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Gabapentin and intraoperative hypotension

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Keypoints

1. Gabapentin is the structural analog of gamma amino butyric acid (GABA). Although its definitive mechanism of action is unknown, gabapentin binds to the $\alpha_2\delta$-subunit of voltage-gated calcium channels thereby inhibiting the influx of intracellular calcium causing a decrease in the release of excitatory neurotransmitters.
2. Gabapentin's postulated mechanisms of action include increased GABA levels and/or decreased glutamate release within the central nervous system.
3. Clinical applications of gabapentin initially included its use as an anticonvulsant; however, it was subsequently demonstrated to be effective in the control of acute and chronic pain related to postherpetic neuralgia, acute surgical pain, diabetic neuropathy, and radicular pain.
4. Despite its potential role in reducing perioperative opioid use, adverse effects of gabapentin may include dizziness, visual disturbances, and intraoperative hypotension.

Abstract

Gabapentin is commonly used perioperatively as an adjunct to decrease opioid requirements and hence opioid-related adverse effects. Despite its widespread use, recent information has provided concern regarding its adverse effect profile. Perioperative gabapentin administration has been associated with greater incidence of dizziness, visual disturbances, and increased risk for postoperative pulmonary complications. We present a 13-year-old female who experienced intraoperative hypotension which was eventually attributed to the preoperative administration of gabapentin. The perioperative use of gabapentin is discussed, its adverse effect profile reviewed, and its potential role in perioperative blood pressure changes presented.

Keywords

Gabapentin, intraoperative hypotension, posterior spinal fusion

Introduction

Blood pressure (BP) monitoring has played an important role in ensuring patient safety during the delivery of anesthesia since the sphygmomanometer was endorsed by Dr. Harvey Cushing in the early 1900s. It remains a standard for intraoperative monitoring required by the American Society of Anesthesiologists (ASA) during any general anesthetic.[1] Pediatric anesthesiologists routinely administer fluid, blood products, and inotropic agents based on deviations from what is considered a normal BP as intraoperative hypotension may be a risk factor for postoperative morbidity and mortality.[2-5] A study

surveying over 450 members of the Society of Pediatric Anesthesia (SPA) and the Association of Paediatric Anaesthetists (APA) of Great Britain and Ireland reported that 76% of respondents defined significant hypotension in children undergoing anesthesia as a 20-30% reduction from the baseline systolic blood pressure (SPB).[6] Physicians' definitions for intraoperative hypotension in children may vary based on factors such as age, type of surgery, and health status of each patient.

Various factors may be responsible for intraoperative hypotension including vasodilation from anesthetic medications, intravascular hypovolemia, blood loss, myocardial depression with low cardiac output, high intra-thoracic pressure, impairment of sympathetic nervous system function or compromised baroreflex regulation.[7] We present a 13-year-old who developed intraoperative hypotension during posterior spinal fusion (PSF) which was eventually attributed to the preoperative administration of gabapentin. The perioperative use of gabapentin is discussed, previous reports of intraoperative hypotension related to its use reviewed, and its potential role in perioperative BP changes presented.

Case report

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). The patient was a 13-year-old, 53.4 kilogram adolescent female who presented for PSF to treat progressive idiopathic scoliosis of the thoracic region. Her past surgical history was negative with no past medical concerns besides idiopathic scoliosis. She denied any recent health issues and her vital signs were unremarkable. Her airway examination revealed a Mallampati class II airway with a thyromental distance greater than 3 fingerbreadths. Her cardiorespiratory examination was unremarkable. The patient was held *nil per os* for 8 hours. Premedication included gabapentin 600 mg and aprepitant 40 mg by mouth. She was transported to the operating room and routine American Society of Anesthesiologists' monitors were placed. Anesthesia was induced by the intravenous administration of propofol (100 mg), 2 mg midazolam (2 mg), and sufentanil (20 µg). Endotracheal intubation was facilitated by the administration of rocuronium (15 mg). Following anesthetic induction and endotracheal intubation, two large bore peripheral intravenous cannulas and an arterial cannula were placed. Neurophysiological monitoring was performed in accordance with our previously reported protocol.[8] Maintenance anesthesia included desflurane titrated to maintain the bispectral index at 50-60, ketamine at 0.25 mg/kg/hour, methadone (10 mg), and a sufentanil infusion adjusted from 0.1-0.3 µg/kg/hour to maintain the mean arterial pressure at 60-70 mmHg. The patient was positioned prone on the operating room table. Baseline arterial blood pressure was 106/41 mmHg with a mean arterial pressure of 70-75 mmHg. Measures to decrease the need for allogeneic blood products included tranexamic acid (50 mg/kg bolus followed by 5 mg/kg/hour) and intraoperative cell salvage. Early into the procedure (within the first 2 hours), the patient developed hypotension with a low BP of 34/29 mmHg (MAP 30 mmHg). This was treated with isotonic fluid (10 mL/kg) and incremental bolus doses of phenylephrine (10-50 µg/mL). Although the BP was maintained with intermittent doses of phenylephrine, there was persistent and recurrent episodes of hypotension as the effects of the phenylephrine boluses subsided. The sufentanil infusion was decreased to 0.1 µg/kg/hour. The desflurane remained at an expired concentration of 3.5-4% to maintain the bispectral index at 50-60. Laboratory analysis revealed no base deficit, an ionized calcium of 1.06 mmol/L (normal: 1.22 – 1.35 mmol/L), a hemoglobin of 11 g/dL, and a hematocrit of 34.2%. Estimated blood loss was 200 mL at this point. A phenylephrine infusion was started at 0.5 µg/kg/min and titrated to maintain the MAP at 60-70 mmHg. The phenylephrine infusion was continued at 0.5-2 µg/kg/min for the majority of the surgical procedure and then slowly decreased and discontinued toward the end of the case after 4-5 hours. No specific etiology was determined for the hypotension other than the preoperative gabapentin. Total

