Expert Opinion

Crystallisation within transdermal rotigotine patch: is there cause for concern?

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Expert Opin. Drug Deliv. (2008) 5*(11):1169-1171*

1. Background

Rotigotine transdermal patch is the first transdermal non-ergot dopamine agonist, being a selective dopamine $D_1/D_2/D_3$ receptor agonist [1-4]. Rotigotine patch is effective over 24 h and provides a continuous dopaminergic stimulation (CDS) in 'real life' in patients with Parkinson's disease (PD) and was approved for use in PD by the FDA and EMEA [1-4]. A total of 674 subjects have been evaluated in Phase I trials showing constant drug delivery to the skin, reproducible absorption and stable 24-h plasma levels [5-7].

In terms of composition, the drug is dispersed in a silicone adhesive and then spread evenly across a silicone backing to allow uniform and constant delivery of the drug [3,4]. The patch has been viewed as an advance in the therapeutic arena for PD exploiting the theoretical advantages of CDS and showing significant reduction of dyskinesias in animal models of PD [2-8]. In PD, doses used have been in the range of 2 – 16 mg/day, and patch sizes of 2, 4, 6 and 8 mg have been available for clinical use. In September 2008, rotigotine patch (2 – 4 mg) also received approval from the EMEA for use in moderate-to-severe restless legs syndrome (RLS), a condition that has a prevalence of about 8 – 12% in the Western population [9].

In PD, the promising clinical use of rotigotine was recently interrupted after healthcare professionals received notification regarding the rotigotine patch due to the appearance of 'snowflake-like' crystals within the patch (**Figure 1**). This issue led to a specific batch recall in March 2008 in Europe; this resulted in a complete out-of-stock situation in the United States, where the drug is currently unavailable. There was at this time minimal disruption to supply in Europe; however, in May 2008 the EMEA directed that physicians in Europe should not start any new PD patients on rotigotine patch. At the same time, physicians, distributors, pharmacists and patients were advised to store the product in the refrigerator, and the patch was available only at 2 and 4 mg strengths for use in patients currently on rotigotine therapy.

2. The crystallisation and toxicity issue

The crystallisation occurs because of the appearance of a new polymorph of rotigotine within the patch. This new polymorph was previously unknown, is thermodynamically more stable than the original form, and is less soluble. It therefore has the potential to crystallise in the patches in certain conditions and become visible to the naked eye as 'snowflakes'. In this 'snowflake' the crystals consist of pure rotigotine, the difference being that the rotigotine molecules in this new polymorph have a slightly different packing structure with each other, compared to the original rotigotine form (**Figure 2**) [4]. This anomaly of configuration is common in nature and is known as polymorphism, which essentially implies a different three-dimensional configuration of the same

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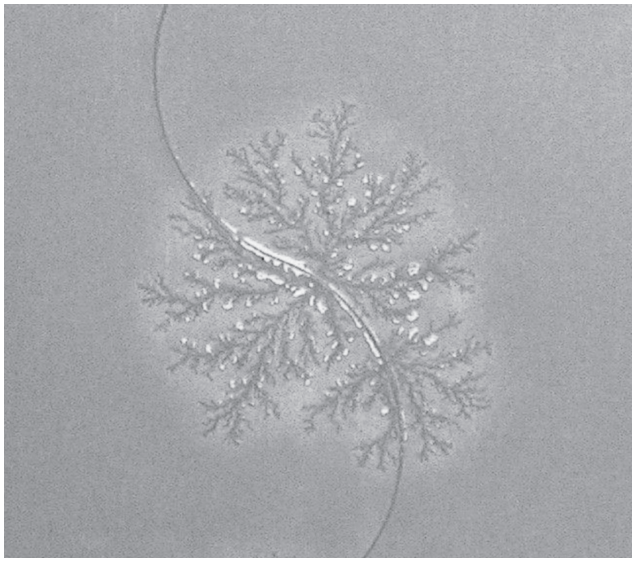

Figure 1. The snowflake in a rotigotine patch.

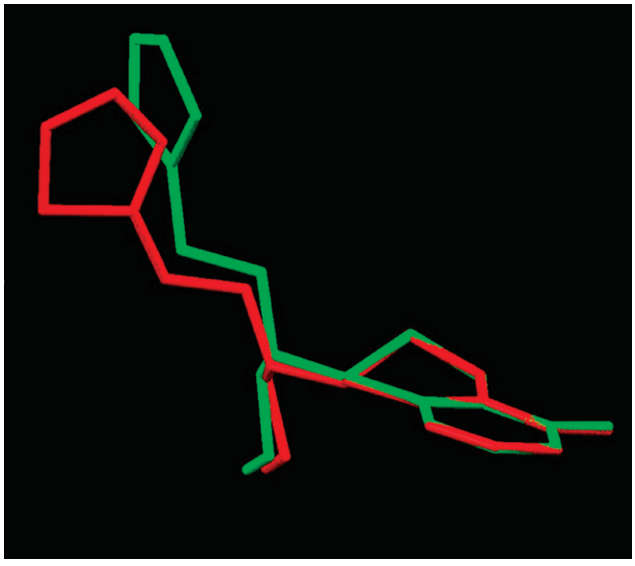

Figure 2. The rotigotine polymorphs.

molecule. An example of polymorphism is that of carbon, which can occur as graphite (essential for pencils!) or as diamonds. Although these 'snowflakes' consist of rotigotine, and are not due to contamination of the patch, they do lead to questions about possible toxicity, therapeutic efficacy and uncertain 24-h CDS profile of rotigotine.

