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CASE REPORT

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Potential anaphylactoid reaction to nicardipine

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Abstract

Anaphylactic and anaphylactoid reactions are both acute allergic responses known to be potentially fatal if not treated emergently. Signs include bronchospasm, urticaria, nausea and vomiting, pharyngeal edema and cardiovascular collapse. Nicardipine hydrochloride is a dihydropyridine calcium channel blocker that has emerged as a first-line antihypertensive in which emergent blood pressure control is critical. The patient in this case is a 52-year-old male who arrived at the emergency department (ED) with right-sided hemineglect, severe dysarthria, and aphasia, and he was diagnosed with an acute left thalamic hemorrhage. His blood pressure readings were initially 252/135 mmHg despite multiple intermittent boluses of intravenous hydralazine. He was administered a nicardipine hydrochloride infusion at 2.5 mg/h. Due to poor blood pressure control, the rate was titrated up in increments of 2.5 mg/h in the span of 30 min. While up titrating the infusion rate, he developed diffuse swelling and erythema to his left upper extremity in which the medication was being infused, a body wide urticarial rash, tachycardia, diaphoresis, wheezing, and hypoxemia saturating 85% on room air.

1 | INTRODUCTION

Anaphylactic and anaphylactoid reactions occur due to release of mast cell and basophil chemical mediators, such as histamine and beta tryptase. Both reactions are clinically indistinguishable as they include respiratory, gastrointestinal, dermatologic, and cardiovascular signs and symptoms; however, these reactions are treated similarly.

An anaphylactic reaction, or IgE-mediated anaphylaxis, occurs when first-time allergen exposure stimulates the production of IgE antibodies. When re-exposed, IgE-bound mast cells and basophils begin a massive release of chemical mediators. Common causes of IgE-mediated anaphylaxis include certain foods, latex, and penicillin antibiotics. An anaphylactoid reaction, or non-IgE-mediated anaphylaxis, occurs when allergens cause direct release of chemical mediators from mast cells and basophils without IgE mediation. It is typically associated with vancomycin, opioid medications, and blood products, with dosing and rate of delivery being key factors in the occurrence of a reaction.[1]

Our case involves a 52-year-old male patient who was administered a nicardipine hydrochloride infusion for blood pressure control in the setting of an acute left thalamic hemorrhage. Nicardipine is a dihydropyridine calcium channel blocker, which is effective in blood pressure control in states of acute uncontrolled hypertension. Well-known adverse reactions of the drug include flushing, headache, dizziness, nausea with vomiting, pedal edema, chest pain, and tachycardia. We present the case of a dose-related non-IgE-mediated reaction to nicardipine hydrochloride.

2 | CASE REPORT

A 52-year-old male with history only significant for alcohol use disorder, not on any prescribed medications, and no allergies presented by ambulance to the ED for sudden onset confusion and right-sided paralysis while at home with his family. His first set of vitals obtained

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by ambulance personnel included a blood pressure of 214/101 mmHg, heart rate of 85 beats/min, an oxygen saturation of 97% on room air, respiratory rate of 17 breaths per minute, and was afebrile (37.2°C). On arrival, the only significant change in the patient's vitals was an upward trend in blood pressure to 242/122 mmHg. On the initial examination, the patient had severe aphasia and dysarthria, left-sided hemineglect including paralysis, as well as loss of sensation to the face, upper and lower extremity, and absent deep tendon reflexes. His point-of-care glucose was 149 mg/dL. The hospital's stroke protocol was activated, and the patient had computed tomography (CT) imaging of the brain, which revealed an acute left basal ganglia/thalamic hemorrhage with a midline shift toward the right of 4.5 mm.

