CASE REPORT

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Combine Midazolam-Fentanyl-Ketamin for Evisceration Surgery in Patient with Multidrug Allergy in acute on Chronic Exacerbation of Hypersensitivity Reaction

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ABSTRACT

A multidrug allergy is a relatively rare immunology abnormality. Generally, it is caused by a congenital genotype and influenced by the environment. After treating the acute symptoms of chronic exacerbation of hypersensitivity type 1, the inflammation can alleviate and the patient will need to be scheduled for evisceration oculi dextra with general anaesthesia. The ophthalmologist was curious about the procedure because evisceration requires an antibiotic to wash the oculi, but there was no antibiotic available for the patient. With respect to general anaesthesia, the patient had no history and therefore we could not predict an allergy to the anesthetic drug. We chose to combine ketamine-midazolam-fentanyl to facilitate the anaesthesia. Ketamine significantly reduces the production of inflammatory cytokines without affecting the production of anti-inflammatory cytokines. Fentanyl is an opioid that rarely causes allergy and has strong potential. Finally, midazolam can help the sedation.

Keywords: Allergy, multidrug, fentanyl, ketamine, midazolam

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INTRODUCTION

Allergies were discovered by Von Pirquet in 1906 which basically includes advantages or disadvantages. The advantages including a favourable excessive immune response such as vaccination, while the disadvantages are like harm and disease.[1,2]

The pathogenesis concept of an allergy is the role of gene interaction with the environment. A sensitive person is called susceptible and the occurrence of allergies, in addition to environmental exposure, is also due to the role of the body in producing IgE. The formation of IgE is determined by various factors such as the cell response to Th1 / Th2. Th1 is responsible for the formation of IL-2, IFN-γ, and TNF-ß that activate macrophages and Th2 produces IL-4, IL-5, IL-10, and IL-13 which are responsible for the antibody response, including IgE production and inhibit macrophage function.[3,4,5]

The path ophysiology of a drug allergy is different from an allergy to food or pets because of excessive drug doses or drug side reactions. Drug allergies are caused by induction of specific immunological reactions and the sensitization of lymphocytes. The resulting substances are antibodies and cytokines. The difference between toxic drug allergies or side effects is the reaction to medications that elicit an inappropriate immunologic response to the drug or its metabolites.[3,6,7,8]

Herein, we report a case of a 66 year old woman with spontaneous prolapse of bulbi oculi sinistra with absolute glaucoma and histories of asthma, diabetes mellitus, moderate renal insufficiency, hypertension, and history of allergies. She had been given antibiotics in the emergency room that resulted in anaphylactic shock that was worsening. Two weeks following the anaphylactic shock, she was scheduled for an elective surgery and for prophylaxis she was given an antibiotic during the desensitization procedure. At this time, acute exacerbation of hypersensitivity occurred and she had developed pruritus, edema palpebra, and shortness of breath. The antibiotic was discontinued immediately. This posed a challenge to the operator because the evisceration procedure required an antibiotic to wash the eye.

CASE REPORT

A 66-year-old woman was admitted to hospital with a sudden severe pain in her left eye associated with nausea and vomiting. There was a history of asthma, diabetes mellitus, multiple drug allergies, and the use of antihistamine medicine. Physical examination revealed a marked left prolapse bulbi dan postreaction of acute on chronic hypersensitivity type1 due to antibiotic prophylaxis allergy.

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There was pruritus with skin itchiness on the body, edema palpebra, cough, edema of lips and mouth, and shortness of breath.

The patient was scheduled for evisceration on the oculi sinistra under general anaesthesia. Several hours before the time of surgery, the internist planned to administer 500 mL of levofloxacin, but after 50 mL a reaction of hypersensitivity type I arose and the patient began to suffer from dyspnea including wheezing, pruritus, and edema palpebra. After the procedure, she was monitored and given a corticosteroid. Anaesthesia was used during surgery to minimize the allergic reaction, a corticosteroid was administered for premedication, and an adjusted combination of fentanyl, midazolam, and ketamine was used for induction.

Rocuronium was used as muscle relaxants and to maintain the depth of anaesthesia. Intubation was performed with smooth intubation without lidocaine intratracheal because the patient had a history of an allergy to xylocaine spray. For maintenance, we used sevoflurane and propofol continuously. We also maintain blood pressure with mean arterial pressure (MAP) 70 mmHg and systolic pressure about 100 mmHg to make sure renal blood flow (RBF) kept renal perfusion.

