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Case Report

Propranolol Use for a Psychiatric Indication Contributing to Intra-anesthetic Hypotension: A Case Report

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Abstract

Intra-operative hypotension is generally responsive to decreasing anesthetic depth and/or intravenous fluid boluses. We present a 20-year-old male with multiple refractory intra-anesthetic hypotensive episodes, determined to have multifactorial etiology. Using propranolol to treat anxiety and Asperger's syndrome, an indication likely to increase due to recent research efforts, was identified as a key contributing factor. There are no published recommendations regarding the peri-operative management of beta-blocker therapy prescribed for non-cardiac indications, and anesthesiologists should consider preoperative discontinuation because there is no elevated risk of major adverse cardiac events.

ABBREVIATIONS

IV: Intravenous; MRI: Magnetic Resonance Imaging; SSRIs: Selective Serotonin Reuptake Inhibitors; ER: Extended-Release; PO: By Mouth; QAM/QPM: Every Morning/Every Evening; BP: Blood Pressure; HR: Heart Rate; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ASD: Autism Spectrum Disorder; MACE: Major Adverse Cardiac Events

INTRODUCTION

Intra-operative hypotension is a common occurrence under general anesthesia. This can be particularly notable during general anesthesia for imaging studies, as the lack of surgical stimulation compounds the decrease in sympathetic outflow. Generally, hypotension of this sort is responsive to decreasing anesthetic depth, IV fluid boluses and, if necessary, vasopressor boluses; however, hypotension refractory to these interventions warrants further investigation. Written consent to publish this case report has been obtained from the patient and the patient's family in accordance with HIPAA Privacy Regulations.

CASE PRESENTATION

The patient is a 20 year-old male with a history of metastatic medulloblastoma, status-post gross total resection, treatment with 6 cycles of high-dose chemotherapy and craniospinal radiation with boost to the 4th ventricle and infundibular regions, who presents every 3 months for post-treatment evaluations including MRI of the brain and spine (no evidence of recurrent or progressive tumor to date). His past medical history is significant for diagnoses of Asperger's syndrome, attention deficit hyperactivity disorder, depression, and anxiety at the approximate age of 15 years, which were treated with regimens including propranolol, stimulants (amphetamine/dextroamphetamine or methylphenidate), and SSRIs. Propranolol was prescribed as 160 mg extended-release (ER) PO QAM and 40 mg standard-release PO QPM or 240 mg ER PO QAM. On these propranolol regimens, he experienced infrequent symptoms of orthostatic hypotension without syncope and mild exercise limitation due to fatigue. Because of anxiety and claustrophobia, the patient requested general anesthesia during diagnostic imaging studies.

During four consecutive anesthetics for MRI of the brain and spine with propofol total intravenous anesthesia, the patient experienced significant refractory hypotension, necessitating multiple interventions with IV fluid boluses and vasopressors. The recurrence and escalating severity of these events prompted us to evaluate all of the previous anesthetic records and the concurrent medical status documentation to determine the cause and mechanisms of the intra-anesthetic hypotensive episodes.

During the previous 2 years, the patient underwent 14 anesthetics (6 brain/spine MRIs, 3 radiation therapy treatments, 3 lumbar punctures and 2 central line surgeries). All but 2 of the anesthetics were propofol-based total intravenous anesthesia with fentanyl boluses; 1 anesthetic for central line surgery and 1 for MRI were sevoflurane-based anesthetics following induction with propofol. Hypotension (defined as systolic BP <90 mm Hg and diastolic BP <60 mm Hg) and bradycardia (defined as HR<60) were noted during 13 of 14 and 3 of 14 anesthetic sessions, respectively. Interventions to treat the intra-anesthetic hypotension included IV fluid bolus administration in 8 anesthetic sessions and vasopressors in 4 (Table 1).

