

Anaphylactoid reaction to paliperidone palmitate extended-release injectable suspension in a patient tolerant of oral risperidone

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Paliperidone palmitate extended-release suspension is a long-acting, injectable antipsychotic agent administered intramuscularly as a once-monthly maintenance dose for the treatment of schizophrenia in adults.¹ After administration, the active ingredient, paliperidone palmitate, is hydrolyzed to paliperidone, the major active metabolite of risperidone, before being systemically absorbed. To ensure the tolerability of this suspension, a trial of the oral formulation of either risperidone or paliperidone is necessary before initiating therapy with the suspension. Here we report a case of an anaphylactoid reaction after the injection of paliperidone palmitate extended-release suspension in a patient with established tolerance of oral risperidone.

Case report

A 19-year-old white man (height, 175 cm; weight, 84 kg) with schizophreniform disorder and generalized anxiety disorder was admitted to the emergency department experiencing

Purpose. A probable anaphylactoid reaction to the injectable formulation of the atypical antipsychotic paliperidone in a patient with established tolerability to oral risperidone is reported.

Summary. A 19-year-old man with schizophreniform disorder was admitted to the emergency department experiencing command hallucinations and persecutory delusions. The patient was treated with oral risperidone during which time his presenting symptoms improved; no risperidone-related adverse effects were noted. Due to concerns about long-term adherence to daily risperidone use, it was decided to initiate once-monthly injections of paliperidone palmitate extended-release suspension. Within 15 minutes of the first paliperidone injection, the patient developed flushing of the face, neck, and head, and he soon developed chills, rigors, and difficulty breathing; after treatment to resolve those symptoms, oral risperidone was restarted. No further drug-related problems occurred during the man's hospital stay. The pharmacy subsequently received notice that the medication lot

from which the patient had received the paliperidone dose had been recalled due to reports of cracked syringes, but a possible link between the syringe defect and the man's anaphylactoid symptoms could not be determined. The temporal relationship between paliperidone palmitate administration and the onset of the man's symptoms, as well as application of the Naranjo nomogram, indicated a probable anaphylactoid reaction associated with the paliperidone formulation.

Conclusion. A man who had tolerated oral risperidone developed an anaphylactoid reaction after receiving an injection of paliperidone palmitate extended-release suspension. After recovering from the reaction, the patient again received oral risperidone without adverse effects.

Index terms: Anaphylaxis; Antipsychotic agents; Compliance; Drugs, adverse reactions; Injections; Paliperidone palmitate; Patients; Psychotic disorders; Risperidone; Sustained action medications; Toxicity

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command hallucinations and persecutory delusions. He denied having

any psychiatric disorders and did not believe he needed treatment. The

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patient had recently attempted suicide by jumping from a third-story window, which resulted in multiple lumbar, leg, and foot fractures. His medical history was significant for paraplegia, iron deficiency anemia, sacral ulcer, urinary tract infection, inferior vena cava filter placement, and use of cannabis and lysergic acid diethylamide (the dates of use were unknown, but a urine toxicology screen performed on admission was negative for illicit drugs).

Medications being used by the patient at the time of his admission to the hospital were ziprasidone hydrochloride 80 mg orally twice daily, clonazepam 0.5 mg orally twice daily, ferrous sulfate 325 mg orally three times daily, heparin sodium 5000 units subcutaneously three times daily, doxazosin 4 mg orally at bedtime, esomeprazole 40 mg orally daily, ascorbic acid 500 mg orally daily, and one multivitamin tablet daily; all medications were continued throughout the hospitalization. The man had no known drug or food allergies.

The patient's vital signs were within normal limits. Pertinent abnormal laboratory data were as follows: white blood cell (WBC) count, 26,300 cells/mm³ (reference range, 4,800–10,800 cells/mm³); red blood cell (RBC) count, 4.49 million cells/mm³ (reference range, 4.7 million to 6.1 million cells/mm³); hemoglobin concentration, 13.5 g/dL (reference range, 14.0–17.9 g/dL); and hematocrit, 39.5% (reference range, 42–52%). The patient's medical problems were treated in the inpatient medicine unit. When his medical condition stabilized, he was transferred to the inpatient psychiatric unit.

