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Case Report

Postponed Immediate Hypersensitivity Reaction to Ceftriaxone

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Abstract

Ceftriaxone is a widely used and generally safe 3rd generation cephalosporine. Immediate, IgE-mediated hypersensitivity reactions to ceftriaxone have been reported. We present a case of an elderly woman who received ceftriaxone 3 times over a period of 1 year. During the 1st course 1 year before the current event, the patient developed an atypical eruption on the seventh dose. Three months afterwards (9 months prior to the current event), unaware of the previous reaction, ceftriaxone was administered again. The first dose went uneventfully. Subsequently, being informed on the recent eruption, no second dose was administered. Noticing no hypersensitivity reaction to the unintentional re-challenge, skepticisms rose regarding the allergic nature of the former event. Nine months later (the current event), ceftriaxone was started for the third time. The 1st dose passed event-free, but after the second dose the patient mounted an immediate hypersensitivity reaction in the form of wide-spread urticaria. Postponed hypersensitivity reaction in this patient was explained by a three-step immune response: primary sensitization in earlier exposures, boosting the immune memory by 1st dose, to fast secretion of specific antibody, and the second dose to eliciting the immediate hypersensitivity reaction. We learned that on re-exposure of the sensitized patient the immediate hypersensitivity reaction may be postponed and that tolerance to the first dose of the antibiotic is no guarantee to being tolerant to the second dose.

Keywords: Ceftriaxone; Cephalosporins; Hypersensitivity; IgE mediated

Introduction

Ceftriaxone, under the brand name Rocephin, is a widely used and generally safe third generation cephalosporine for intramuscular or intravenous administration. Nevertheless, Hypersensitivity Reactions (HR) to ceftriaxone is not uncommon. Mainly immediate HR that occur within 1 to 6 hours from administration have been reported. These reactions are primarily IgE-mediated and may manifest as urticaria, angioedema, rhinitis, bronchospasm, or anaphylaxis [1,2]. An immediate HR can occur after the latest dose of the first course of ceftriaxone treatment, or during a subsequent exposure in subjects who have tolerated ceftriaxone earlier. An immediate HR can occur upon rechallenge, whether a prior HR has or has not been experienced. A postponed immediate HR to ceftriaxone is the subject of the present report.

Case Presentation

An 89-year-old woman was resident in our facility for several years. Having suffered bilateral thalamic stroke, she was in unaware wakefulness state and on prolonged mechanical ventilation. Her medical history included arterial hypertension, hypothyroidism, and iron deficiency anemia. Chronic medications included ramipril, levothyroxine, and esomeprazole. The patient developed a urinary tract infection with E-coli and was treated with ceftriaxone. On the following day, one hour after the administration of the second ceftriaxone dose, circumscribed wheals with erythematous borders and raised pale centers typical for urticaria appeared over her torso and extremities. The blood pressure remained stable, no wheezes were perceived, and no aggravation of the ventilation parameters was noted. Intravenous hydrocortisone 200mg and a single oral dose of

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loratadine 10mg were administered. The urticaria disappeared within 4 hours. Ceftriaxone was discontinued and levofloxacin was administered for 5 days with clinical and laboratory improvement.

Review of the patient's medical records showed several courses of cephalosporine treatments, including cefazolin, cefalexin, ceftazidime, and ceftriaxone, with the latter being administered twice. One administration was a year earlier for urosepsis, during which an eruption appeared after receiving the 7th and last dose of ceftriaxone. Three months afterwards (9 months before the current event), under urgent circumstances, ceftriaxone was started for sepsis. The first dose passed free of adverse reactions. Being informed afterwards on the eruption noticed on prior ceftriaxone treatment, possibly a HR, no second dose was administered; the treatment switched to amikacin. In not having developed a HR on re-challenge, doubt rose concerning the allergic nature of the previous event. When ceftriaxone was started for the third time (the current event) for another infectious episode, again the initial dose was administered uneventfully, alike the prior re-challenge. However, shortly after the second dose the patient mounted an immediate HR. We wondered if this "postponed immediate HR" was unpredictable, or maybe predictable, after paying closer attention to the patient's history?