intraoperative time was approximately 7 hours with an estimated blood loss of 1000 mL. Intraoperative fluids included 2000 mL of normal saline. A total of 475 mL of blood was washed and returned via the cell saver. Prior to completion of the surgical procedure, postoperative prophylaxis to prevent nausea and vomiting included ondansetron (4 mg) and dexamethasone (4 mg). Postoperative pain management included acetaminophen (15 mg/kg), ketorolac (0.5 mg/kg), and hydromorphone. This was followed by patient-controlled analgesia with hydromorphone for postoperative analgesia. Residual neuromuscular blockade was reversed with sugammadex. Once the procedure was completed, the patient was turned supine and her trachea was extubated. She was transferred to the post-anesthesia care unit (PACU) and then admitted to the inpatient ward. There were no episodes of hypotension in the PACU or on the inpatient ward. No postoperative gabapentin was administered. The patient's postoperative course was unremarkable and she was discharged home on post-operative day 2.

Discussion

Gabapentin, a structural analog of gamma amino butyric acid (GABA), was initially approved by the United States Food & Drug Administration as an anticonvulsant for patients older than 12 years of age in 1993.[9] In 2004, approval was added for use in the treatment of pain related to postherpetic neuralgia.[9] In recent years, the off-label uses of gabapentin have expanded as has its use in various age groups. From 2013 to 2017, gabapentin prescriptions increased from 44 million to 68 million annually, making it one of the most commonly prescribed medications.[10]

Gabapentin, and its structurally similar compound, pregabalin, both fall under the class of drugs known as gabapentinoids. These medications (gabapentin and pregabalin) share similar half-lives of 6 hours; however, they differ in other pharmacokinetic parameters with pregabalin having a more rapid absorption and higher bioavailability than gabapentin.[10,11] Gabapentin (1-aminomethyl-cyclohexaneacetic acid) varies in structure from gamma-aminobutyric acid (GABA) only by the addition of a cyclohexyl group to the carbon backbone of the GABA molecule.[12] Gabapentin's mechanism of action has not been fully defined and remains somewhat controversial. It is known to cross the blood brain barrier via large amino-acid transporters.[13] Gabapentin binds to the $\alpha_2\delta$-subunit of voltage-gated calcium channels of neurons in the spinal cord and peripheral nerves. This binding is postulated to reduce excitatory neurotransmitter release resulting in decreased neuronal hyperexcitability.[13] Gabapentin also reduces the release of glutamate in the dorsal horn of the spinal cord.[14] These proposed mechanisms of action are supported by the limited efficacy of analogues of gabapentin which do not bind to the $\alpha_2\delta$-subunit.[15,16] Gabapentin has also been shown to increase GABA levels in the CNS, which may account for its anticonvulsant activity.[17] Gabapentin administration results in decreased excitatory neurotransmitter release from activated nociceptors, inhibition of ascending pain transmission, activation of descending inhibitory pathways, and prevention of hyperalgesia.[18]

