

Table 1

The Protocol of the Tolerance Induction to Sorafenib

Treatment	Time, min	Dose, mg	Reaction	Treatment
Oral premedication with 30 mg of prednisolone and 20 mg of bilastine on day 1	0–60 60–120 120–180	0.4/0.8/1.6/3.2 6/12/24/50 100/200/400	No No No	No No No
Cumulative Dose of 798 mg (Every 15 Minutes)				
Oral premedication with 30 mg of prednisolone and 20 mg of bilastine on day 2	0 180 300	100 100 200	30 min later: pruritus, face and neck urticaria No 180 min later: pruritus, face and neck urticaria	20 mg of bilastine, symptoms reduced within 30 min No 20 mg of bilastine, symptoms reduced within 30 min
Cumulative Dose of 400 mg (Every 180 Minutes)				
Oral premedication with 30 mg of prednisolone and 20 mg of bilastine on day 3	0 120 240	100 200 200	No No 5 hours later: pruritus, face and neck urticaria	No No 30 mg of bilastine
Cumulative Dose of 500 mg (Every 120 Minutes)				
Oral premedication with 30 mg of prednisolone and 20 mg of bilastine on day 4	0 120 240	200 200 200	No No 12 hours later: pruritus, face and neck urticaria	No No 20 mg of bilastine
Cumulative Dose of 600 mg (Every 120 Minutes)				
Oral premedication with 20 mg of bilastine on days 5–7	Every 120 min	200	No	No
Cumulative Dose of 800 mg (Every 120 Minutes)				

We then changed the tolerance induction protocol and discontinued premedication with prednisolone, although theoretically it could be beneficial in alleviating late skin reactions appearing 5 to 12 hours after the last dose.

Induction of drug tolerance consists of the progressive administration of increasing doses of a particular drug to render immune effector cells less reactive. Immunologic mechanisms, including IgE-mediated and/or cell-mediated mechanisms, or even nonimmunologic unknown mechanisms are involved in this process. The resulting state is temporary, and continuous administration of particular drugs is required to maintain the tolerance. Case reports of successful oral tolerance induction in patients with severe cutaneous reactions have been presented in literature, including reports on 2 multikinase inhibitors, sorafenib (in metastatic renal cancer)² and imatinib (in chronic myeloid leukemia).⁹ Unfortunately, we could not measure the tumor necrosis factor for the patient. Others who use this protocol might want to measure tumor necrosis factor before and after the desensitization because it might play a role in such situation. We conclude that the induction of tolerance to sorafenib is possible, allowing highly efficient treatment to be continued.

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Paracetamol-induced fixed drug eruption in a patient with recurrent fever and rash



We describe a 3-year-old boy with recurrent fever and rashes on the same areas of his body and diagnosed multiple fixed drug eruption (FDE) induced by paracetamol. The boy was admitted to a pediatrics clinic with recurrent fever (39°C–40°C) and rash attacks every 2 to 3 months during last year. The skin lesions were painless, without itching above the mouth, around both eyes, above chin and

nose, and on the right elbow and right knee. The lesions were red at the beginning and then turned purple in 2 to 3 weeks, leaving hyperpigmentation. The patient was hospitalized for a differential diagnosis of periodic fever syndromes, autoinflammatory syndromes, and dermatomyositis. He presented with hyperpigmentation on the periorbital and perioral area, on the second and fifth fingers, and at the abdominal region. Blood cell count, kidney and liver function test results, and muscle enzyme, serum electrolyte,

serum glucose, C-reactive protein, and immunoglobulin (including IgD) levels were all within normal limits. Antinuclear antibody, anti-double-stranded DNA, and antinuclear cytoplasmic antibody test results were negative. Complement levels (C3 and C4) were within normal ranges. The results of testing for familial Mediterranean fever DNA were negative. Genetic analyses for cryopyrin-associated periodic fever syndrome revealed a heterozygous P/Q703K mutation of the cryopyrin *NLRP3* gene. The patient was evaluated for reasons of recurrent fever, but all laboratory test results were normal, and we did not find any reason of recurrent fever.

The medical history revealed that the skin lesions were appearing after every paracetamol intake to treat fever. In view of the strong history linking paracetamol with this unusual reaction, a diagnosis of FDE was considered. One month after discharge, delayed-reading intradermal tests and a patch test with a 10% paracetamol concentration to the upper back area and abdominal region on the residual pigmented lesions were performed. All the results were negative. We did not perform a provocation test with paracetamol because the parents did not give consent. The parents were advised to avoid the use of paracetamol for any indication. Ibuprofen was recommended for treating fever. Skin lesions did not reoccur during the 2-year follow-up.

FDEs are characterized by single or multiple well-defined erythematous plaques or bullous eruption that recurs at the same site as the result of systemic exposure to a causative drug and resolves with or without hyperpigmentation.^{1–3} Nonsteroidal anti-inflammatory drugs, paracetamol, and antibiotics are the most frequent causes of FDE. Paracetamol is a widely used drug in children, and physicians should be aware that cutaneous adverse effects may occur. As far as we know, paracetamol-induced FDEs, especially multiple FDEs in children, are rarely reported in the literature.^{4,5} FDEs may occur anywhere on the body. Sites of predilection include the lips, genitalia, perianal area, hands, and feet. Intraepidermal CD8⁺ T cells are thought to have a key role in mediating the localized epidermal lesion that characterizes FDEs.¹

The most important method of preventing recurrence of any adverse drug reaction is identification of the causative drug, followed by complete avoidance of repeated exposure to this drug. The diagnostic hallmark is recurrence of eruptions at previously affected sites when the offending agent is reused. Provocation tests are the gold standard for identifying the culprit drug when the history is unclear or multiple medications are suspected. Because the provocation test induces reactivation of a resting FDE lesion, patch tests are useful and preferred as the first step for diagnosis.¹ Patch test is a simple and safe method to confirm drug reactions.

However, specificity and sensitivity for the patch test are not well defined. In a 20-year review of patch testing for FDEs, the results of patch tests on pigmented lesion were positive in 40.4% of 21 patients, but none of the 8 patients tested for paracetamol had positive results.⁶ In our case, the results of patch tests on the upper back and pigmented lesions were negative.

Patients with recurrent fever and rash can have the same clinic symptoms of periodic fever syndromes and autoinflammatory syndromes, so these patients can be difficult to manage. A history of medication use should be taken in detail, and a diagnosis of multiple FDEs attributable to antipyretics should be considered.

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