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Erythema Multiforme in a Patient with Reactive Arthritis: Usefulness of Lymphocyte Stimulation Test for Detection of Sulfasalazine Hypersensitivity in a Case Report

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Abstract

Skin eruption from sulfasalazine (salazosulfapyridine, Salazopyrin-®) was indicated by lymphocyte stimulation test using various concentrations of the metabolites, sulfapyridine and 5-aminosalisylic acid. Only sulfapyridine produced a clear positive stimulation index. Later after about one year, the oral challenge resulted in negative results. The explanation of the developed tolerance for sulfasalazine remains unknown.

The results show that Lymphocyte Stimulation Test (LST) can be useful but may necessitate the use of a series of multiple dilutions in case of studying suspected allergens that possess antilymphocytic proliferative properties.

Keywords: Lymphocyte stimulation test • Sulfapyridine • Salazopyrin-®

Introduction

Salazopyrin is often used as an antirheumatic drug and for treatment of inflammatory bowel diseases. Occasionally, it may cause various kinds of skin reactions. Type I reactions are rarely seen. LE-like syndrome and allergic vasculitis are reported. Phototoxic and photoallergic skin eruptions, and also erythematous rash, exfoliative dermatitis, erythema fixum, erythema multiforme, and even severe skin eruptions, that is, Stevens-Johnson syndrome and Lyell syndrome [1]. It is a non-steroidal drug that exhibits anti-inflammatory, analgesic and anti-pyretic properties and the therapeutic blood serum concentration is 5-50 µg/ml.

Case Presentation

The patient was a 41-years-old female who had been treated with Salazopyrin, two 500 mg tablets bid, because of prolonged reactive arthritis for 4 years. There was no personal history of atopy or allergy. The patient used simultaneously verapamil 120 mg retard tablets every second day for migraine prophylaxis.

The patient was found to have an infected eczema on the left elbow site and was treated with topical corticosteroid cream (0.1%betamethasone valerate–2% fucidic acid) and antibacterial compresses 2 weeks prior to rapid development of a multiformic itchy skin eruption with exanthematous urticarial with partially eczematous lesions on the trunk and extremities. The diagnosis of erythema multiforme was set in August 1998. Topical clobetasone butyrate and betamethasone 17-valerate creams with oral cephalexin 500 mg bid did not give any marked response, and antihistamines (ceritizine 10 mg/d+hydroxyzine 25 mg/d) produced only partial response to the itch. Thereafter, an oral prednisolone 30 mg per day together with topical betamethasone cream along with discontinuing the Salazopyrin medication resulted in a rapid response.

Laboratory studies for infective etiology for bacteria and viruses were negative and no titer increases were detected. Antinuclear antibodies, C-reactive protein, sedimentation rate, and Waaler-Rose were normal or negative. Skin biopsy showed eosinophilic infiltrates being suggestive for a drug eruption.

Two months later, the skin eruption was healed and steroid treatments were gradually tapered off. The Lymphocyte Stimulation Test (LST) was performed for diagnostic purposes. About one year later, an oral challenge with gradually increasing doses of 125-250-250-500-500 mg Salazopyrin during 3-day period was performed.

Materials

5-Aminosalisylic Acid (5-ASA) was obtained from Orion Corporation (Turku, Finland), Sulfapyridine (SP) from Yliopiston Apteekki (University Pharmacy, Helsinki, Finland), and

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Salazopyrin (SAP) FROM Sigma (St. Louis, MO, USA).

The LST test was performed in triplicate with 3-or 6-7 day treatments using 3H-labeled thymidine incorporation technique [2]. Using various concentrations of the tested compound (final concentration 0.1-50 µg/ml), and liquid scintillation counter with quench correction. The LST index is defined as the ratio of DPM (allergen)/DPM (control), and the Index being over 2.5 is considered as positive [3].

Results

In the case of SAP, the LST test with the 3-day stimulation revealed only a slight and inconclusive LST index of about 1.6-1.8 at about 10 µg/ml. Therefore, the LST test with both 3- day and 6-day treatments using the SAP metabolites, i.e., SP and 5-ASA, was performed. As a result, 3 day treatment showed no stimulation, whereas the 6 day incubation revealed a peak-like positive stimulation index 3,6 for SP at 3 µg/ml, but not clearly for 6-10 µg/ml SAP. No stimulation was noted for 5-ASA (Table 1).

Table 1. Lymphocyte stimulation test results.

