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Use of Clevidipine as an Alternative to Nitroglycerin in Cardiac Surgery: Case Report and Current Literature

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Abstract

Cardiac surgery requires periods of therapeutic hypotension. Anesthesia providers often administer intravenous nitroglycerin to accomplish these meticulous hemodynamic goals. However, patients can manifest adverse responses to nitroglycerin, such as decreased stroke volume; decreased cardiac output; decreased renal, splanchnic, and cerebral perfusion; and tolerance. This report summarizes a case of tachyphylaxis to nitroglycerin that occurred intraoperatively in a patient undergoing cardiac surgery in whom therapeutic hypotension was being induced. In situations such as this, an alternative medication is needed that is just as effective and safe. Clevidipine is currently the best choice for this because of its rapid onset and termination of action and specific arterial effects. Multiple studies have shown that clevidipine is as effective and safe as nitroglycerin.

INTRODUCTION

This report summarizes a case of tachyphylaxis to nitroglycerin that occurred intraoperatively during cardiac surgery in a patient in whom therapeutic hypotension was being induced. The anesthesia providers were prepared with an ample supply of nitroglycerin and had other antihypertensive agents such as hydralazine, labetalol, and esmolol available in the operating room. However, the ideal medication for inducing therapeutic hypotension and most similar to nitroglycerin in its ability to create rapid-onset, transient hypotension, ie, clevidipine, was not readily available. The therapeutic hypotension had been requested by the surgeon for surgical optimization; thus, the patient experienced no harm despite the lack of expected response to nitroglycerin and delay in onset of therapeutic hypotension. However, the anesthesia providers recognized the need to avoid similar hemodynamic delays, particularly in less forgiving scenarios in which timing is crucial.

CASE SUMMARY

A 70-year-old man presented for off-pump coronary artery bypass grafting (CABG) surgery. The patient was 170 cm tall, weighed 89 kg, had a body mass index of 31, and received a physical status indicator of 4. He denied any drug allergies. Aspirin 81 mg orally twice a day was his only home medication. However, his medical history included hypertension, coronary artery disease, angina with exertion, peripheral vascular disease, chronic obstructive pulmonary disease, osteoarthritis, degenerative disc disease, vertigo, and an asymptomatic infrarenal abdominal aortic aneurysm. The patient quit smoking 10 years ago, and reported alcohol consumption 3 times per week.

A chest x-ray showed signs of mild emphysema, and the patient's lungs were clear to auscultation bilaterally. A 2D echocardiogram revealed mild concentric hypertrophy of the patient's heart, left ventricular diastolic dysfunction, and an ejection fraction of about 55%-65%. Heart tones were regular to auscultation. Preoperative laboratory results included a hemoglobin of 14 g/dL, hematocrit of 44%, creatinine of 0.9 mg/dL, and potassium of 4.3 mEq/L. Airway assessment showed the patient to have full range of motion of his neck, interincisor distance of 3 cm, temporomandibular distance of 3 cm, and a Mallampati score of 2.

General anesthesia was induced with midazolam 5 mg intravenous (IV), sufentanil 50 mcg IV, propofol 150 mg, and inhaled sevoflurane. The patient also received vecuronium 10 mg IV. The airway was secured with an 8-mm endotracheal tube. Acetaminophen 1000 mg and cefazolin 2 g were given as IV infusions. A central venous introducer and pulmonary artery catheter were placed. Transesophageal echocardiography (TEE) was performed. The mediastinum was accessed via midline sternotomy, and the surgeon began to harvest the internal mammary artery and tack up the pericardium. When the heart was manipulated for off-pump grafting, the pulmonary arterial systolic pressure increased suddenly from 30 mm Hg to 80 mm Hg. ST segment changes were noted per electrocardiogram, and TEE revealed hypokinesis of the lateral wall of the heart.

