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Hypersensitivity to tramadol and paracetamol combination drug

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I. INTRODUCTION

Tramadol hydrochloride is an opioid analgesic medication that has been prescribed for nearly 2 decades as a centrally acting analgesic for the treatment of moderate to severe pain [1, 2].

It has a dual mechanism of action that includes weak agonistic effects on the mu-opioid receptor and inhibition of neurotransmitter (e.g. serotonin and norepinephrine) reuptake.Paracetamol is one of the most commonly used analgesic agents worldwide has excellent safety profile when administered at recommended doses [3]. Paracetamolis a para-aminophenol derivative that exhibits analgesic and anti-pyretic activity through inhibition of prostaglandin synthesis, primarily within the central nervous system. Paracetamol is also a weak inhibitor of cyclooxygenase 1 (COX-1), but is not considered a non-steroidal anti-inflammatory drug (NSAID) [4].

II. CASE REPORT-

A 21-year-old male presented to cardiovascular and thoracic surgery department with pseudo aneurysm of left axillary artery. Patient had chronic kidney disease and was on maintenance haemodialysis for five years. There was no history of asthma, rhinitis and conjunctivitis due to inhalant allergen. There was no known history of drug allergy.

Patient underwent surgery for arterio-venous fistula creationat left arm, brachial artery level for haemodialysis in another centre. During the induction phase of anaesthesia, glycopyrrolate, propofol, fentanyl and rocuronium bromide were used. The surgery was performed without any adverse events.

During postoperative period he was treated with oral combination of tramadol and paracetamol (Ultracet). Patient developed itching and maculopapular rash all over the body after five doses of paracetamol and tramadol analgesic combination. Medication was stopped and patient received injection hydrocortisone and chlorpheniramine maleate and symptoms subsided.

After a period of five months patient developed a pseudoaneurysm of left axillary artery,
Surgical intervention was planned. Duringsurgery patient was treated with fentanyl as intraoperative analgesia and during postoperative period he received ketorolac as analgesics and no adverse effect were reported .

III. DISCUSSION

Allergic reactions to tramadolare rare and reported incidence about less than 0.1% for adverse reaction, therefore the drug considered safe [5]. Hallberg P et al reported 11 cases of angioedema that was possibly related to tramadol with a likely typeI IgE-antibody-mediated mechanism in which 6 were serious cases, 4 patients needed emergency treatment, and half of those were treated in an intensive care unit [6].Grassmann C et al reported incidence of tramadol's angioedema is 1 in 1,000 to 1 in 10,000 [7].In addition to possible IgE antibody-mediated responses, other delayed hypersensitivities to tramadol include a maculopapular toxic skin reaction [8], hypersensitivity pneumonitis [9], and uncertain cases of Stevens-Johnson and Lyell's syndromes [10].

The majority of suspected paracetamol reactions occur in conjunction with NSAID intolerance and related to the pharmacological action of COX-1 inhibition [11]. Cyclooxygenase inhibition blocks the conversion of arachidonic acid to prostaglandins and thromboxane resulting in a therapeutic anti-inflammatory effect [12]. The resultant increase in free arachidonic acid can be alternatively converted into cysteinyl leukotrienes. These leukotrienes may result in clinical features of allergy such as angioedema, urticaria and bronchospasm [12]. These reactions occur in 1.6% of all patients taking NSAIDs [13]. Although this is the most common mechanism by which

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paracetamol hypersensitivity occurs as well, it is still relatively uncommon with 97% of patients intolerant of NSAIDs being able to safely take paracetamol [14]. Hypersensitivity reactions to paracetamol have been reported in patients who are tolerant of NSAIDs and therefore involve an alternative mechanism [14]. Reactions to paracetamol can range from immediate type I hypersensitivity reactions such as angioedema, urticaria and anaphylaxis, which are likely immunoglobulin E (IgE)-mediated, to delayed type IV reactions such as fixed-drug eruptions, Stevens–Johnson syndrome and toxic epidermal necrolysis, which are likely mediated by T cells.

Although multiple adverse effects have been reported with tramadol [15,16] and paracetamol, this is the first case of hypersensitivity to tramadol & paracetamol combination (Ultracet) that has been described thus far.This is the first case of hypersensitivity to tramadol and paracetamol in a patient that has been described thus far. Despite the heavy and constant worldwide usage of opioid analgesics, IgE-mediated immediate hypersensitivity cases are rare, the reason for which is intriguing. The tramadol molecule is quite different in molecularstructure compared with morphine, and probably quite different from enkephalins.

Our case highlight that although tramadol and paracetamol allergy is rare, it isimportant for clinicians to be awareof it as a potential cause of immediate hypersensitivity reactions, particularlyin cases of idiopathic anaphylaxis. In-vivo and in-vitro testing have poor sensitivityand specificity for selective paracetamol and tramadol allergy and therefore referral to an immunologist for a supervised graded oral challenge is required for formal diagnosis.

In conclusion, besides the rarely induced IgE antibody responses to tramadol, this case shows the importance of a well-conducted allergy work-up and provides insight into possible severe reactions to such a drug in children. The mechanism of selective immediate paracetamol allergy remains unknown but is presumed to be IgE mediated.

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