Random blood sugar was also checked regularly to avoid hyperglycemia (>180 mg/dL) due to a diabetic history and using corticosteroid at full dose. Sedation and analgesics were given to avoid any agitation. In this patient, we administered fentanyl (100 mcg), ketamine (10 mg), and midazolam (1 mg) as an analgesic during induction and to maintain the anaesthesia with propofol continuous. We also gave the patient methylprednisolone (125 mg) intravenously every 8 hours to protect from any allergic reaction. The patient was extubated after surgery and recovered well with no hyperglycemia or asthma attack. Ofloxacin eye drops were given as an antibiotic without antibiotic intravenously.

DISCUSSION

In the last 30 years, before there was an increase in the incidence of allergies, even in developing countries, atopic allergies could be found in 20% of the population. These allergies included many kinds of disorders associated with IgE, such as asthma, allergic rhinitis, atopic dermatitis, food allergies and others.[9] Decreased exposure to microbes at an early age, known as "hygiene hypothesis", has led to the polarization of allergen-specific memory T cells. This leads to Th2 rather than Th1 driven IgE production and this becomes more dominant than the macrophage production of Th1.[4]

A hypersensitivity reaction is the term used when the response of the immune system to a foreign antigen results in an adverse response in the host. These reactions can be divided into several types defined by the effector molecules produced and activated during the process. A type 1 hypersensitivity reaction (anaphylaxis) is in response to a specific allergen. When the specific allergen is introduced into the body, plasma cells release IgE antibodies during normal immune reactions, which bind strongly to Fc receptors located on the surface of mast cells or basophils. Cross-linking of these sensitized mast cells and basophils leads to their degranulation and the mediators released, including histamine, induce various biophysiological reactions.[10]

Anaphylactic reactions are associated with IgE. The main effector cells in IgE-mediated reactions are mastocyte cells that are activated by antigens that in 3-5 seconds release histamine and other mediators. Anaphylaxis is caused not only by the effects of these compounds but by secondary reactions in other cells, including eosinophils, neutrophils, T lymphocytes, monocytes, and platelets. This leads to airway constriction, edema, and erythema. Substances associated with anaphylaxis include histamine, protease, eosinophil chemotactic factor, neutrophil chemotactic factor, heparin, platelet activating factor, leukotrienes, prostaglandins, bradykinin, and cytokines. Leukotriene is a potent bronchoconstrictor that also causes increased vascular permeability and mucus production. Prostaglandin D2 is also a bronchoconstrictor. In addition, cytokines released by the mast cells are associated with type 1 hypersensitivity.[11]

Four types of histamine (H) receptors are distributed throughout the body. The H4 receptors are found in the innervations of the vasculature and cells of the blood, lung, liver, spleen, and gut; stimulation of the H4 receptors precipitates inflammation. The central nervous system is regulated by H1, H2, and H3 receptors. The H3 neurons are located in the tuberomammillary nucleus of the hypothalamus control neurotransmitters. The release of histamine is modulated by feedback from the H3 autoreceptors and from muscarinic, α2-adrenergic, and peptidergic receptors. The tuberomammillary nucleus controls the release of acetylcholine and other neurotransmitters. This hypothalamic centre is regulated by H3 autoreceptors that are inhibited by histamine. Inflammatory mediators released by tissues stimulate the afferent sensory fibres to the central nervous system, which causes the efferent vagus nerve release of acetylcholine. At the parasympathetic ganglion, via autoinhibitory mechanisms of the postganglionic nerves, the

nicotinic or muscarinic receptor release acetylcholine. Stimulation of the H3 receptors in the presynaptic terminals of sympathetic nerves inhibits epinephrine release from the adrenals, heart, and the peripheral vasculature.[23]

The drug related to the immune response is because it binds proteins and produce the bond hapten-protein complex which is immunogenic (hypothetical hapten).[11] Some drugs do not bind proteins directly but rather its metabolites conjugate through cytochrome P450 enzymes that produce hapten. Referred to as T-cell-sensitized, these processes occur in penicillin and other beta-lactam drug classes. T-cells are thought to release pro-inflammatory cytokines in response to antigens. It suggests that the T-cell-specific to allergens are present in large amounts in the mucosa of the respiratory tract of patients with asthma. Activated T-cells can provide contact signals that induce T-cells to perform Ig switches and produce IgE.[10]