During the patient's hospitalization, the dosage of ziprasidone was gradually reduced over 13 days while oral therapy with risperidone was started and gradually increased to 2 mg twice daily. The risperidone was effective, the patient's condition was improving, and no adverse

effects were noted. Although the patient was adherent to all medications throughout his hospital stay, concerns about the potential for suboptimal long-term adherence after his discharge led to a clinical decision to initiate maintenance treatment with paliperidone injectable suspension.

On the morning of day 33 of the patient's hospitalization (the 5th day after the initiation of oral risperidone), paliperidone palmitate extended-release suspension 234 mg^a was administered intramuscularly to his right deltoid. After the dose was administered, the pharmacy department received notice from the manufacturer of a recall of several lots of paliperidone palmitate extended-release injectable suspension, including that particular lot of medication, due to possible cracks in the syringe barrel. Fifteen minutes after the administration of paliperidone, the patient developed pruritus and flushing of the face, neck, and ears. Diphenhydramine hydrochloride 50 mg intramuscularly was given, and the flushing was reduced. Forty minutes after the paliperidone injection, the patient developed chills and rigors and had difficulty breathing. His vital signs were as follows: temperature, 97.8 °F; blood pressure, 90/70 mm Hg; pulse, 121 beats/min; respiratory rate, 28 breaths/min; and oxygen saturation, 84%. He was transferred to the emergency department, where he received methylprednisolone 125 mg i.v., diphenhydramine hydrochloride 50 mg i.v., famotidine 20 mg i.v., and 0.9% sodium chloride injection 1 L by i.v. infusion. Blood tests revealed a negative toxicology screen and the following abnormal laboratory values: WBC count, 15,200 cells/mm³; RBC count, 3.75 million cells/mm³; hemoglobin concentration, 11.5 g/dL; hematocrit, 35.8%; mean corpuscular volume, 95.5 µm³ (reference range, 80–94 µm³); WBC differential for neutrophils, 30% (reference range, 0–8%); and WBC differential

for lymphocytes, 4% (reference range, 20–40%).

The patient's symptoms resolved, and he was able to return to the psychiatric unit later the same day. Risperidone 2 mg orally twice daily was reinitiated. The patient was counseled on the risk of developing an anaphylactoid reaction with the future use of paliperidone suspension and the importance of reporting the reaction described here as part of his medical history. Paliperidone suspension was added to the patient's allergy profile. During the rest of the patient's hospital stay, no further anaphylactoid signs or symptoms occurred. Counseling and disease state education regarding the importance of adherence to therapy was provided to the patient. His psychiatric symptoms resolved, and he was discharged to an inpatient rehabilitation center.

Discussion

In the case reported here, the acute onset of pruritus, flushing, hypotension, and respiratory distress after the injection of paliperidone suspension met the criteria for an anaphylactoid reaction.^{2,3} The reaction was unexpected, as no signs or symptoms of any adverse events during treatment with oral risperidone indicated that the patient would be at risk for an adverse reaction to paliperidone suspension. A search of MEDLINE (1948–February 2011) and International Pharmaceutical Abstracts (1970–February 2011) using the terms *paliperidone*, *paliperidone palmitate*, *Invega*, *Invega Sustenna*, *anaphylaxis*, and *anaphylactoid* revealed no documented cases of paliperidone palmitate extended-release suspension causing anaphylactoid or allergic reactions, although such cases have been reported in association with oral formulations of risperidone and paliperidone.¹

Due to the temporal relationship between the administration of paliperidone suspension and the anaphylactoid reaction described

here, it is highly probable that the reaction was due to the injected formulation. The reaction was classified as anaphylactoid because there was no sensitization period (i.e., the reaction occurred after the first dose of the suspension).^{2,3} The reaction was unpredictable; the treatment team obtained a thorough clinical history of the patient, which was negative for any food or drug allergies or previous anaphylactoid reactions. Additionally, the tolerability of oral risperidone in this patient was established before the injection of paliperidone suspension, and no significant adverse events occurred on reinitiation of oral risperidone. Although the reaction occurred after the administration of paliperidone suspension, a specific reason for the reaction could not be determined.