The $\alpha_2\delta$-subunit of the voltage-gated calcium channels are prevalent in the cerebellum and hippocampus, providing an explanation for the adverse CNS effect profile of gabapentin including dizziness, ataxia, balance disorders, visual disturbances, sedation, somnolence, and cognitive impairment.[18] During the perioperative period, gabapentinoid use has been linked with a dose-dependent increased risk of postoperative pulmonary complications (such as respiratory failure or the need for reintubation of the trachea) and intensive care unit admission.[18] This association was noted without a true postoperative benefit such as shorted duration of stay or decreased opioid requirements.[18] In a recent systemic review, Evoy et al. noted the potential for significant patient harm from the misuse or abuse of gabapentinoids.[19] Although the gabapentinoids may produce beneficial effects when used alone, they are often prescribed with other medications including opioids.[19] The authors cautioned that there was growing evidence of potential patient harm

when gabapentinoids were administered to patients with a history of opioid abuse including increased hospitalization and opioid-related overdose mortality risk.[19] Despite the recognized limitations of their study design, they suggested that the misuse or abuse of the gabapentinoids is growing and that it represents a public health threat.[19] Similar evidence suggesting the potential for an increased risk of opioid-related deaths with the concomitant administration of opioids and gabapentinoids in adults was published from the Drug Benefit program and registries for chronic illnesses from Ontario, Canada.[20]

In addition to the potential for patient harm and adverse effects, others have questioned the analgesic benefits of gabapentin or pregabalin in various acute and chronic pain conditions.[10] A meta-analysis of more than 24,000 adult patients from 281 trials demonstrated no clinically significant analgesic effect with the perioperative administration of gabapentinoids.[21] Although gabapentinoids decreased postoperative nausea and vomiting, they were associated with a longer hospital length of stay and a higher incidence of dizziness and visual disturbances.[21] However, a 2016 report by the American Pain Society recommended gabapentin or pregabalin as options for components of multimodal analgesia for many commonly performed surgical procedures.[22] Despite these opinions, the general consensus remains that there is a lack of data showing the efficacy of gabapentin perioperatively and there appears to be a clinical shift away from its use in this setting.[18,21]

As noted in our patient, gabapentin may be associated with intraoperative blood pressure changes and perhaps a limitation of the normal physiologic response to anesthetic agents, fluid shifts, and blood loss that may result in intraoperative hypotension. Our patient developed intraoperative hypotension early during the procedure. There was limited response to decreasing the dose of the anesthetic agents (sufentanil and desflurane). At the time of the hypotension, blood loss had been limited and therefore was not thought to be a significant contributing event. Despite treatment with isotonic fluid and incremental bolus doses of phenylephrine, hypotension recurred. Laboratory analysis demonstrated a low normal ionized calcium (which was treated with limited blood pressure response). No other end-organ effects of the hypotension were noted as there was no increasing base deficit or lactic acidosis. The hypotension was eventually attributed to gabapentin resulting in systemic vasodilatation. Treatment was initiated with a phenylephrine infusion for the majority of the surgical procedure until it was gradually discontinued toward the end of the case.

The potential effects of gabapentin on blood pressure have been described in the adult population. In a prospective, randomized trial evaluating sodium nitroprusside (SNP) requirements in adults undergoing endoscopic sinus surgery, gabapentin decreased SNP dosing.[23] When compared with placebo, patients who received oral preoperative gabapentin (1200 mg) required significantly less SNP to maintain the desired blood pressure value. Gabapentin has also been shown to decrease the hypertensive response to direct laryngoscopy and endotracheal intubation.[24,25] Potential mechanisms proposed for the hemodynamic effects of gabapentin include vasodilation via inhibition of voltage gated calcium channels in peripheral vasculature and a direct action on skeletal/smooth muscle.[26-29] Preoperative gabapentin has also been demonstrated to reduce postoperative catecholamine and cortisol levels as well as blunting similar changes occurring in response to nocioception.[29-31] Additional hemodynamic effects may occur in related central effects via the nucleus tractus solitarii (NTS) effects.[13] The NTS, which is located in the brainstem of the central nervous system, is highly involved in the regulation of cardiovascular function.[13] In the 2011, the FDA-approved labeling text for Neurontin®, with data from two large clinical trials listed hypotension as an infrequent adverse cardiovascular events. Despite these findings occurring in less than 1% of the patients, gabapentin-induced hypotension was reported as an adverse event for a small subgroup of this population. One anecdotal case report describes the development of complete

atrioventricular block due to an overdose of pregabalin.[32] In summary, we present the development of intraoperative hypotension which was eventually attributed to the preoperative administration of gabapentin. Various factors may be responsible for intraoperative hypotension including vasodilation from anesthetic medications, intravascular hypovolemia, blood loss, myocardial depression with low cardiac output, high intra-thoracic pressure, impairment of sympathetic nervous system function, and compromised baroreflex regulation. Although uncommon, hemodynamic effects have been reported with gabapentin and the mechanism of action of the gabapentinoids on voltage-gate calcium channels suggest that hemodynamic changes may be seen with these agents or that they may blunt the normal intraoperative response to changes in intravascular volume, surgical stimulation, and anesthetic agents. Although still commonly used as part of a multi-modal approach to improve analgesia and limit opioid needs, given the potential for adverse effects, continued evaluation of the role of these agents in perioperative care is needed.

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