The decision was made to abort the off-pump attempt at grafting and to initiate cardiopulmonary bypass (CPB) to complete the procedure. Nitroglycerin was administered in 40-80 mcg intermittent IV boluses to maintain systolic blood pressure (BP) at less than 100 mm Hg during placement of the aortic cannula. Milrinone infusion was started at 0.375 mcg/kg/min. CPB was initiated and mean arterial pressure was maintained at or greater than 60 mm Hg.

The grafts were completed, and the patient was weaned from CPB. When it was time to remove the aortic cannula, the surgeon requested a systolic BP less than 100 mm Hg. Nitroglycerin 200 mcg was given intravenously. The systolic BP changed from 147 mm Hg to 144 mm Hg. Nitroglycerin 400 mcg IV was given. The systolic BP then decreased to 131 mm Hg. Nitroglycerin 1400 mcg IV was given, and the systolic BP decreased to 120 mm Hg. Minutes passed and the surgeon still waited to remove the aortic cannula. Sufentanil 50 mcg IV and vecuronium 4 mg IV were given at that point. Nitroglycerin was attempted again, in a dose of 2000 mcg IV. The systolic BP remained at 124 mm Hg. Another dose of nitroglycerin 2000 mcg IV was given, and the systolic BP decreased to 111 mm Hg. Nitroglycerin 2000 mcg IV was repeated, and the systolic BP decreased to 103 mm Hg. The aortic cannula was then removed without complications. Seven minutes had passed since the surgeon's initial request for systolic BP less than 100 mm Hg. The surgical site was closed and the patient was transported to the intensive care unit with stable vital signs.

DISCUSSION

The patient's lack of hemodynamic response to IV nitroglycerin during this case was unexpected. It was also unprecedented, as the patient had responded to the nitroglycerin earlier in the case. By definition, this was a case of *tachyphylaxis*: rapidly developed desensitization to the therapeutic effects of the medication. Nitroglycerin tolerance was ruled out, because tolerance would have required development over a longer period of time during which nitrates were administered consistently. Fortunately, the surgeon's request for a decrease in BP was a matter of surgical optimization rather than a matter of life or death for the patient. However, IV nitroglycerin is a drug that anesthesia providers rely on during episodes of hemodynamic crisis in the operating room. Failure of hemodynamic response to nitroglycerin, coupled with lack of an alternative antihypertensive readily available could be detrimental to the patient. Therefore, an alternative antihypertensive should be chosen before initiation of the surgical procedure and should be readily available throughout the case. While there are many options for IV antihypertensive therapy, current literature reports many benefits to the use of clevidipine. Clevidipine has fast onset and termination of action times similar to those of nitroglycerin that make it an appealing alternative therapy. A literature search was conducted through the Embase (Elsevier), Medline (National Library of Medicine), and Web of Science databases using the terms *nitroglycerin, clevidipine, tolerance, tachyphylaxis,* and *mechanism of action*.

CURRENT LITERATURE

Nitroglycerin is an organic nitrate that can be administered sublingually or intravenously. It causes dilation of peripheral veins and large coronary arteries. These mechanisms yield decreased venous return and preload, decreased myocardial wall tension, decreased myocardial oxygen demand, and improved myocardial oxygen supply. Nitroglycerin does not cause dilation of small coronary vessels, which helps to prevent coronary steal syndrome. Nitroglycerin also causes a slight decrease in platelet aggregation. These characteristics make nitroglycerin ideal for the treatment of patients with coronary artery disease.

Intraoperatively, IV nitroglycerin can be used for rapid yet meticulous BP management. It acts within seconds after administration, and the medication effects last only 3 to 5 minutes, allowing for the quick changes in BP that are often required in vascular surgeries. In CABG procedures that use cardiopulmonary bypass, 2 specific moments require a normal but low systolic BP to prevent dissection or bleeding from the aorta: 1) aortic cannulation and 2) removal of the aortic cannula. These procedures occur at the very beginning and the very end of CPB, respectively. Anesthesia providers routinely use nitroglycerin at these times to adjust the BP to the surgeon's requested level. Although this technique is effective for most patients, some patients have tolerance to organic nitrates such as nitroglycerin.