A review of the patient's home medication list revealed no anticoagulation or antiplatelet therapy, and the head of the bed was elevated as part of intracranial bleed management protocol. Due to his persistently elevated blood pressure of 213/103 mmHg, a nicardipine infusion was administered intravenously into a left forearm vein at a rate of 2.5 mg/h. The patient required upward titration of this drug in increments of 2.5 mg/h every 5–15 min as the systolic blood pressure was persistently well over 200 mmHg. The patient's lab work was largely unremarkable. He had normal electrolytes, renal function, glucose, a negative Ethanol screen, a white blood cell count of 11,000 cells/μL (reference range: 4500– 11,500 cells/μL), an international normalized ratio (INR) of 1.0 (reference range: 0.8–11), and a partial thromboplastin time of 33.4 (reference range: 24.5–35.1 s). His urinalysis revealed 40 mg/dL of ketones (reference range: 0). About 1 min after the infusion rate was increased to 12.5 mg/h, the patient developed severe erythema and swelling to the left forearm, in addition to a body-wide urticarial rash. The patient's heart rate increased to 130 beats/min, and he appeared extremely diaphoretic and hypoxemic with an oxygen saturation of 85% on finger pulse oximetry. The patient had wheezes on auscultation, and his blood pressure then peaked at 264/152 mmHg. The nicardipine infusion was stopped immediately, a 1-liter bolus of IV normal saline was given, and 125 mg of IV methylprednisolone, 50 mg of IV diphenhydramine, and 20 mg of IV famotidine were administered. Intramuscular epinephrine therapy was avoided due to concerns of worsening hemorrhage in the setting of an elevated heart rate and blood pressure. The patient's signs and symptoms alleviated thereafter, and he was transitioned to intermittent IV labetalol and hydralazine boluses, as well as an esmolol IV infusion. Due to refractory hypertension, IV labetalol infusion was initiated at 0.5 mg/min and titrated to appropriate blood pressure control. The patient was then admitted to the neurosurgical intensive care unit for further care of his intracranial hemorrhage; he had complete resolution of his anaphylactoid reaction without recurrence. He was admitted to the hospital during which he had persistent aphasia and failed his speech and language assessment. He ultimately had a percutaneous endoscopic gastrostomy tube inserted and was discharged to a nursing facility 10 days later.

3 | DISCUSSION

Anaphylactic and anaphylactoid reactions are clinically indistinguishable as they both commonly affect the integumentary, cardiovascular, respiratory, and gastrointestinal systems. Anaphylactic reactions are due to allergens interacting with allergen specific IgE antibodies attached to mast cells, causing degranulation and release of various biochemical mediators including histamine, tryptase, and cytokines.[2] Anaphylactoid reactions are non-IgE mediated, or not immunologically mediated; anaphylactoid reactions tend to occur in a dose-dependent manner.[3] Complement activation with release of anaphylatoxins, C3a and C5a, is correlated with more severe degrees of cardiovascular collapse and hypotension.[4,5] IgE-mediated anaphylactic reactions typically occur on subsequent exposures to an allergen, while non-IgE-mediated anaphylactic reactions can occur on first exposure by means of direct mast cell, basophil, and complement activation. The occurrence of Ig-mediated reactions on first exposure is not typical.[6]

The dihydropyridine channel, also known as the L-type calcium channel, is responsible for excitation–contraction of skeletal, smooth, and cardiac muscle.[7] Nicardipine is a dihydropyridine calcium channel blocker which controls blood pressure by inhibiting the influx of calcium through these channels. Calcium has several physiologic functions besides vasoconstriction and inotropic effects, including the synthesis and release of chemical mediators.[8]

A 1988 article by E. Giannella and colleagues hypothesized that some calcium channel blockers were effective in reducing the release of some of the mediators from mast cells and basophils, including histamine, during hypersensitivity reactions such as anaphylaxis. Notably, only non-dihydropyridine medications such as verapamil and diltiazem were effective in reducing amount of histamine released after antigen exposure to guinea pigs, whereas nifedipine, a dihydropyridine calcium channel blocker—the same class as nicardipine—did not cause any significant changes in the response in sensitized hearts challenged with antigen exposure. The reason for this has not been studied yet and remains unknown. In the same experiment, BAY K 8644, a calcium channel agonist, was trialed. Its use, which potentiates the effects of calcium up to 10-fold, did not potentiate anaphylactic histamine release.[9] Therefore, calcium channel agonism and antagonism have not yet been proven to have a direct correlation with incidence of anaphylactic reactions. Other studies, in fact, have shown that calcium channel antagonists, whether in dihydropyridine or non-dihydropyridine classes, lack the ability to block the release of histamine and leukotrienes.[10,11]

