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Reply



To the Editor:

We thank Liccardi et al¹ for their interesting comments on our article. They suggest that some clinical markers of increased cholinergic tone might characterize a subgroup of patients with asthma with a potential better response to tiotropium in comparison to long-acting β_2 agonists (LABAs). We and other authors^{2,3} have demonstrated that tiotropium added to low- or medium-dose inhaled corticosteroids (ICSs) was able to improve FEV₁ to a similar degree as salmeterol or other LABAs, suggesting that tiotropium may be a good alternative to LABAs when asthma is not controlled by ICSs alone. However, no predictor of a better response to tiotropium versus LABAs has been demonstrated in the only study that tested the short-term response to tiotropium and to salmeterol in the same patients with asthma using a cross-over design⁴: in that study, the number of patients who responded to tiotropium but not to salmeterol was similar to that of patients who responded to salmeterol and not to tiotropium, and the only characteristics able to distinguish between these 2 groups were acute response to salbutamol, lower baseline FEV₁/forced vital capacity ratio, and lower heart rate. Polymorphisms of beta2-receptor leading to the potential downregulation of beta2-receptors has not been demonstrated to influence a differential response to LABAs or long-acting anticholinergic antagonists (LAMAs).^{5,6} Therefore, as suggested by Liccardi et al in their Figure 1, we need to have other measurements of an increased cholinergic tone in this subgroup of patients who may respond to tiotropium better than to LABAs. Nonrespiratory symptoms suggestive of an increased cholinergic tone before asthma attacks might be a potential marker, but we probably need a more “objective” way to demonstrate this increased cholinergic tone. Bronchial hyperresponsiveness to methacholine is influenced by several structural changes in the airways and not only by an increased sensitivity to cholinergic mediators.⁷ Heart rate variability spectral analysis has been demonstrated to be capable of distinguishing subjects with bronchial hyperresponsiveness from nonhyperreactive subjects, suggesting that the autonomic nervous system, which contributes to the pathogenesis of airway hyperresponsiveness, is closely linked to cardiac modulation.⁸ Large studies comparing the response to tiotropium with that to salmeterol in patients with asthma well characterized in terms of “increased cholinergic tone” should be performed. At the present time, tiotropium may be recommended as an alternative to LABAs in patients with mild to moderate asthma when some risk of side effects to LABAs may be suspected. Demonstrated

predictors of tiotropium responsiveness could identify patients in whom tiotropium could be recommended as the add-on therapy of first choice in patients uncontrolled by low- to medium-dose ICS.

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Conflicts of interest: P. Paggiaro has received consultancy fees from Boehringer Ingelheim, AstraZeneca, Chiesi, and Nycomed; is on the boards for AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Teva; has received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Guidotti, Menarini, Mundipharma, Novartis, and Teva. M. Latorre declares no relevant conflicts of interest.

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Safe and Time-Saving Desensitization Protocol to Intravenous Etoposide



To the Editor:

Recently, a successful rapid desensitization to etoposide has been published in *The Journal of Allergy and Clinical Immunology: In Practice*.¹ This report¹ and a previous report of 2010² are the only desensitization protocols to etoposide published to date. However, despite being safe and effective, these protocols have the disadvantage of being very time-consuming because they require up to 15 hours to be completed.

We present a case of etoposide hypersensitivity in which a novel rapid desensitization protocol was used.

A 63-year-old man with non-small cell lung cancer was referred to our outpatient clinic after presenting with anaphylaxis (cutaneous redness and sudden and intense dizziness, dyspnea, bronchospasm, and oxygen desaturation) while receiving a

second intravenous dose of etoposide (after 7 mg) requiring urgent treatment with intramuscular adrenaline, supplementary oxygen, corticosteroids, and antihistamines, which led to rapid clinical improvement. During the reaction, serum tryptase levels were 5.98 $\mu\text{g/mL}$ at 15 minutes and 4.86 $\mu\text{g/mL}$ at 2 hours of onset (normal values, $<10 \mu\text{g/mL}$). This is in accordance with previous publications in which tryptase levels are normal in up to 36% of anaphylactic reactions.³

An allergy workup was performed with skin prick test (20 mg/mL) and intradermal test (2 mg/mL), yielding negative results.

On the basis of previous publications,⁴ we used a modified rapid drug desensitization protocol consisting of the administration of the target dose in 10 consecutive steps at increasing infusion rates using an automatic multistep infusion pump (Table I). The total calculated dose (176.1 mg) was achieved over the span of 3 hours and 25 minutes, with no complications or breakthrough reactions. Only standard antiemetic premedication according to prescribing information by our hospital protocols was used (dexamethasone 8 mg intravenous). The same protocol was applied in 2 subsequent cycles of chemotherapy, allowing him to receive the target dose with no further hypersensitivity reactions (HSRs).

HSRs to etoposide are rarely described in the literature. The reported incidence of HSRs varies notably between studies from 2% to 6%^{5,6} and may involve both immunologic and nonimmunologic factors. A publication on the adverse event reports to chemotherapeutic agents submitted to the US Food and Drug Administration between 2004 and 2009⁷ reported a very low percentage of HSR to etoposide (50 HRS/28,264 adverse reactions).

This is in agreement with the experience in our hospital, with a high complexity cancer treatment unit. Over the past 5 years, 497 adult patients have been treated with etoposide cycles, with 6114 administered doses and only 1 report of an HSR, yielding an incidence rate of 0.016%.

Over the last decade, desensitization schemes have been proven to be effective and safe,⁸ but the lengthy protocols make their application impossible in centers with high volumes of patients or scarce numbers of allergists. Recent protocols have shortened the time needed for completion, and a slight variation

of those allowed us to administer an effective desensitization protocol in just 3 hours and 30 minutes.

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TABLE I. Ten-step/3-h desensitization protocol to etoposide

Step	Solution*	Rate (mL/h)	Volume infused (mL)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	100	25	15	0.08805	
2		200	50	15	0.1761	0.26415
3		400	100	15	0.3522	0.61635
4	2	100	25	15	0.8805	1.4968
5		200	50	15	1.761	3.2578
6		400	100	15	3.522	6.7798
7	3	50	12.5	15	4.4025	11.1823
8		100	25	15	8.805	19.98
9		200	50	15	17.61	37.59
10		400	393	59	138.502	176.10†

Solution 1: volume 250 mL, concentration 0.003522 mg/mL, total dose in solution 0.88 mg.

Solution 2: volume 250 mL, concentration 0.03522 mg/mL, total dose in solution 8.8 mg.

Solution 3: volume 500 mL, concentration 0.3522 mg/mL, total dose in solution 176.1 mg.

*The sum of the doses in the 3 solutions is 185.78 mg because solutions 1 and 2 were partially administered; the total dose infused is 176.10 mg.

†A target dose of 176.10 mg was infused in 1268 cc of solution over 3 h 25 min.

Reply

To the Editor:

We appreciate the letter to the editor by Gomez-Duque et al,¹ and find the information useful and valuable.

The following are our observations:

- The accuracy of allergy testing must be considered. The authors mention an allergy workup on their patient but with no specific time frame reference. Was the skin prick testing performed within 4 weeks of the reaction? If so, skin testing results may have been falsely negative. The authors note that tryptase levels were within normal limits 2 hours post the onset of the reaction. The authors further note that normal tryptase levels can be seen in a large percentage of anaphylactic reactions. An equivocal or negative laboratory and skin testing workup may create a false sense of confidence in accelerating a drug desensitization schedule.



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