Ketamine is an NMDA (N-methyl-D-aspartate) receptor antagonist administered as an additional pain management drug pain. NMDA receptors are ligand-gated ion channels that allow the entry of calcium, sodium, and potassium into cells. The receptor is activated by glycine and glutamate and does not open when the membrane breaks potential. Glutamate is a major excitation neurotransmitter in the central nervous system and has a significant role in pain modulation at the level of the spinal cord.[12]

Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist that is structurally related to meperidine. As an analgesic, fentanyl is 75 to 125 times more potent than morphine. Analgesic concentrations of fentanyl greatly potentiate the effects of midazolam and decrease the dose requirements of propofol. The opioid-benzodiazepine combination displays marked synergism with respect to hypnosis and depression of ventilation.[20] In clinical practice, the advantage of the synergism between opioids and benzodiazepines to maintain patient comfort is carefully weighed against the disadvantages of the potentially adverse depressant effects of this combination.[21] High doses of morphine produces peripheral vasodilation and frequently significant hypotension. These effects are thought to be due, in part, to the release of histamine. One putative advantage of high-dose fentanyl anaesthesia is its relatively small effect on peripheral vascular resistance. In a randomized study, the authors examined the possibility that the hemodynamic differences between morphine and fentanyl might be attributable to histamine release.[22]

Ketamine has effects in inflammation. Ketamine significantly reduces the production of inflammatory cytokines without affecting the production of anti-inflammatory cytokines. Ketamine reduces the occurrence of exacerbation of inflammatory reactions and speeds up the inflammation resolution by assisting inflammatory cell apoptosis. Ketamine has no effect on the immune cells that produce inflammatory cytokines when there is no inflammatory stimulus. This regulatory effect is more meaningful when ketamine is administered before inflammation. This is also the basis of why ketamine is given during induction of anaesthesia before surgery. Ketamine at a dose of 0.5 mg/kg increases the ratio of Th1/Th2 thus improving the patient's immune function. In some studies, ketamine lowers TNF-α, IL-6, IL-1, and IL-8, which in turn provides results such as reducing the acidosis and improving cure rates.[13,14]

The addition of a small dosage of an NMDA to opioid results in a synergistic effect largely due to a combination of opioid presynaptic inhibition, reducing afferent transmission by reducing the release of neurotic- loaders, and post-synaptic inhibition of NMDA, which reduces wind-up and central sensitization. Central sensitization occurs through a stimulus (surgery) that causes activation of protein-kinase-C (CCP). The CCP is very sensitive to calcium, therefore any stimulus that increases intracellular calcium in the dorsal horn will activate it. NMDA receptor phosphorylation decreases magnesium inhibition of resting membrane potential and results in continuous synaptic activity. This activation underlies the central sensitivity. From a variety of drugs or techniques only NMDA antagonists can restore the sensitization that has occurred. Precise analgesia aims to prevent or reduce this sensitization to reduce postoperative pain.[15] Opioids produce anti-nociceptic through the receptor and activation of the monoaminergic descending pathway at the level of the spinal cord, which in turn activates NMDA receptors.[16] The activation of NMDA receptors in the central nervous system is a mechanism involved in adaptive changes that underlie opioid tolerance and delayed hyperalgesia. The activation of the opioid receptor causes the activation of NMDA receptors via the protein kinase. The development of acute tolerance to rapid opioids in animals happened on various opioids. Inhibition of this tolerance by ketamine has received serious attention.[17,18] Nociceptive stimulation leads to activation of NMDA receptors, which can also occur due to high doses of opioids. The addition of ketamine can prevent this process.[19]

SUMMARY

A multidrug allergy is a rare condition and requires selective treatment and medicine. The prophylaxis treatment is started before the surgery and after the surgery, especially before induction and after extubation, by giving corticosteroid treatment to prevent the inflammation. Fentanyl rarely causes allergies and ketamine significantly reduces the production of inflammatory cytokines without affecting the production of anti-inflammatory cytokines.

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