

Case report

Severe drug rashes in three siblings simultaneously

Background: Adverse reactions to drugs commonly occur sporadically. Certain individuals seem to have an increased susceptibility to develop reactions to multiple drugs. Genetic predisposition has not been elucidated. Our objective was to describe a case of three siblings who developed severe rashes to the same drug simultaneously.

Methods: Review of the patients' medical records for information on the clinical course, and comparing their serum immunoglobulin (Ig) levels initially and during follow-up.

Results: The rashes were compatible with erythema multiforme and Stevens-Johnson syndrome and developed in the three siblings within 1–3 weeks after the intake of thiabendazole. Follow-up of serum Ig levels did not show any particular pattern, except for an initial mild to moderate elevation in IgG, IgA and IgM.

Conclusions: The occurrence of such severe cutaneous drug reaction in the three siblings to the same drug suggests a genetic predisposition to adverse drug reactions.

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Adverse drug reactions (ADR) have been increasingly causing major health and economic impact (1). In the United States, ADR account for 106 000 deaths annually (2). The incidence of ADR in children is estimated to be 0.7–2.7% in the outpatient setting, 4.37–16.78% in hospitalized children, and responsible for 0.59–4.1% of all pediatric hospital admissions (3). Although most first-time reactions are unpredictable, some can be prevented by judicious prescription of medications and knowledge about cross-reactivities. Certain individuals seem to have an increased tendency to develop ADR to multiple pharmaceutical agents, but familial or genetic predisposition has not been elucidated. We report a case of three siblings who developed severe rashes to the same drug simultaneously.

Methods and results

Case reports

A 4-year-old Mexican girl (GP) presented to a pediatrician with abdominal pain. Her stool analysis revealed *Ascaris* ova and she was treated with thiabendazole. The pediatrician prescribed the same therapy for her four siblings (ages 2–7 years) without stool analysis to save cost. All five children received thiabendazole syrup 375 mg t.i.d. for 3 days. Subsequently, a generalized rash appeared in three of the five siblings: (i) NP after 7 days, (ii) JP after 10 days, and (iii) GP after 21 days. No rashes developed in the other two siblings (MP and RP).

The 7-year-old sister, NP, developed a rash 7 days after therapy. The rash was generalized erythematous maculopapular with target-like lesions that resolved spontaneously within a few days. JP, her 5-year-old brother, developed a rash 10 days after therapy. His rash was in the form of macules, papules, vesicles, and bullae on the trunk, extremities, palms, and soles. In addition, he had inflamed, itchy eyes and conjunctival injection. A throat culture revealed few β -hemolytic group A *Streptococci*. He improved on atarax and prednisone (20 mg po qd for 3 weeks). GP, whose positive stool analysis showed *Ascaris* ova, was initially treated with thiabendazole for 3 days, which was repeated after 1 week. Twenty-one days later, she developed inflamed eyes and an erythematous maculopapular rash on the soles which became generalized. The rash developed into target-like lesions and numerous bullae. A throat culture also revealed few β -hemolytic group A *Streptococci*. The pediatrician treated her with atarax and cloxacillin. Upon admission, prednisone was added (20 mg po qd for 3 weeks).

With the approval of the Institutional Review Board and the parents consent, serum levels of the five immunoglobulins (Ig) were followed for any possible change. This was performed initially and during follow-up (43–84 days postonset) (Table 1). Immunoglobulin G, IgA, and IgM were slightly to moderately higher during the first 2–3 weeks of the illness in the three affected children. Immunoglobulin E was elevated in two of the affected siblings (JP and GP) then declined after therapy. Immunoglobulin E was also elevated in one of the two unaffected siblings (MP). Immunoglobulin D did not show any particular trend.

Discussion

The severe rashes in these children developed after the administration of thiabendazole and are compatible with

Table 1. Clinical and serum immunoglobulin changes in three siblings with thiabendazole-induced erythema multiforme /Stevens-Johnson syndrome