Drug concentration	Stimulation index		
(µg/ml)	Salazopyrin	Sulfasalazine	5-ASA
0.1	1.25	1.35	1.25
1	1.15	1.9	1.3
3	1.2	3.6	1.5
6.0	1.5	1.3	1.6
10.0	1.65	1.35	1.25
20.0	1.1	1.15	1.6
50.0	1.15	1.15	0.75

5-ASA: 5-aminosalisylic acid

The oral challenge with SAP revealed completely negative result with respect to skin symptoms as performed about one year after the initial skin reaction.

Discussion

The LST test was utilized for the diagnostics of salazopyrin hypersensitivity, and it resulted in the LST index of 3.6, though only with the metabolite SP. There are some case reports using the LST test for the detection of salazosulfapyridine hypersensitivity, e.g., a 20-year-old male patient with ulcerative colitis [4] and a 22-year-old female patient [5] with stimulation indexes of 5.4 and 2.4, respectively.There is also a case, a 13-year-old boy with ulcerative colitis, who developed intestinal hypersensitivity for mesalazine (i.e., 5-ASA) as indicated by the LST index of 2.55, but the index was negative for salazosulfapyridine that was used later for his treatment [6].

In the present case, the LST test revealed no stimulation in the 3-day incubation. Further, the 6-day incubation resulted in only marginal stimulation index for SAP at 6-10 µg/ml.

The other metabolite of SAP, 5-ASA, did not show any apparent stimulation, whereas SP showed a clear positive index at about 3 µg/ml.

The reason for the variable concentration-dependent stimulation of lymphocytes can be explained by the simultaneous activatory and inhibitory effects of SAP, and the net effect is seen under the conditions in the standard LST test.

Imai, et al. have reported the effect of sulfasalazine (i.e.,SAP) on B-cell hyperreactivity in patients with active Rheumatoid Arthritis (RA)[7].They found that 5 µg/ml sulfasalazine markedly decreased the lymphocyte hyperproliferative function by about 80%-90%. They found that sulfasalazine decreased B-cell hyperreactivity induced by Staphylococcus aureus Cowan I in RA patients in dose-dependent manner by 67% at 0.5 µg/ml, by 85% at 5 µg/ml and by 94% at 50 µg/ml.

In RA-patients, the lymphocytes (stimulated by Staphylococcus aureus Cowan-I) showed markedly more active stimulatory capacity (about 1.7 to 2-fold) after a 3-day incubation compared to a 6-day incubation [7]. In the 6-day incubation in this study, the patient's cells showed, however, about a double stimulatory capacity compared to the stimulation for 3 days, which differs from the previous results of RA patients. Thus, the incubation time can markedly affect the results obtained, possibly depending on the immunologic capacity of the subject.

Variable lymphocytic reactivities were noted for SAP, SP and 5-ASA in the present patient. Interestingly, SP has been found to possess clear mitogenic effects in rat jejunum and ileum, and a weaker effect in colon [8]. However, SAP had mitogenic effects only in the colon and the mitogenic index was less than half of that with SP. These findings also indicate that SAP and SP can have distinct biological responses.

Another important factor in studying the possible hyperreactivity by salazopyrin is the concentration of the drug. If it causes an immune reaction, it may also attenuate it by acting as an anti-inflammatory drug. Thus, a series of dilutions are needed to obtain a reliable LST test for diagnostic purposes.

It remains unclear why the first LST test gave a low positive stimulation index with SAP and a clearly positive index with the metabolite SP, but the oral challenge performed with SAP about one year later was negative. We could speculate that a non-specific activation of the FAS/FADD/caspase-8 pathway [9] leading to death of the epidermis. Also, sulfasalazine reactivity would not give again any skin symptoms after keeping the drug temporarily removed from the patient's medication. Also, as described by Kunisaki et al [5], an HHV-6 activation might influence salazopyrin reactivity, and thus, some other virus infection parallelly in our patient, but we did not detect any evidence for this. Therefore, we can not exclude the involvement of some concomitant other yet-unknown factor together with sulfasalazine, or the development of tolerance.

Conclusion

In conclusion, the literature describes that an HHV-6 activation might influence salazopyrin reactivity, and thus, some other virus infection parallelly in our patient, but we did not detect any evidence for this. Therefore, we cannot exclude the involvement of some concomitant other yet-unknown factor

together with sulfasalazine, or the development of tolerance. The findings suggest that the Lymphocyte Stimulation Test (LST) can be beneficial, but that it may require a series of repeated dilutions and 3- and 6- day incubations when investigating potential allergens with antilymphocytic proliferative capabilities.

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Conflict of Interest

All authors declare that there are no conflicts of interests.

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