
LETTERS TO THE EDITOR

Unsuspected polymorphic metabolism of rupatadine via its primary metabolite, desloratadine

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Dear Sir,

In their systematic review published in this issue of the *Primary Care Respiratory Journal*,¹ Katiyar and Prakash have extensively and eloquently summarised the clinical pharmacology and metabolism characteristics – including the safety and efficacy parameters – of rupatadine in the treatment of allergic rhinitis. However, while their systematic review is thorough and provides perspectives and guidance for the effective use of rupatadine, it inadvertently does not mention the latest data with regard to genetic polymorphism in the metabolic disposition of rupatadine which may have significance in the clinical treatment options. Nevertheless, it is important to note that the existence of such genetic polymorphism in rupatadine's metabolic pathway has gone unnoticed for a considerable length of time (due to a lack of appropriate study population data) until very recently.²

Recently, Frick *et al* published a report that documented the involvement of polymorphic metabolism in the disposition of desloratadine, such that two distinct phenotypes of poor metabolisers (PM) and extensive metabolisers (EM) were observed.³ This was substantiated by the human disposition data in a [¹⁴C] study of desloratadine where there was a single individual considered to be a PM.⁴ As the primary metabolic pathway of rupatadine catalysed by cytochrome P450 (CYP) 3A4 leads to the formation of desloratadine, it could be deduced that the risk of genetic polymorphism would be imminent in the disposition of rupatadine. This direct evidence linking rupatadine to polymorphic metabolism through desloratadine was elusive until the recent report of Solans *et al*,² published in 2008, that described the pharmacokinetics of rupatadine, desloratadine and 3-hydroxydesloratadine in healthy volunteers as part of a drug-drug interaction study. In this study, there were two subjects who exhibited very high levels of desloratadine paired with very low levels of 3-hydroxydesloratadine, although the levels of rupatadine appeared to be within the range observed for other volunteers.² While the evidence supported the notion that the formation of 3-hydroxydesloratadine from desloratadine was polymorphic in nature, the CYP isozyme(s) responsible for this metabolic pathway is still unknown.² It was reported that the impaired metabolism of desloratadine to 3-hydroxydesloratadine was found to occur with a frequency of 17% in blacks, 2% in whites and 2% in Hispanics.⁵

The significance of this observation may be because the major circulating moiety following rupatadine oral dosing is the primary desloratadine metabolite (with approximately 4-fold higher exposure when compared to rupatadine at steady state).² The exposure of the active 3-hydroxydesloratadine itself at steady state was found to be almost twice that of rupatadine.² Additionally, the elimination half-life values for both desloratadine and 3-hydroxydesloratadine (25-35 h) were reported to be at least 4-5 times longer compared to rupatadine (6 h).²

Since the impact of genetic polymorphism has been well documented across different therapeutic areas,⁶ this interesting observation on rupatadine's primary metabolite disposition raises important questions. Firstly, the notion that rupatadine is not subject to polymorphic metabolism like some other compounds in the class^{1,7} should be viewed with caution, since the primary metabolite (i.e. desloratadine) is a substrate for polymorphic metabolism.²⁻⁴ Secondly, from a therapeutic perspective, it is possible

that in a small cohort of PM patients there may be a significant accumulation of desloratadine – and while efficacy may not be compromised this may lead to safety issues. Thirdly, although somewhat speculative in nature, if the CYP enzyme(s) responsible for the formation of the hydroxylated metabolite from desloratadine can be induced by other co-substrates, could it lead to compromised efficacy of rupatadine?

An alternate view may be to question the relevance of this recently-reported genetic susceptibility (which hitherto was not an impediment for rupatadine's development and/or clinical use), given the low frequency of its occurrence. However, this view should be dismissed, and a pragmatic approach should be developed in order to understand more about this genetic polymorphism and its consequences (if any) on the clinical effectiveness of rupatadine in the patient population.

Conflict of interest declaration

The author works as a Consultant for Life Sciences at Suramus Biopharm specialising in the early discovery and development of medicines. He is not involved in either the promotion or development of rupatadine, and therefore has no conflicts of interest to report.

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