Discussion

HR is IgE-mediated and is called type I reaction; it manifests as urticaria, bronchoconstriction, angioedema, and anaphylaxis. Sensitization requires the primary stimulation of T cells and subsequent expansion of specific T lymphocytes. Usually, the active compound of the drug is a molecule that is too small to induce an immune response. Nevertheless, drug-protein complexes may become immunogenic. Drug-protein complexes taken up by antigen-presenting cells are transported to lymphoid tissues where they are presented to major histocompatibility complexes. Naïve T cells having acquired specificity to recognize drug-protein complexes proliferate as primed T cells. Their clone diverges into effector T cells which are short lived and memory T cells which are long lived. In parallel, B cells generate drug specific IgE antibodies. After a primary sensitization, a second exposure may prompt the specific T cells and antibodies to enter the elicitation phase [1-3]. After a period that is antigen-free, the antibody levels and drug-reactive T cell numbers fall. Upon renewed exposure, the first dose of the drug may find low numbers of reactive cells that are insufficient to invoke a clinically manifest reaction. However, memory B cells that are rechallenged by the first dose become boosted and mature into plasma cells to secrete the specific antibody fast and in high titers. So, the second dose of the drug finds the immune system fully armed and reactive to elicit an over HR. Dose, duration, and repeated treatments may enhance the likelihood of symptomatic reactions after the last administered dose [2,4].

Mast cells are responsible for initiating the symptoms of allergic reactions. When the allergen cross-links mast cell bound IgE molecules, the mast cell is activated to release histamine, leukotrienes, prostaglandins, and cytokines. These molecules provoke eosinophil recruitment, induce vasodilation, increase vascular permeability, and enhance mucus production and bronchoconstriction. IgE-mediated reactions to drugs often manifest as urticaria or angioedema, but may also cause bronchoconstriction, and shock. The symptoms improve after an hour as the immediate response begins to fade [1]. In addition to the classical pathway of immediate HR, other mechanisms can elicit a similar response. Unorthodox, alloimmune-like stimulations of T cells without previous exposure to the causative drug can elicit HR-like syndrome [3,5]. Furthermore, mast cells can be activated by complement in response to changes in temperature and cause allergic reaction. Therefore, diagnosis of dur HR may be challenging [5].

We propose that earlier treatments have caused primary sensitization to ceftriaxone in our patient. During the current treatment, the first dose of ceftriaxone provided a booster effect to induce overt HR on the second dose. The latter was "immediate" in timing after the second dose, but imperceptible after the first dose: a "postponed immediate HR". Indeed, due to the immunologic memory, a dramatically enhanced reaction occurred on re-exposure.

In clinical practice, diagnosing drug-induced HR makes advantage of guidelines such as those relating to antibiotics [6]. Thus, patients with a history of non-anaphylactic cephalosporin reaction such as urticaria may undergo direct challenge, without prior skin testing, using a cephalosporin with dissimilar side chains. In contrast, those with a history of cephalosporin-induced anaphylaxis should ideally undergo skin testing using a nonirritating concentration of the compound [6,7]. Skin testing is a useful tool for evaluating immediate reactions to cephalosporins. Initially tested on the volar forearm skin by the skin-prick method, and the reaction reading made 20 minutes later. A positive test suggests the presence of drug specific IgE, but a negative test does not rule out drug allergy. Skin testing should be delayed at least 2 weeks after an acute anaphylactoid episode when the mast cells are depleted and unreactive to avoid a false negative reaction [4,7]. It is important to remember that testing by skin-prick and intradermal injection is only helpful for identifying risk for immediate reactions. A simple diagnostic protocol uses skin tests with the suspected cephalosporin and, in case of negative results, perform challenge test if there are no contraindications [4]. Skin testing was not performed in our patient considering the compelling anamnestic data: the prior skin eruption on day 7 of ceftriaxone treatment and the immediate HR to ceftriaxone in the present event. Ceftriaxone had to be avoided in our patient, opting for other classes of antibiotics.

A threefold message emerged at the patient's bedside: First, at initial exposure to the antibiotic, an immediate HR may occur lately close to completion of the course of treatment. Second, on re-exposure of the sensitized patient, an immediate HR, contra-intuitively, may not occur immediately but be postponed to the second dose. Third, tolerance to the first dose of the antibiotic is no guarantee for tolerance to the second dose. In any case the drug should be banned for future use. Furthermore, medical intelligence calls attention to immediate HR on first dose in ceftriaxone-naïve patients, but also to allosensitization by non-IgE mechanisms, and lastly mast cell degranulation by non-immune mechanisms. Sophistication of knowledge may complicate the diagnostic process while simple solutions are at hand in practice, such as circumventing exposure when there is uncertainty about drug hypersensitivity.

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