Days postdrug	Clinical course	IgG mg/dl	IgA mg/dl	IgM mg/dl	IgD mcg/dl	IgE IU/ml
Patient 1 (NP)						
19	Well, no trace of rash	1180	134	190	70	12
49	Well	1115	134	135	90	13
84	Mild URI	1050	120	105	110	8
Patient 2 (JP)						
10	Severe rash	920	254	255	170	180
19	Improved	1010	228	300	500	125
33	Well	900	170	215	300	33
47	Well	785	154	195	230	37
Patient 3 (GP)						
6	Very severe rash and mucositis	895	111	240	400	106
15	Improving	1055	126	270	400	65
29	Healing well	965	127	230	170	70
43	Well, trace rash	910	75	155	470	28

erythema multiforme (EM) and Stevens-Johnson syndrome (SJS). That the rashes might have resulted from infection (group A *Streptococcus*) is a possibility but is unlikely because only two of the three affected children had such infection and the rash appeared after the administration of thiabendazole. It was unfortunate that the drug was administered to four children (two of whom were affected) without documentation of a need (i.e. stool analysis). From our literature search, reports on cutaneous reaction to thiabendazole are rare. A case of EM has been reported in an adult after the administration of two doses of 1500 mg each (4). Thiabendazole was implicated in causing toxic epidermal necrolysis (TEN) in an adult after two doses of 900 mg each (5).

Erythema multiforme has an acute onset of fixed, erythematous, maculopapular lesions that subsequently develop into target lesions. The rash is usually preceded 1–2 weeks by prodromal upper respiratory symptoms and fever (6). These lesions are usually not tender or painful and may resolve spontaneously within 5–15 days or progress to bullous or vesicular eruptions (7, 8). The mucous membranes, particularly the mouth, may be involved. Erythema multiforme is frequently caused by infectious agents, most commonly *Herpes simplex* virus and *Mycoplasma pneumoniae* (6, 9–11). Drugs that are most commonly implicated are: antibiotics (especially sulfonamides and β -lactams), NSAIDs, and anticonvulsants (phenytoin, phenobarbital, and carbamazepine) (12, 13).

Erythema multiforme is often classified into EM minor (cutaneous lesions only) and EM major (cutaneous and mucous membrane lesions). The latter is also known as SJS in which the mucous membrane lesions vary in extent and severity and may involve the eyes, oral cavity, upper airways, gastrointestinal tract, or urogenital areas. Painful blister formation and hemorrhagic crusting of the lips are common. A third severer form of drug reactions is TEN whose skin lesions start as diffuse erythema with subsequent large bullae formation that coalesce and

resemble scalding, and results in sloughing of the epidermis (10, 14, 15). Toxic epidermal necrolysis is associated with severe mucous membrane involvement and high rates of complications and mortality. There is controversy as to whether EM, SJS, and TEN are different entities or are manifestations of one clinical spectrum (8). The observation of a variation in the clinical presentation of our three patients, in spite of being siblings and caused by the same drug, would support the notion of a single clinical spectrum.

The differential diagnosis of EM, SJS, and TEN include urticaria pigmentosa (mastocytosis), Kawasaki disease, and staphylococcal scalded skin syndrome. The underlying mechanism of EM/SJS/TEN syndrome is unknown (6, 8). The total serum Ig levels in our patients showed no specific pattern of change, except for a tendency of increased IgG, IgA, and IgM at the initial stage of the disease.

Treatment of this syndrome is primarily avoidance of the offending agent, treating any underlying infection, and providing fluid-electrolyte support. Some severe cases may require special care in an intensive care unit or burn unit. Certain patients may need frequent ophthalmologic examination or corrective plastic surgery. The use of systemic corticosteroids has been a highly debatable issue. Some authorities consider corticosteroids life-saving in severe cases (7). The two previously reported cases of thiabendazole-induced EM and TEN apparently responded well to systemic corticosteroids (4, 5). The argument against its use is the potential for corticosteroids to enhance susceptibility to infection and increasing the risk of mortality (16). In our patients, corticosteroids seemed to be useful without apparent side-effects. Other therapeutic modalities that have been tried in TEN or SJS include intravenous Ig therapy and plasmapheresis (8, 15).

In conclusion, we present a case of three siblings who developed EM/SJS to the same drug, thiabendazole, simultaneously. The case had several peculiarities: three

of five siblings were affected, the same drug was implicated, the onset varied from 1–3 weeks, the skin and mucous membrane involvement varied from mild to severe, and the recovery occurred within a few days up to 6 weeks. Our limited humoral immunity evaluation was inconclusive, except for a slight to moderate elevation of IgG, IgA, and IgM during the first few weeks of illness. Our findings suggest that EM/SJS may have a genetic

predisposition, thiabendazole can be a potent offender, and the manifestations can be any of a continuum from mild rash (EM minor), a severe rash and mucositis (EM major or SJS), or extensive large bullae and diffuse epidermal necrosis (TEN). Lastly, had the stool analysis been performed on all siblings, perhaps some of them would not have needed the drug or developed such a severe drug reaction.

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