Correspondence

Methemoglobinemia as a biomarker of dapsone-induced mania severity

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ABSTRACT

Background: The underlying mechanism involved in dapsone-induced mania remains unknown.

Methods: We report the case of a 54-year-old man with a dapsone-induced mania.

Results: The maximum of manic symptoms was correlated with the maximum of methemoglobinemia and mania decreased concomitantly with the methemoglobinemia level.

Limitations: This is a single case.

Conclusions: This case shows that dapsone-induced mania severity is correlated with methemoglobinemia level, leading for the first time to the hypothesis of a physiopathological mechanism by which dapsone could induce mania.

1. Introduction

Psychiatric adverse effects of dapsone have been suspected for the first time in the fifties, when numbers of leprosy patients were treated with dapsone. However, the clinical picture was poorly described as “psychosis”. Furthermore because of the high frequency of psychiatric symptoms in leprosy patients, even before dapsone treatment, the association with treatment was unclear (Daneshmend, 1989). Then in 1989, two cases of manic syndromes induced by dapsone were published (Carmichael and Paul, 1989; Gawkrodger, 1989). Interestingly, they occurred in non-leprosy patients without any history of mental disorder. However, the underlying mechanism involved in dapsone-induced mania remains unknown.

2. Case report

A 54-year-old man diagnosed with immune thrombocytopenic purpura (ITP) with no personal or familial history of mental disorder received dapsone (diaminodiphenylsulfone), 100 mg/d, as a second line treatment after a relapse with prednisone treatment.

Four days after dapsone onset, he presented manic symptoms with psychomotor agitation, elevated mood, logorrhea, disinhibition, and excessive involvement in activities. Since previous reports described psychiatric symptoms (Carmichael and Paul, 1989; Hill, 2015) with dapsone, drug treatment was stopped, and manic symptoms disappeared after three days. The diagnosis of manic episode induced by dapsone can be proposed based on the temporal sequence and the absence of history or current mental or neurological disorder. Indeed the manic symptoms appeared four days after the beginning of treatment and completely recovered after dapsone stop without mania specific treatment. In this case, the maximum of manic symptoms (YMRS: 31) (Young et al., 1978) was correlated with the maximum of methemoglobinemia (9%). And mania decreased concomitantly with the methemoglobinemia level (respectively YMRS: 26 and methemoglobinemia: 5.3% two days later, and YMRS: 0 and methemoglobinemia: 3.1% three days later.

3. Discussion

During dapsone treatment, methemoglobinemia is systematically measured because a dapsone metabolite, dapsone hydroxylamine (DH), can increase methemoglobinemia (Ash-Bernal et al., 2004; Veggi et al., 2008). Indeed, DH acts directly by oxidizing Fe2+ in Fe3+ of hemoglobin heme and indirectly by enhancing oxidative stress (Ash-Bernal et al., 2004; Reilly et al., 1999; Veggi et al., 2008; Winter et al., 2000), leading to methemoglobinemia. The normal range of methemoglobinemia is <1.5%. Pathological methemoglobin levels <15% may be associated with few side effects (i.e cyanosis), high levels (20%−30%) may cause severe symptoms such as exercise intolerance, dizziness, and syncope and levels greater than 50% may result in dysrhythmias, seizures, coma, and death (Ash-Bernal et al., 2004).

Based on this observation, we suggest that dapsone could induce mania by enhancing oxidative stress, of which methemoglobinemia could be a proxy. Indeed, oxidative stress has been identified as a molecular mechanism leading to mania (Kim et al., 2017) and dapsone can induce both oxidative stress and methemoglobinemia (Ash-Bernal et al., 2004; Reilly et al., 1999; Veggi et al., 2008; Winter et al., 2000), with a bidirectional association (Hamirani et al., 2008). This hypothesis should be tested in bipolar patients.

Informed consent: The patient provided written informed consent for anonymized publication of his data.

Conflict of interest

Romain Colle, Abd El Kader Ait Tayeb, Pierre Mesdom, Mathilde de Menthon, Céline Verstuyft, Olivier Lambotte, Emmanuelle Corruble have no conflict of interest to disclose.

Denis J. David: Currently receives investigator-initiated research support from Lundbeck and served as a consultant in the areas of target identification and validation and new compound development to Lundbeck Inc., Roche and Servier. Laurent Becquemont: investigator for Antisense Therapeutics, Alnylam Pharmaceuticals, Alexion, Actelion, Auris Medical, Gilead Sciences, Ionis Pharmaceuticals, MedDay
Pharma, Novartis, PregLem SA, Ultragenix pharmaceutical. Received consulting fees from Sanofi-Aventis, Pfizer, Kyowa Kirin and Servier; lecture fees from Genzyme, GlaxoSmithKline, Bristol-Myers Squibb, Merck Sharp and Dohme; a close family member works at Sanofi France.

Informed consent

The patient provided written informed consent for anonymized publication of his data.

Contributors

Romain Colle: Managed the literature searches, wrote the first draft of the manuscript, assessed the patient, reviewed the case and contributed to the final version of the manuscript.

Abd El Kader Ait Tayeb, Pierre Mesdom: Literature searches, reviewed the case and contributed to the final version of the manuscript.

Mathilde de Menthon, Olivier Lambotte: Assessed the patient, reviewed the case and contributed to the final version of the manuscript.

Laurent Becquemont, Céline Verstuyft, Denis J. David: Reviewed the case and contributed to the final version of the manuscript.

Emmanuelle Corruble: Wrote the first draft, reviewed the case and contributed to the final version of the manuscript.

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Supplementary materials


References


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