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Hypersensitivity to sub-Tenon's topotecan in fibrin adhesive in patients with retinoblastoma

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Sub-Tenon's space delivery of topotecan in a fibrin sealant was used as an adjunct to laser therapy for small retinoblastoma tumors in 25 children (77 injections). We report serious hypersensitivity reactions in 2 children on their third sub-Tenon's injection of topotecan in fibrin sealant. One child subsequently had topotecan in an autologous blood clot with no allergic reaction. Although allergic reaction to topotecan has been reported in the literature, fibrin glue reactions are more common and are likely due to aprotinin hypersensitivity.

Topotecan powder dissolved in thrombin solution was injected with an equal volume fibrinogen stabilized by aprotinin (Tisseel; Baxter, Deerfield, IL) in 77 times in 25 children treated at the Hospital for Sick Children, Toronto, for small retinoblastoma tumors. We report hypersensitivity reactions in 2 patients.

Case 1

A 2-year-old girl with bilateral retinoblastoma and no history of allergy had right eye enucleation and 9-cycle chemotherapy (elsewhere) and laser therapy that did not control left eye tumors. We treated the child with focal sub-Tenon's topotecan in Tisseel; 7 days after the first

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and second injections, 3 weeks apart, she developed upper lid swelling that resolved with diphenhydramine. However, within 10 minutes of the third dose of topotecan in Tisseel 3 weeks later she developed upper lid swelling and generalized urticaria. Intravenous diphenhydramine and epinephrine improved the rash and eyelid swelling. Laryngeal edema prevented immediate extubation, and she was admitted to intensive care. She was extubated in 48 hours and discharged without complications.

Case 2

A 2.5-year-old boy with bilateral retinoblastoma had left eye enucleation after 6-cycle chemotherapy. There was no history of allergy. He had a high hepatitis B viral load. We gave focal sub-Tenon's topotecan in Tisseel. He developed conjunctival erythema at the injection site the next day, which resolved in 2 days. He did not react after the second dose of topotecan in Tisseel given with subconjunctival triamcinolone 3 weeks later. However, 7 weeks later, 2 days after the third dose of topotecan in Tisseel he developed periocular edema, pruritus, and increased tearing, which responded to diphenhydramine. He did not react after the fourth dose of sub-Tenon's topotecan in his own blood used to form an autologous clot depot, administered with intravenous diphenhydramine and hydrocortisone.

Discussion

Sub-Tenon's chemotherapy is a useful adjunct in the management of retinoblastoma. Topotecan is a topoisomerase I inhibitor with proven efficacy in the treatment of retinoblastoma,¹ with less orbital tissue toxicity than carboplatin.²

In transgenic murine models of retinoblastoma, subconjunctival topotecan were injected with a fibrin sealant to form a depot that increased the rate of transcleral diffusion while reducing spread to periocular tissues.³ The increased drug level in the vitreous prolonged the effective duration without systemic toxicity.⁴ There is little literature on hypersensitivity reactions to topotecan. One 38-year-old woman presented with cellulitis after intravenous topotecan but tolerated further topotecan exposures.⁵

Tisseel is a Health Canada-approved adhesive for use in human tissues. When the first component (human fibrinogen, plasminogen, fibronectin, and factor XIII) in an aprotinin solution is mixed with the second component (reconstituted human thrombin), the thrombin converts fibrinogen to fibrin. Factor XIII crosslinks the fibrin monomers and reacts with collagen tissues to form a clot.⁶

Aprotinin, a proteinase inhibitor derived from bovine lung, was added to the fibrin adhesive mixture to retard fibrin clot lysis and increase the duration of tissue adhesion.⁶ Because it is a foreign protein, it can induce an immune response. In a 40-year review of aprotinin-induced hypersensitivity reactions, 93% were due to intravenous

aprotinin, and 7% to local application of fibrin glue. The incidence of allergic reaction to fibrin glue is 0.5 per 100,000 usage.⁷ Aprotinin-related allergic reactions occurred mainly at reexposure (80%), with 76% within 36 months of the first exposure.⁷ The reactions included pruritus,⁸ urticaria, anaphylaxis, and cardiac arrest,⁹ from a few minutes to 3 months after exposure.^{7,8} In ocular surgeries, Tisseel is generally used only once. These single-usages may explain why there is no reported case of Tisseel allergy in ophthalmology literature.

Our patients had sub-Tenon's injections of Tisseel prior to the hypersensitivity reactions. Their reactions were similar to the other cases of allergy to fibrin adhesives⁷ and resolved rapidly with antihistamines and steroid. We infer that the allergic reactions in our patients were most likely due to the aprotinin component of Tisseel. We have previously reported that focal topotecan is a proven effective adjunct to laser therapy for treatment of small volume retinoblastoma tumor,² and the fibrin sealant allows sustained delivery of the drug over time.¹⁰ Because repeated injections are often necessary, repeated exposure to Tisseel poses a small but important risk for development of hypersensitivity. Our recognition of the risk of hypersensitivity reaction on repeated injection of Tisseel has caused us to replace it in these procedures with Evicel (Johnson & Johnson, Ethicon Inc, Somerville, NJ), an aprotinin-free fibrin adhesive that we have used for sub-Tenon's topotecan injection without incidence.

Literature Search

EMBASE and MEDLINE were searched, without date restrictions, in December 2013 using the following terms with synonyms and related words: *hypersensitivity* AND *topotecan* and *hypersensitivity* AND *fibrin adhesive*.

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Malaria retinopathy and cerebellitis in a 9-year-old boy in the United States

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Malarial retinopathy is characterized by retinal whitening, vessel change, and hemorrhages usually associated with a white center. We present the case of a 9-year-old boy who presented with a systemic *Plasmodium falciparum* infection, hemorrhagic cerebellitis and malarial retinopathy characterized by "fire flare" hemorrhages (scleral icterus with subconjunctival hemorrhages), Roth spot-like hemorrhages, and subhyaloid hemorrhage. To our knowledge, this is the first reported case of hemorrhagic cerebellitis secondary to *P. falciparum* infection in the United States.

Case Report

A 9-year-old African American boy presented to the emergency room at Children's Memorial Hermann Hospital, Houston, Texas, with complaints of lethargy, nausea, abdominal pain, tachypnea, a blood pressure of 98/38 mm Hg, and bilateral "fire flare hemorrhages"—a combination of icteric sclera with overlying patchy subconjunctival hemorrhage. Blood smear analysis was positive for *Plasmodium falciparum*. Two weeks prior he had returned from 2 months of travel in Tanzania, a country known as an endemic region of *P. falciparum* malaria.^{1,2} He subsequently developed hypovolemic shock, respiratory distress and was intubated for airway protection. Peripheral blood analysis showed thrombocytopenia, severe microcytic hypochromic anemia, and leukocytosis. Liver function tests and

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