



## Preliminary report

## A case of pediatric Steven–Johnson Syndrome associated with albuterol consumption



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## ABSTRACT

We describe a case of Steven–Johnson Syndrome (SJS) associated with albuterol exposure in a 6-year-old male. A possible contributing role of albuterol in SJS occurrence in the present case is strongly suggested by the temporal relationship between the event and the initiation of drug therapy as well as by the positive rechallenge. To the best of our knowledge, albuterol had not been previously associated with SJS in medical literature. It can be therefore possible that physicians, pediatricians in particular, probably not aware of the possible risk of albuterol-induced SJS, might underestimate skin reactions in children taking the drug, thus underreporting this kind of severe adverse drug reaction.

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## 1. Introduction

Stevens–Johnson Syndrome (SJS), an immune-mediated life-threatening cutaneous reaction, is defined as epidermal detachment of <10% body surface area and it is caused by various etiological factors [1]. A review confirmed four highly suspected causative drugs: sulfonamide, phenobarbital, carbamazepine, and lamotrigine [2]. Albuterol is a short acting  $\beta_2$ -agonist indicated for prevention and treatment of bronchospasm in patients 4-years of age and older [3]. It can induce adverse effects, such as increased heart rate, palpitations, transient decrease in PaO<sub>2</sub>, and tremor whilst systemic cutaneous eruptions are rare [4].

## 2. Case report

A 6-year-old male child without known chronic diseases was admitted to the emergency department (ED) of the Meyer Children Hospital with fever, bronchospasm, wheezing, stomatitis and purulent conjunctivitis. Tachycardia and oxygen saturation of 93% were observed

on his arrival. Before admission, the child was treated with amoxicillin and clavulanic acid, oral betamethasone 0.5 mg and nebulized fluticasone 50 mcg, for a severe respiratory tract infection and with 600 mcg of inhaled albuterol (IA) for bronchospasm. In ED, the child was treated with other 1200 mcg of IA in 24 h but his conditions worsened. He was hospitalized with a diagnosis of bronchitis and treated with rehydration, intramuscular ceftriaxone, ophthalmic tobramycin and 1600 mcg of IA in 24 h. The following day, his clinical conditions were substantially unchanged, but the muco-cutaneous lesions worsened: physical examination showed signs of cheilitis, pharyngeal hyperemia, stomatitis with palate vesicles and many severe skin lesions. The child repeated 1200 mcg of IA, and afterwards he was transferred to pediatrics medical department with a diagnosis of bronchospasm, dyspnea and stomatitis. Few days later his clinical condition worsened again and he was transferred in the intensive care unit, where he was fed by total parenteral nutrition and required mechanical ventilation. A dermatological consultation attributed the vesiculobullous lesions extended to eyes, face, ears, trunk and lower limbs to a SJS (Fig. 1). A complete recovery was achieved with 3 consecutive cycles of intravenous immunoglobulins.

Nine months later, the child was again treated with 1200 mcg of IA and 50 mcg of nebulized fluticasone, for cough and dyspnea. The following day he presented at ED with tachycardia, oxygen saturation of 93% and tachypnea. A physical examination showed upper lip swelling, hyperemic and painful oral mucosa and conjunctivitis.

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Fig. 1. Muco-cutaneous lesion of the mouth during intensive care unit stay.

Clinicians treated the child with IA and oral betamethasone. Then he was admitted to pediatrics medical department with a diagnosis of dyspnea and suspected initial onset of SJS, eventually confirmed by a dermatological consultation.

Albuterol administration was suspended and a rapid recovery was observed. All known causal factors for SJS were excluded, including a thorough infective evaluation that yielded negative results for all tested viruses, and a causal role of albuterol in determining SJS was suggested.

### 3. Discussion

As far as we know, this is the first report in medical literature of a SJS associated with pediatric albuterol assumption. Although some concomitant medications may have confounded the SJS-albuterol association, the drug's role is strongly supported by the temporal relationship between therapy initiation and the event as well as by the positive rechallenge. The Naranjo probability scale indicates a probable association and the ALDEN algorithm [5], used for the assessment of drug causality in SJS onset, addressed the causality as 'very unlikely' for the first episode (due to concomitant drugs) and as 'very probable' for the second.

With regard to possible pathophysiological explanations,  $\beta_2$  is the most abundant adrenergic receptor subclass expressed by immune cells such as natural killer cells, neutrophils, macrophages and bone marrow and thymus derived lymphocytes and  $\beta_2$ -agonists have been considered both as immunosuppressive agents and as pro-inflammatory [6]. In addition, it cannot be excluded that unknown

toxic products of albuterol metabolism may have triggered the reaction such as reported for other drugs [1].

In August 2009, the US Food and Drug Administration (FDA) issued a post-marketing review [7] pointing out the possibility that albuterol may cause SJS. In particular two cases were reported in the United States, one of which referred to a 10-years-old male child who received albuterol. Although FDA asserted that "*this potential signal of the serious hypersensitivity reaction, SJS, should be closely monitored for additional cases which are needed for initiation of labeling changes or other regulatory actions*", to our knowledge, in Europe, albuterol has not been previously related with SJS neither in medical literature nor in validated databases. Therefore most physicians are probably still not aware of the possible risk of albuterol-associated SJS, and might therefore underestimate skin reactions in children taking the drug.

### 4. Conclusion

In summary, we believe that post-marketing spontaneous reporting systems are valuable resources for the identification of novel suspected adverse drug reactions, especially rare and serious ones. At the same time the publication of case reports supporting regulatory authority alerts on medical journals is of invaluable help in increasing pharmacovigilance culture in the whole medical community.

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### References

- [1] C. Ferrandiz-Pulido, V. Garcia-Patos, A review of causes of Stevens–Johnson Syndrome and toxic epidermal necrolysis in children, *Arch. Dis. Child.* 98 (2013) 998–1003.
- [2] N. Levi, S. Bastuji-Garin, M. Mockenhaupt, J.C. Roujeau, A. Flahault, J.P. Kelly, et al., Medications as risk factors of Stevens–Johnson syndrome and toxic epidermal necrolysis in children: a pooled analysis, *Pediatrics* 123 (2009) e297–e304.
- [3] M. Cazzola, C.P. Page, P. Rogliani, M.G. Matera, beta2-Agonist therapy in lung disease, *Am. J. Respir. Crit. Care Med.* 187 (2013) 690–696.
- [4] A.N. Jamali, M. Aqil, M.S. Alam, K.K. Pillai, P. Kapur, A pharmacovigilance study on patients of bronchial asthma in a teaching hospital, *J. Pharm Bioallied Sci.* 2 (2010) 333–336.
- [5] B. Sassolas, C. Haddad, M. Mockenhaupt, A. Dunant, Y. Liss, K. Bork, et al., ALDEN, an algorithm for assessment of drug causality in Stevens–Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis, *Clin. Pharmacol. Ther.* 88 (2010) 60–68.
- [6] M. Manni, R.D. Granstein, G. Maestroni, beta2-Adrenergic agonists bias TLR-2 and NOD2 activated dendritic cells towards inducing an IL-17 immune response, *Cytokine* 55 (2011) 380–386.
- [7] FDA, Pediatric Postmarketing Adverse Event Review, August 6, 2009.