J Neurol (2012) 259:375–376
DOI 10.1007/s00415-011-6171-1

LETTER TO THE EDITORS

Increasing histamine neurotransmission in Gilles de la Tourette syndrome

Andreas Hartmann · Yulia Worbe · Isabelle Arnulf

Received: 11 May 2011 / Revised: 1 July 2011 / Accepted: 4 July 2011 / Published online: 22 July 2011

Dear Sirs,

Recently, an autosomal-dominant mutation of the gene coding for histidine decarboxylase, the rate-limiting enzyme in histamine synthesis, was demonstrated in a family with eight members suffering from Gilles de la Tourette syndrome (GTS) [1]. Functional analysis suggested that this mutation acts in a dominant-negative manner, thereby diminishing histaminergic neurotransmission. Accordingly, the authors suggested that raising brain histamine levels may decrease tics.

We report on a male patient born in 1988 who developed several motor and vocal tics from age 6 years on but was only diagnosed as GTS at the age of 17 years. In rapid succession, several antipsychotics were tried, e.g., pimozide, risperidone and tetrabenazine, which slightly decreased tics but induced fatigue and sedation. More recently (April 2008), aripiprazole (5, then 10 mg/day) was introduced with moderate effect on tics but less sedation and weight gain. Interestingly, this patient also experienced narcolepsy without cataplexy, characterized by excessive daytime sleepiness and dyssomnia. His total sleep time was 363 min with a sleep efficiency of 72%, and no apnea/hypopnea or leg movements. During daytime multiple sleep latency tests, he fell asleep within a mean of 5.8 min (abnormal is lower than 8 min) sleep onset latency with three sleep onset in REM sleep periods (abnormal is more than 1) [2]. He carried the HLA DBQ1*0602 genotype. The attempts to reduce daytime sleepiness, first with methylphenidate 10 mg/day, then with modafinil 100 mg/day both resulted in a immediate massive increase in tics as well as behavioral problems (irritability and aggressivity) at the lowest dosage and led to rapid discontinuation of these treatments.

Thus, based on the above-mentioned study, we wondered whether treatment by an inverse agonist of the H3 receptor which raises histaminergic neurotransmission might allow to treat his narcolepsy without increasing or even decreasing his tics. This molecule (BF2.649 or tiprolisant or pitolisant, Bioprojet Ltd, France) [3], promotes wakefulness in a recent proof-of-concept trial in narcolepsy [4]. After having obtained the patient's consent, as well as an individual temporary use authorization from the French drug agency, a baseline evaluation was conducted in May 2010 with two subsequent visits in August and October after slowly increasing the pitolisant doses from 5 to 40 mg/day, as a single morning intake (Table 1).

As can be seen, daytime sleepiness decreased dramatically, whereas tic scores remained constant. The benefit was maintained after 9 months of treatment. We conclude

A. Hartmann · Y. Worbe
Département de Neurologie, Groupe Hospitalier Pitié-Salpêtrière, APHP, Paris, France

A. Hartmann (✉) · Y. Worbe
Centre de Référence National Maladie Rare, 'Syndrome Gilles de la Tourette', Pôle des Maladies du Système Nerveux, Groupe Hospitalier Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France
e-mail: andreas.hartmann@psl.aphp.fr

A. Hartmann · Y. Worbe · I. Arnulf
Inserm U975, Centre de recherche de l'institut du cerveau et de la moelle épinière, Université Pierre et Marie Curie Paris 6, Inserm UMR_S 975, CNRS UMR 7225, Paris, France

I. Arnulf
Unité des Pathologies du Sommeil, Groupe Hospitalier Pitié-Salpêtrière, APHP, Paris, France

I. Arnulf
Centre de Référence National Maladie Rare, 'Narcolepsie et hypersomnie', Paris, France

Table 1 Tic and sleepiness scores following increasing dosages of pitolisant

Date	Pitolisant dose/day (mg)	Yale Global Tic Severity Scale (tic score, max. 50 points)	Modified Rush Video-Based Tic Rating Scale (max. 84 points)	Epworth sleepiness score (max. 24)
May 2010	0	31	25	13
August 2010	20	24	20	6
October 2010	40	24	22	3

Yale Global Tic Severity Scale & Epworth sleepiness score: open evaluation

Modified Rush Video-Based Tic Rating Scale: blinded evaluation

that pitolisant (unlike classic psychostimulants such as methylphenidate and modafinil) is able to decrease daytime sleepiness without worsening tics. Conversely, however, in this single patient, we did not witness a clear decrease in tics as might be inferred from the *histamine hypothesis* of tics. Yet, we feel that these results are encouraging because a non-increase of tics in a sensitive patient may mean a decrease in tics in a 'non-sensitive' GTS patient. The association of narcolepsy and GTS is here fortuitous, but methylphenidate and related molecules are used in GTS patients with attention-deficit/hyperactivity disorder, a frequent co-morbidity. Although methylphenidate does not exacerbate tics on average) [5], some patients, such as ours, may respond rather violently and will require a different treatment approach. Therefore, apart from tics, pitolisant may be helpful in treating attention deficit in children suffering from GTS and in reversing neuroleptic-induced daytime sleepiness based on its mechanism of action. Thus, controlled clinical trials of H3 receptor reverse agonists in GTS patients with or without co-morbid attention-deficit/hyperactivity disorder are warranted.

Conflict of interest None.

References

1. Ercan-Sencicek AG, Stillman AA, Ghosh AK, Bilguvar K, O'Roak BJ, Mason CE, Abbott T, Gupta A, King RA, Pauls DL, Tischfield JA, Heiman GA, Singer HS, Gilbert DL, Hoekstra PJ, Morgan TM, Loring E, Yasuno K, Fernandez T, Sanders S, Louvi A, Cho JH, Mane S, Colangelo CM, Biederer T, Lifton RP, Gunel M, State MW (2010) L-histidine decarboxylase and Tourette's syndrome. N Engl J Med 362:1901–1918
2. Dauvilliers Y, Arnulf I, Mignot E (2007) Narcolepsy with cataplexy. Lancet 369:499–511
3. Ligneau X, Perrin D, Landais L, Camelin JC, Calmels TP, Berrebi-Bertrand I, Lecomte JM, Parmentier R, Anaclet C, Lin JS, Bertaina-Anglade V, la Rochelle CD, d'Aniello F, Rouleau A, Gbahou F, Arrang JM, Ganellin CR, Stark H, Schunack W, Schwartz JC (2007) BF2.649 [1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride], a nonimidazole inverse agonist/antagonist at the human histamine H3 receptor: preclinical pharmacology. J Pharmacol Exp Ther 320:365–375
4. Lin JS, Dauvilliers Y, Arnulf I, Bastuji H, Anaclet C, Parmentier R, Kocher L, Yanagisawa M, Lehert P, Ligneau X, Perrin D, Robert P, Roux M, Lecomte JM, Schwartz JC (2008) An inverse agonist of the histamine H(3) receptor improves wakefulness in narcolepsy: studies in orexin$^{-/-}$ mice and patients. Neurobiol Dis 30:74–83
5. Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF (2009) Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. J Am Acad Child Adolesc Psychiatry 48:884–893