

Is H1-antihistamine (desloratadine 5 mg, orodispersible tablet) premedication in NSAID-associated urticaria really safe and practicable in “real life”?



To the Editor:

We read with interest the article of Trautmann et al¹ showing the effectiveness of desloratadine 5 mg premedication in reducing the rate of hypersensitivity reactions to strong/weak cyclooxygenase-1 (COX-1) inhibitors in reactors to nonsteroidal anti-inflammatory drugs (NSAIDs). The purpose of this study is laudable because it meets the needs of NSAID-intolerant patients requiring these drugs for a sudden or recurrent pain. Nevertheless, we believe that a serious limitation to the impact of this study on current management of NSAID hypersensitivity in “real life” should be considered in addition to those already acknowledged by authors. In fact, it has been widely recognized that immediate reactions, from mild urticaria to anaphylaxis, to a single NSAID may develop within seconds (eg, after intravenous injections) or minutes after oral administration. However, in most patients, symptoms may appear up to 1 hour.²

The authors state “to ensure both the antihistamine’s onset of action and rapid pain relief, our patients received 5 mg desloratadine orally 30 minutes before NSAID administration.” Trautmann et al¹ administered an orodispersible H1-antihistamine tablet for premedication. The reason for using an orodispersible tablet is based on the assumption that this formulation may allow a more rapid absorption of desloratadine and, thus, induce a faster pharmacological effect. Unfortunately, the currently available literature³ and data registered in European Medicines Agency⁴ do not confirm this assumption. The pharmacokinetics of both desloratadine formulations (standard and orodispersible) indicate that the peak plasma concentration is reached about 3 hours after drug administration and, consequently, it is unlikely that desloratadine would reach full clinical effectiveness after only 30 minutes postadministration in the case of a sudden drug reaction. The usefulness of the orodispersible formulation is essentially the intake without water in the case of a sudden need. The article of Yehia et al⁵ reported by the authors to explain the effectiveness within only 30 minutes refers to a formulation of fexofenadine hydrochloride (not desloratadine), which is able to increase the extent of drug absorption and reduce T_{max} . Considering this background, we believe that it could be very hazardous to prescribe a premedication just 30 minutes before the intake of a strong COX-1 inhibitor in NSAID-reactive individuals. To our knowledge, only Asero⁶ has performed a similar study, by using cetirizine premedication 2 to 6 hours before the administration of weak COX-1 inhibitors, which are usually better tolerated compared with a strong COX-1 inhibitor. Finally, it has been shown that in about 8% of healthy individuals, plasma concentrations of desloratadine may increase and decrease more slowly (“Desloratadine Slow Metabolizer Phenotype”).⁷

In conclusion, we believe that the benefit of the rapid relief of a sudden pain in NSAID reactors may be outweighed by an unacceptable risk of developing potentially severe adverse reactions. A possible balance between risk and benefit may be a

premedication at least 2 to 3 hours before taking the drug. In addition, further studies should be performed to explore the occurrence of a more rapid onset of pharmacologic action by doubling the desloratadine dosage.

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Reply



To the Editor:

Liccardi et al¹ discussed 2 aspects of our recent publication,² the risk of nonsteroidal anti-inflammatory drug (NSAID)-induced anaphylaxis and the pharmacokinetics of H1-antihistamines.

The authors suggest “an unacceptable risk of developing potentially severe adverse reactions” despite H1-antihistamine premedication. In this context, they imprecisely refer to “reactors to NSAID,” “NSAID-intolerant patients,” “NSAID hypersensitivity,” and “immediate reactions [...] to a single NSAID.” As a matter of course, a very careful selection of suitable “NSAID reactors” is required before considering H1-antihistamine

premedication. In our series, we exclusively treated patients with an unequivocal history of urticarial skin reactions after NSAID intake, that is, either NSAID-induced urticaria/angioedema (NIUA) or NSAID-exacerbated cutaneous disease (NECD).^{3,4} As a consequence, the worst-case scenario due to an insufficient effect of antihistamine premedication would be a burst of urticaria or angioedema, which could be treated successfully by prolonged administration of H₁-antihistamines. The fear of anaphylaxis is not justified in patients with a reliable diagnosis of NIUA or NECD. An accurate differentiation of NIUA and NECD from NSAID-exacerbated respiratory disease (also denominated as aspirin-exacerbated respiratory disease) or single NSAID-induced anaphylaxis, however, is imperative³⁻⁵ as the latter 2 are considered nonresponsive to antihistamine treatment and may take a severe course. A history of multiple episodes of urticaria/angioedema after intake of different cyclooxygenase-I inhibitors without respiratory or cardiovascular symptoms virtually excludes single NSAID-induced anaphylaxis, and a diagnosis of NSAID-exacerbated respiratory disease/aspirin-exacerbated respiratory disease is highly unlikely in the absence of any nasal or bronchial airway symptoms. However, if any doubts remain concerning the correct diagnosis of NIUA or NECD, the described premedication regimen is, of course, contraindicated.

We are well aware that the peak plasma concentration of H₁-antihistamines is reached only several hours after oral ingestion. Nonetheless, we strongly advocate a time interval of 30 minutes between antihistamine premedication and administration of the NSAID for a number of reasons. First and most important, an additional waiting time of 2 to 3 hours is hardly acceptable because the main therapeutic goal is rapid pain relief. Second, the onset of action of the antihistamine significantly precedes its peak plasma concentration. Third, peak plasma levels of NSAID are likewise reached with a certain delay; for example, peak serum concentrations of ibuprofen are reached in 1 to 2 hours after oral administration.⁶ Accordingly, our study data demonstrate a preventive effect of 5 mg desloratadine as an

orodispersible tablet given 30 minutes before the administration of an NSAID. This outcome is certainly not restricted to the H₁-antihistamine chosen, nor to the specific orodispersible formulation. The use of other H₁-antihistamines, other formulations, and/or higher doses should be investigated in future studies.

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