A possible question posed by the 'snowflake' phenomenon is whether there is any contamination and modified toxic chemicals are being released and absorbed. This can be ruled out, as these crystals are composed of pure rotigotine and are not due to contamination. As such, these do not pose any toxicity risk; but issues remain concerning the effective dose being absorbed. Crystal formation occurs after nucleation and, once formed, a crystal keeps growing by pulling in more free molecules to the stable crystalline form. Since only free molecules of rotigotine can cross the skin, the crystals must dissolve in order to release drug molecules that can be absorbed. If this does not occur, the amount of drug available to the patient could be reduced. The net effect of the 'snowflake' phenomenon is therefore the possibility of reduced drug delivery and therapeutic efficacy, but there is no risk of drug-related toxicity.

3. What is being done?

Although some reduction in the amount of drug available may result from the formation of crystals, any reduction in the release of rotigotine has to be compared to the 15% intra-patient variability for a single application site, and > 50% intra-patient variability when rotating application sites, as is indicated in the rotigotine product information literature [4].

The production process has been modified to inhibit nucleation and the formation of crystals. In addition, a cold chain storage and distribution method has been adopted nationwide since June 2008, as refrigerated storage after production has been shown to substantially reduce the occurrence of crystals and growth. This is subsequent to an agreement with the regulators, who agreed on a decision to implement cold chain distribution in Europe so that over 30,000 patients with PD can continue their treatment. However, some safeguards have been introduced, and these include recommendations from the company that new patients should not be started on Neupro® for the time being. Furthermore, the maximum pack size has been reduced to 1 month, and shelf life shortened to 6 months (previously 24 months) until additional stability data become available.

4. The possible clinical consequences

There is little data available to show any robust evidence that clinical care of a patient has been compromised (such as clear demonstration of increasing 'wearing off' or 'off' states while on the patch) because of snowflake formation. A possible scenario is that a patient abruptly stops treatment with rotigotine patch having noticed the snowflake formation. This may have deleterious consequence and the possibility of precipitating an aggravated parkinsonian state or a Parkinson hyperpyrexia syndrome [10].

The effect of the cold storage method of distribution and manufacturing alterations will be known early in 2009. Whether larger dose patches (6 and 8 mg) will be immune from crystallisation is unclear. At the moment, patients who continue to respond to rotigotine should be allowed to continue on this regimen, with reassurance and information provided to patients and primary care physicians about the

snowflake phenomenon, should this occur. However, currently, no new patient with PD should be started on rotigotine patch until a full supply of cold chain products is available. Given the recent licensing of rotigotine for use in RLS in Europe, and the clinical effect of this agent in RLS, it is hoped that rotigotine use is not halted unnecessarily. In the author's own experience of > 100 PD patients on rotigotine patch treatment, the snowflake phenomenon is yet to be reported; and at the moment, a hasty switch to other agents that may have a possible detrimental effect should be avoided. However, where patients are on bigger doses of rotigotine and dislike using more than one or two patches (e.g., a 12 mg dose will have to be taken as 3 × 4 mg patches) or 'snowflaking' occurs, a switch to a similar agent with a long duration of action would clearly be appropriate [11].

Declaration of interest

K Ray Chaudhuri has worked as consultant for several pharmaceutical companies and has received honoraria from Boehringer Ingelheim, UCB and Schwarz Pharma, Valeant and Novartis for delivering scientific lectures at sponsored symposia.

Bibliography

1. Naidu Y, Chaudhuri KR. Rotigotine, a new transdermal patch for treatment of Parkinson's disease. Expert Opin Drug Deliv 2007;18:111-8
2. Rascol O. Transdermal delivery of dopmainergic agents. Neurology 2005;20:1502-7
3. Rotigotine (Neupro). Summary of product characteristics. UCB Pharma; April 2007
4. Mucke HA. Rotigotine. Schwarz Pharma. Drugs 2003;6:894-9
5. Poewe W, Luessi F. Clinical studies with transdermal rotigotine in early Parkinson's Disease. Neurology 2005;659:S11-4
6. Poewe W, Rascol O, Quinn N, et al. Sp 515 Investigators. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol 2007;6:513-20
7. Watts RL, Wendt RL, Nauseida B. Efficacy, safety and tolerability of the rotigotine patch in patients with early stage idiopathic Parkinson's disease: multicentre, multinational, randomized, double-blinded placebo-controlled trial. Mov Disord 2004;19:S258
8. Heindl M, Scheller D, Lebsanft K, et al. Continuous versus discontinuous administration of rotigotine in a rat model of dyskinesias. Parkinsonism Relat D 2005;11:PS002-6
9. Trenkwalder C, Benes H, Poewe W, et al. SP790 Study Group. Successful use of low-dose rotigotine in RLS: a randomised, placebo-controlled, double-blind, large-scale trial with rotigotine transdermal patch. Lancet Neurol 2008;7:595-604
10. Mizuno Y, Takubo H, Mizuta E, Kuno S. Malignant syndrome in Parkinson's disease: concept and review of the literature. Parkinsonism Relat D 2003;9:S3-9
11. Lewitt PA, Poewe W, Rascol O, et al. Overnight switch from ropinirole, pramipexole and cabergoline to rotigotine transdermal patch. Eur J Neurol 2006;13(Suppl 2):321

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