Multiple factors related to the paliperidone suspension and its administration were assessed as potential causes of the reaction. Due to the confirmed tolerability and the lack of symptom recurrence on reinitiation of oral risperidone, it is unlikely that paliperidone palmitate itself was the cause; if it was, the drug's long half-life (up to 49 days¹) probably would have put the patient at risk for a recurrence of the reaction before the drug's full elimination. The nurse who administered the suspension reported using proper injection technique. The consequences of administering the suspension into a blood vessel are unknown but may include rapid systemic absorption and signs and symptoms similar to those seen after an acute overdose, which include obtundation, seizures, circulatory collapse, hypotension, and extrapyramidal symptoms.¹ No new medications had been started recently, and a negative toxicology screen appeared to rule out other possible causes. The tip cap and plunger stopper of the model of syringe used in this case are made of bromobutyl rubber, a substance that can cause anaphylaxis in patients

allergic to latex.^{1,4} The patient, however, reported no latex allergy and did not react adversely after exposure to latex gloves or after receiving injections from other, similar syringes during his hospital stay.

The inactive ingredients of the paliperidone suspension (polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection) were also assessed as possible causative agents.¹ Polyethylene glycol 4000 has been associated with anaphylactic reactions and may have been the causative factor in the case reported here.⁵ Anaphylactic reactions to long-acting injectable antipsychotics in patients with established tolerance of oral formulations, although rare, have been reported and attributed to ingredients of the injectable formulations.⁶ One published case report described an anaphylactic reaction, manifesting as rash and wheezing, after the first dose of long-acting injectable risperidone in a patient with confirmed tolerance of oral risperidone; the report's authors attributed the reaction to the polymer that encapsulated the risperidone in the long-acting injection.⁶ Injectable haloperidol decanoate and fluphenazine decanoate, whose formulations include sesame oil, may cause anaphylaxis in patients with sesame-seed allergy.⁷⁻⁹

The recall of prefilled syringes containing 234 mg of paliperidone palmitate in an extended-release suspension was initiated after cracks were found in some of the syringe barrels.¹⁰ Although no adverse events were reported in association with the recalled lots, a crack in the syringe barrel might compromise the sterility of the suspension and lead to possible injection site reactions and systemic infections.¹¹ The manufacturer's drug recall letter noted that, if present, a crack would be covered by the label and undetectable to the user.¹⁰

Anaphylactoid and anaphylactic reactions develop via different mechanisms but have similar presentations and are clinically indistinguishable.^{2,3} Anaphylactoid reactions result from the release of histamine from mast cells and basophils, a process that is not mediated by immunoglobulin E (IgE) and does not require previous exposure to an inciting agent. Anaphylactic reactions result from sensitization to a drug during the initial administration, with the IgE-mediated release of inflammatory mediators on reexposure. The similar chemical structures of risperidone and paliperidone suggest a likely allergic cross-reactivity.^{1,12} In the case reported here, the initial use of risperidone might have caused sensitization, and the administration of the paliperidone suspension might have induced IgE-mediated anaphylaxis. This hypothesis could not be ruled out or confirmed, as diagnostic tests for hypersensitivity, such as allergen skin tests and determination of IgE serum levels, were not performed. The disposal of the implicated syringe prevented the assessment of the syringe for cracks or for contamination or adulteration.

The application of the nomogram of Naranjo et al.¹³ yielded a score of 5, indicating that paliperidone palmitate extended-release suspension probably caused the patient's anaphylactoid reaction.

It is important to be cognizant that, although rare, anaphylactoid reactions may occur with the use of paliperidone palmitate extended-release suspension, even in patients tolerant of oral risperidone and paliperidone. Clinicians should be aware of the signs and symptoms of anaphylactoid reactions and the importance of rapid treatment.

Conclusion

A man who had tolerated oral risperidone developed an anaphylactoid reaction after receiving an injection of paliperidone palmitate

extended-release suspension. After recovering from the reaction, the patient again received oral risperidone without adverse effects.

^aInvega Sustenna, Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Titusville, NJ, lot 9JBK000.

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