of nitrous oxide. This request was made in hopes of facilitating mapping of the myocardium. The gas mixture was changed to 50% air and 50% oxygen. An isoproterenol infusion was begun at a rate of 1 µg/min. At the time, the patient's BIS value was 41 with a 50 µg/kg per minute infusion of propofol. With the introduction of isoproterenol and the withholding of nitrous oxide, the BIS value began to climb steadily. At the time, the rise was attributed to the withdrawal of nitrous oxide. This rising BIS value was treated by increasing the dose of the propofol. The propofol infusion was at 160 µg/kg per minute. Also given in divided doses were 50 µg of fentanyl and 200 mg of propofol. With the passing of time, it was felt that the dose required to lower the BIS value exceeded the expected need attributed to the withdrawal of nitrous oxide.

After 35 minutes the isoproterenol was stopped because of the onset of supraventricular tachycardia that required cardioversion. The patient was successfully cardoverted at 300 J. Withdrawal of isoproterenol resulted in the BIS value dropping from 64 to 6 over 4 minutes. Propofol was titrated back to a BIS value of

45. Myocardial mapping was continued, and the patient was again placed on an isoproterenol infusion. As before, the BIS value was noted to rise. During this time the patient's BIS value was as high as the mid-70s. This was treated with propofol, fentanyl, and midazolam. Propofol, as high as 240 µg/kg per minute, was required to maintain the BIS value below 60, at which time the patient's electrocardiogram reverted to supraventricular tachycardia. Isoproterenol was withheld. The patient was successfully cardioverted again. The withdrawal of isoproterenol was again followed by the patient's BIS value dropping to a low of 5. Propofol was retitrated to a BIS value of 45. Myocardial mapping was continued, and the patient was placed on an isoproterenol infusion once again. Because of difficulty in the mapping process, the cardiologist requested the isoproterenol infusion be increased to 2 µg/min. At this time the propofol infusion was at 260 µg/kg per minute with a BIS value of 67.

Dexmedetomidine was added to the anesthetic at a dose of 1 µg/kg over 15 minutes, followed by an infusion of 0.5 µg/kg per minute. The use of dexmedetomidine allowed for the reduction of the propofol infusion to 150 µg/kg per minute. After 90 minutes of both dexmedetomidine and propofol infusing, the BIS values stayed in the mid-50s. Once again the patient experienced supraventricular tachycardia requiring cardioversion. Over the next 105 minutes, this scenario repeated itself twice. Each time the isoproterenol was withheld or added, the BIS value would plummet or rise respectively.

After 10 hours from the time of induction, the ablation process was complete and the case ended. The isoproterenol was discontinued, and, as before, the BIS value plummeted following its withdrawal. The BIS value was now 0. Both the dexmedetomidine and propofol were discontinued, and the patient was allowed to recover over a 45-minute span. Following the return of airway reflexes and BIS values in the low 90s, the patient was extubated. She was then transported to the postanesthesia care unit and admitted to a monitored setting for 24 hours. During this admission the patient had 2 asymptomatic episodes of hypotension (blood pressure, 80/40 mm Hg). Both responded to fluid administration. Aside from the hypotension, the patient had an uneventful hospital admission. The patient was discharged reporting only a headache. No other ill effects from anesthesia were reported.

Discussion

The use of BIS for monitoring neuronal function under general anesthesia has been expanding. Interestingly, so have the reports of altered BIS values in response to drug administration. Hans and colleagues[1] confirmed a paradoxical elevation in BIS values and a deepening of hypnosis with the addition of ketamine to a sevoflurane-based anesthetic. Results regarding the effects of ketamine on BIS were similarly reported by Morioka[2] as well as Hirota.[3] Overestimated BIS values due to muscle activity also have been reported. Vivien et al[4] demonstrated that the administration of neuromuscular blocking agents to sedated intensive care unit patients decreased BIS values and correlated with electromyographic data. Fodale[5] recently summed up the work of Ghoneim[6] regarding the ability of physostigmine and other cholinesterase inhibitors to antagonize the hypnotic effect, resulting in arousal and higher BIS values. Further studies by Meuret et al[7] showed that physostigmine can reverse propofol-induced unconsciousness in human volunteers. Based on his work, Meuret et al concluded that "unconsciousness produced by propofol is mediated, in part, via interruption of central cholinergic muscarinic transmission."[7]