The mechanism of tolerance to organic nitrates is currently

unspecified. Nitroglycerin undergoes complex biotransformation upon administration, making it difficult to identify a single source of tolerance. Nitroglycerin can be considered a prodrug; it is metabolized to yield nitric oxide (NO), the actual substance that stimulates smooth muscle cell relaxation. After administration of nitroglycerin or another organic nitrate, NO is formed in healthy vascular endothelium from L-arginine by endothelial nitric oxide synthase (eNOS). NO then activates soluble guanylyl cyclase (sGC), which increases levels of cyclic guanosine monophosphate (cGMP). cGMP has multiple effects that ultimately cause a decrease in intracellular calcium, which inhibits myosin activity, and thereby leads to vascular smooth muscle cell relaxation. This effect may appear clinically as decreased BP or improved myocardial oxygenation.

However, if a patient is tolerant to organic nitrates, these expected effects will not occur. Tolerance to organic nitrates develops in the presence of nitrate therapy lasting 24 hours or longer. The result is a lack of response to subsequent doses of nitrates. This tolerance dissipates rapidly in the absence of organic nitrates and can therefore be avoided by daily pauses in nitrate therapy.

In contrast, tachyphylaxis develops rapidly after initial administration of a drug. It may occur within minutes to hours of administration. A key characteristic of tachyphylaxis is diminishing response to the medication despite increased doses. Eventually, there may be no noticeable response to the medication. Tachyphylaxis after administration of intravenous nitroglycerin is rare, and the cause is unknown. It is possible that tachyphylaxis is caused by similar mechanisms proposed for tolerance to organic nitrates but in an accelerated timeframe. Or nitroglycerin tachyphylaxis may be due to something completely different. Regardless, tachyphylaxis is by nature unexpected. Therefore, the primary goal for anesthesia providers is to be prepared at all times with an alternative treatment for the patient, should the initial treatment fail. Current literature indicates that clevidipine is a good alternative in this situation.

NEW TREATMENTS TO INDUCE HYPOTENSION

Clevidipine is a dihydropyridine, L-type, vasoselective calcium channel blocker. Due to this composition, clevidipine blocks intracellular calcium influx in arterial vasculature only, not in veins. Therefore, administration of clevidipine leads to decreased systemic vascular resistance, decreased BP, and increased stroke volume. These effects allow for a decrease in myocardial oxygen demand. Unlike nitroglycerin, venous beds are not dilated, and so venous return and preload remain constant, allowing for maintenance of cardiac output.

Clevidipine has a rapid onset and produces effects within 1 minute. Termination of clevidipine action is also rapid. Plasma esterases hydrolyze clevidipine, and the effects are almost completely terminated within 5 minutes. The metabolites produced by ester hydrolysis are most likely excreted via biliary and intestinal tracts. Because metabolism remains independent from both renal and liver function, clevidipine can be administered to patients with renal or liver impairment. This ester hydrolysis metabolism is dependent on the temperature of the patient's body, however. The deliberate hypothermia used during CPB reduces the metabolism of clevidipine to just half of the regular rate of metabolism.

Clevidipine is prepared as a lipid emulsion in soybean oil. At steady state, the volume of distribution is 0.6 L/kg. Clevidipine is also highly protein bound. It has been found to help reduce ischemia in renal, splanchnic, and myocardial tissues during reperfusion. No tolerance to clevidipine has been reported in the published literature to date.

SUMMARY

Overall, nitroglycerin and clevidipine have many similarities: protection against reperfusion injury, rapid onset and offset, and decreased BP. However, the mechanism of action of each of these drugs is distinct and is the basis of therapeutic decisions in the clinical setting. Of these 2 drugs, nitroglycerin administration is most likely to result in adverse hemodynamics or tolerance and lack of effectiveness. Therefore, while nitroglycerin is still useful during cardiovascular procedures, clevidipine must also be readily available.

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