Upon further investigation of the possible contributing factors to intra-anesthetic hypotension, we found that the patient tolerated the radiation phase of his therapy well without significant complications. His high-dose chemotherapy course was complicated by two episodes of febrile neutropenia and uncompensated septic shock requiring vasopressor support. He had normal cardiac function as assessed by serial echocardiography (Table 1) until 1 month prior to completion of therapy when mild (grade 1) diastolic dysfunction was noted that resolved on reassessment 2 weeks later.

The patient's post-therapy course was notable for a diagnosis of acute chemotherapy-induced cardiomyopathy 2 months after completion of chemotherapy, which was treated with low-dose carvedilol for several weeks. Subsequently, echocardiograms demonstrated a return to baseline cardiac function off carvedilol (Table 1). He had regular follow-up appointments with a cardiologist, and echo/electrocardiograms were performed per protocol every 3 months given the risk for chronic cardiomyopathy.

One year after completion of therapy, treatment with enalapril was started. His low normal systolic function (ejection fraction, 50-55%) did not seem to explain the trend toward hypotension episodes according to the cardiologist. Evidence supportive of mild adrenal insufficiency as well as hypothyroidism was found at the last anesthetic session (Table 1). Overall, treatment with propranolol was identified as a contributing factor concurrent with 6 of 14 anesthetic sessions (Table 1).

DISCUSSION

Hypotension under general anesthesia is a common phenomenon, particularly in adult patients undergoing general anesthesia for non-stimulating procedures or, as in this case, imaging modalities. However, it is much less common that hypotension is refractory to repeated fluid and vasopressor boluses without a known underlying cause. The patient presented above almost certainly had a multifactorial explanation for hypotension, including, but not limited to, subclinical cardiomyopathy, endocrinologic abnormalities, or both. One cannot ignore, though, the role of his psychiatric medications; namely amphetamines and beta-blockers. Chronic amphetamine use is known to decrease the body's catecholamine stores, creating a type of adrenal insufficiency [1]. Beta-blockers

Table 1: Summary of Clinical Picture.

Phase of Treatment	Months From Diagnosis	Procedure	Lowest SBP/DBP; HR	Interventions Required		TTE Findings	Serum Cortisol Level	Beta-Blocker Regimen
				Fluid Bolus(es)	Vasopressors			
RT	1	LP	**74/34**; 70	No	None	Normal		**Propranolol**
	1	RT	**72/24**; 66	No	None			**Propranolol**
	1	RT	**78/38**; 64	No	None			**Propranolol**
	1	RT	**68/28**; 64	No	None			**Propranolol**
CHEMOTHERAPY	3	Line placement; LP	**70/34**; **45**	**Yes**	None	Normal		**Propranolol**
	5	MRI brain/spine	**68/30**; 65	**Yes**	None		97.8 (H)	None
	8	Line removal	**66/32**; 102	**Yes**	None	Normal (s/p septic shock)		None
	8	PICC insertion	**68/34**; 90	No	None			None
OFF THERAPY	10	MRI brain/spine	**88/35**; 85	**Yes**	None		23.3	None
	10	LP	90/**38**; 88	No	None	**EF 50%**	15.8	None
	13	MRI brain/spine	**55/24**; 70	**Yes**	**Phenylephrine 200 mcg IV**			**Carvedilol**
	16	MRI brain/spine	**45/20**; **54**	No	**Phenyle-phrine200 mcg IV**	Normal		None
	19	MRI brain/spine	**62/26**; **45**	**Yes**	**Ephedrine 15mg IV/50mg IM**			**Propranolol**
	22	MRI brain/spine; LP	**70/26**; 78	**Yes**	**Epinephrine infusion**[b]	EF 50-55%	**7.3/13.4**[c]	None

Legend: [a]Bold text indicates notable findings/interventions; [b]Started prophylactically to prevent hypotension; [c]Failed ACTH stimulation test
Abbreviations: RT: Radiation Therapy; SBP/DBP: Systolic/Diastolic Blood Pressure; HR: Heart Rate; TTE: Transthoracic Echocardiogram; LP: Lumbar Puncture; PICC: Peripherally Inserted Central Catheter; EF: Ejection Fraction; S/P: Status Post; IM: Intramuscular

were likely a contributing factor to this patient's hypotension. He had been intermittently taking high-dose propranolol (up to 240 mg ER per day) for psychiatric reasons, a potential up-and-coming indication. A primary role for propranolol was easily conceived during his initial anesthetic exposures in the absence of consequential comorbidities and could be identified as a significant compounding factor when he later developed toxicities secondary to oncologic treatment.