Perhaps more relevant to our case is the report by Ishiyama and colleagues[8] who demonstrated that the use of ephedrine, an indirect acting noncatecholamine that stimulates alpha and beta receptors, significantly elevated BIS values. Ishiyama and colleagues also reported, in the same study, the lack of effect on BIS with the use of phenylephrine, a noncatecholamine that is a selective $alpha_1$ agonist. This report indicates that beta stimulation by ephedrine resulted in a similar elevation of BIS values as we report with the use of the direct beta-stimulating drug isoproterenol.

The ability of isoproterenol to stimulate beta receptors centrally and increase arousal has been supported by research using rodent models. Studies conducted by Berridge and colleagues[9,10] document noradrenergic beta receptors in the medial septal and medial preoptic area of the locus coeruleus. Stimulation of these receptors exerts wake-promoting actions and overall arousal states in the rat model. Beta stimulation and increased anesthetic requirement should not be surprising. Work by Johansen et al[11] demonstrated a decreased anesthetic requirement and promoted electroencephalogram burst suppression with the use of esmolol, a beta blocking agent.[12]

At the time of this case, it was our impression that the isoproterenol was responsible for the elevations in BIS values. The mechanism was suspected to be an increase in neuronal discharge caused by beta receptor activation. We based our suppositions on the well-established ability of isoproterenol to produce central nervous system stimulation. Agitation and restlessness are common side effects of the use of isopro-

terenol as a bronchial dilator in its nebulized form.[13]

Isoproterenol, a synthetic catecholamine, is formed by the addition of an isopropyl group to the terminal amine of norepinephrine. Isoproterenol acts on both $beta_1$ and $beta_2$ receptors to produce an increase in heart rate, myocardial contractility, and automaticity. Isoproterenol is devoid of alpha activity and is metabolized quickly in the liver by catecholamine *O*-methyl transferase, therefore requiring an infusion to maintain therapeutic levels.[13-15]

Based on the assumption of sympathetic feedback it was felt that the addition of dexmedetomidine would be an excellent choice as an adjunct to propofol. Dexmedetomidine was chosen for its $alpha_2$ stimulating ability. This choice was based on past experience with the $alpha_2$ stimulant clonidine. More recently, Fehr et al[16] confirmed clonidine's ability to decrease BIS values and decrease anesthetic requirements. Dexmedetomidine is highly specific for $alpha_2$ receptors and is considered a true selective agonist. Dexmedetomidine has dose-related sedative, anxiolytic, analgesic, and anesthetic sparing effects.[17] Its major site of hypnotic effects is mediated via $alpha_2$ adrenergic receptors found in the locus coeruleus.[18] Dexmedetomidine undergoes biotransformation in the liver via the cytochrome P-450 system and has a half-life of 2 hours. It is administered as an intravenous infusion in a loading dose of 1 µg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 µg/kg per hour.[19]

Significance

In reviewing the literature, there appears to be no reports of correlation between isoproterenol and anesthetic requirements. Nor are there any studies relating isoproterenol to a patient's level of awareness while under anesthesia. This may be due to 2 factors. Isoproterenol is now used very infrequently, and the ability to monitor neuronal activities by using the BIS monitors is relatively new.

In light of this case some interesting questions arise. Questions such as can isoproterenol and other drugs that increase neuronal outflow generate consistently higher BIS values? If so, do these elevated BIS values represent an organized or random activity of the central nervous system? And finally, do these elevated BIS values then translate into a greater sense of awareness under general anesthesia. If the answer is yes to any of these questions, we must carefully consider how we use the BIS monitor and how it relates to drug administration for each case.