When further assessing our patient's course, he did not have any known documented allergies. However, it is important to note all potential medicinal causes to which the patient was exposed during his treatment in the ED. On presentation, the patient's ethanol level was undetectable. There have been two described mechanisms of ethanol-induced anaphylactoid reactions. First, ethanol is responsible for increasing extracellular adenosine by inhibiting intracellular uptake. After prolonged exposure to ethanol, intracellular uptake is no longer inhibited due to cellular tolerance. An increase in extracellular adenosine can only be explained by acute alcohol exposure, however this mechanism suggests that an adenosine-mediated effect, along with increased gut permeability, may play a role in ethanol induced anaphylactoid reactions.[12]

IV nicardipine hydrochloride contains several excipients, which differ depending on the manufactured product. In this case, excipients

included benzoic acid, sodium hydroxide, and sodium chloride. Of note, alternative nicardipine hydrochloride preparations also contain additional excipients, including sorbitol and citric acid monohydrate. Each of these excipients help to maintain an acidic pH, prevent precipitation, and maintain isotonic properties. Benzoic acid is utilized as an antimicrobial preservative within intravenous preparation and has been found to have its strongest antibacterial activity at a pH between 2.5 and 4.0. After administration, benzoic acid is metabolized to hippuric acid, which is renally excreted.[13] Within the IV preparation, each 1 mL (2.5 mg) of nicardipine hydrochloride contained 0.305 mg of benzoic acid. Considering the patient in this case received <1 hour of the nicardipine infusion before the reaction, the total amount of benzoic acid that was administered is estimated to be between 1.5 and 1.8 mg. The safe acceptable daily intake (ADI) of benzoic acid recommended by the World Health Organization ranges from 0 to 20 mg/kg of body weight.[14] The amount of administered benzoic acid to which the patient was exposed was <0.1% of the recommended maximum ADI. However, small studies have suggested urticaria induced by benzoic acid after topical administration contained within cosmetic products. This reaction is thought to be due to increased synthesis of prostaglandin D2 within the skin.

The signs of anaphylaxis the patient experienced could have been related to the iodinated contrast he received during CT imaging; however, this seems less likely due to the patient having previously received iodinated contrast. Additionally, his signs and symptoms occurred approximately an hour after the study was complete. It is also worth considering that the occurrence was moments after increasing the nicardipine hydrochloride infusion rate to 12.5 milligrams per minute, which was approaching the maximum rate of administration. Additionally, the left arm in which the infusion was being administered appeared the most swollen and erythematous. The timing and constellation of the anaphylactic signs in this case suggested the patient's hypoxemia was related to an anaphylactoid reaction, rather than a primary pulmonary or cardiac source.

Using the Naranjo scale,[15] we calculated a score of +5, which indicates a probable causal relationship between nicardipine hydrochloride and the reported non-IgE-mediated anaphylactic reaction. The score was calculated using the following criteria: 0 for no previous conclusive reports on this reaction, +2 for the reaction appearing after administering the drug, +1 for the event improving after the drug was discontinued, 0 as the drug was never re-administered, −1 as the contrast that he had received an hour prior could have contributed to this reaction, +1 as there were no additional anaphylactic symptoms with other anti-hypertensive drug administration thereafter, 0 as drug levels were not tested on the patient, +1 for a more severe reaction when the dose was increased, 0 as he had never received nicardipine hydrochloride in the past, and +1 for the adverse event occurring objectively at high rates of infusion.

In summary, any drug can cause a hypersensitivity reaction. There are no studies that prove protective effects of calcium channel blockers from mediator release. It is not clear why nicardipine specifically would have caused a reaction to occur on a molecular level; however, given that the patient had not been previously exposed to this drug and the reaction's onset correlated directly with an increased administration rate, the presentation is highly suspicious for an anaphylactoid reaction to the drug's infusion.

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