Propranolol, a centrally and peripherally active nonselective beta-adrenergic antagonist that readily crosses the blood-brain barrier, reduces noradrenergic system activity and has been used off-label for treatment of anxiety since the late 1960s. Acting in the cardiovascular system, it inhibits tachycardia, reduces blood pressure, and diminishes palpitations during acute anxiety and panic [2]. Efficacy of beta-blockers against the physical symptoms of anxiety, however, has not been systematically and rigorously validated. A recent systematic review and meta-analysis demonstrated the lack of well-designed clinical studies [3]: no randomized controlled trials on the effects of propranolol in generalized anxiety disorder were available. The meta-analysis demonstrated no statistical difference between the effects of propranolol and benzodiazepines on anxiety and panic attack frequency. However, statistical equivalence of the efficacy of propranolol versus that of benzodiazepines in treating individuals with panic disorder has not been shown [3]. Regardless, many prescribers in primary care settings favor propranolol over medications such as benzodiazepines because they are non-addicting and non-sedating [2]. Additionally, there has been increasing interest in the use of propranolol in children with concomitant anxiety and migraine headache because propranolol is effective for migraine prophylaxis in pediatric patients [4].

Recently, the psychopharmacological properties of propranolol have regained research attention related to the drug's amnesic effect on retrieved fear memory [2,5] and specific application in autism spectrum disorder (ASD) given evidence of increased anxiety in ASD [6] and a potential association between autonomic dysregulation and anxiety in this population [7]. Clinical use of propranolol for anxiety in ASD is likely to increase in light of these research interests and efforts.

The anesthetic implications of propranolol have been well defined by studies dating back to the 1960s [8]. Multiple studies, guidelines, and recommendations highlight the risks and benefits of perioperative beta-blocker therapy, with the general consensus being to continue beta-blocker therapy for those undergoing chronic therapy [9]. However, the entirety of the literature relating to beta-blockers and anesthesia does so under the assumption that the beta-blockers are taken for cardiovascular diagnoses (e.g., coronary artery disease, congestive heart failure, cardiac arrhythmia). Therefore, recommendations exist for patients taking beta-blockers for cardiac surgery and non-cardiac surgery; however, there are no recommendations for patients undergoing anesthesia to whom beta-blockers are prescribed for non-cardiovascular indications. Perioperative beta-blocker therapy has known risks, including hypotension, stroke, and death [10]; however, the aforementioned guidelines recommend continuing the therapy in spite of these risks to concomitantly reduce the risk of major adverse cardiac events (MACE). In patients without the elevated risk of MACE, such as those taking propranolol for ASD, it may be prudent to hold the beta-blocker perioperatively to avoid the increased risk of hypotension, stroke, and death. One must be aware, though, of the possibility of propranolol withdrawal syndrome and the resultant increased sensitivity to catecholamine surges seen within just 2-3 days of propranolol cessation [11]. As there are no randomized controlled trials involving perioperative beta-blocker therapy for non-cardiac indications, management decisions should be made on a case-by-case basis with input from the patient's prescriber and anesthesiologist.

Hypotension not responsive to conventional management (e.g., lowering the anesthetic dose, changing anesthetic medications, fluid boluses, vasopressors) should be investigated. Often, a multi-factorial etiology will be determined. However, one cannot neglect the contents of a patient's medication list. Medications prescribed for psychiatric indications are frequently overlooked although they may play an important role in intraoperative cardiovascular pathophysiology.

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