REFERENCES

1. Hans P, Dewandre PY, Brichant JF, Bonhomme V. Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflorene anaesthesia. *Br J Anaesth.* 2005;94:336-340.
2. Morioka N, Ozaki M, Matsukawa T, Sessler D, Atarshi K, Suzuki H. Ketamine causes a paradoxical increase in the bispectral index [abstract]. *Anesthesiology.* 1997;87:A502.
3. Hirota K, Kubota T, Ishihara H, Matsuki A. The effects of nitrous oxide and ketamine on the bisectral index and 95% spectral edge frequency during propofol-fentanyl anaesthesia. *Euro J Anaesthesiol.* 1999;16:779-783.
4. Vivien B, Di Maria S, Ouattara A, Langeron O, Coriat P, Riou B. Overestimation of Bispectral Index in sedated intensive care unit patients revealed by administration of muscle relaxant. *Anesthesiology.* 2003;99:9-17.
5. Fodale V, Tescione M, Pratico C. Cholinesterase inhibitors, neuromuscular blocking drugs and perioperative memory enhancement [letter]. *Anesthesiology.* 2004;101:1483-1484.
6. Ghoneim MM. Drugs and human memory (part 2) Clinical, theoretical, and methodologic issues. *Anesthesiology.* 2004;100:1277-1297.
7. Meuret P, Backman SB, Bonhomme V, Plourde G, Fiset P. Physostigmine reverses propofol-induced unconsciousness and attenuation of the auditory steady state response and bispectral index in human volunteers. *Anesthesiology.* 2000;93:708-717.
8. Ishiyama T, Oguchi T, Iijima T, Matsukawa T, Kashimoto S, Kumazawa T. Ephedrine, but not phenylephrine, increases bispectral index values during combined general and epidural anesthesia. *Anesth Analg.* 2003;97:780-784.
9. Berridge CW, Bolen SJ, Manley MS, Foote SL. Modulation of forebrain electroencephalographic activity in the halothane-anesthetized rat via actions of noradrenergic beta-receptors within the medial septal region. *J Neurosci.* 1996;16:7010-7020.
10. Berridge CW, Isaac SO, Espana RA. Additive wake-promoting actions of medial basal forebrain noradrenergic alpha1- and beta-receptor stimulation. *Behav Neurosci.* 2003;117:350-359.
11. Johansen JW, Flaishon R, Sebel PS. Esmolol reduces anesthetic requirement for skin incision during propofol/nitrous oxide/morphine anesthesia. *Anesthesiology.* 1997;86:364-371.
12. Johansen JW. Esmolol promotes electroencephalographic burst suppression during propofol/alfentanil anesthesia. *Anesth Analg.* 2001;93:1526-1531.
13. McEvoy JK et al, eds. *American Hospital Formulary Service (AHFS) Drug Information 2004.* Bethesda, Md: American Society of Health-System Pharmacists, Inc; 2004:1260-1263.
14. Barnes P, Mueller R. Bronchodilators. In: Munson PL, Mueller RA, Breese GR, Berndt WO, eds. *Principals of Pharmacology: Basic Concepts and Clinical Applications.* New York, NY: Chapman & Hall; 1995:585-589.
15. Murphy AW, Platts-Mills TAE. Drugs used in asthma and obstructive lung disease. In: Brody TM, Larner J, Minneman KP, eds. *Human Pharmacology: Molecular to Clinical.* 3rd ed. St Louis, Mo: Mosby-Year Book, Inc; 1998:797-810.
16. Fehr SB, Zalunardo MP, Seifert B, et al. Clonidine decreases propofol requirements during anaesthesia: effect on bispectral index. *Br J Anaesth.* 2001;86:627-632.
17. Ebert T, Maze M. Dexmedetomidine: Another arrow for the clinician's quiver [editorial]. *Anesthesiology.* 2004;101:568-570.
18. Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats. *Anesthesiology.* 1992;76:873-875.
19. McEvoy JK et al, eds. *American Hospital Formulary Service (AHFS) Drug Information 2004.* Bethesda, Md: American Society of Health-System Pharmacists, Inc; 2004:2411-2412.

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