

Levocetirizine-induced Psychiatric Disorders in a Pediatric Patient: A Case Report and a Pharmacovigilance Database Analysis

Sir,

Levocetirizine is a third-generation antihistamine drug with high selectivity for H₁-receptors that is commonly prescribed for the treatment of allergic diseases in children. The safety data from the clinical trials on administration over long periods and in almost all pediatric age groups suggest that levocetirizine use is safe and it is not associated with relevant adverse effects on the central nervous system (CNS).^[1] However, recent postmarketing surveillance studies have reported cases of aggression, hyperactivity, and agitation in pediatric patients using levocetirizine.^[2,3] In addition, it has been suggested that levocetirizine possibly leads to hallucinations and suicidal ideation.^[2] The relevance of these psychiatric disorders in clinical practice, the pharmacological mechanisms likely involved and the causal relationship with levocetirizine use have not yet been investigated.

To shed light on these aspects, we here report on a pediatric case of psychiatric adverse reactions (ADRs) likely related to levocetirizine and an extensive analysis of similar reports sent to five spontaneous reporting system databases (DBs) for postapproval safety surveillance. Furthermore, we provide a possible involved mechanism.

A 9-year-old child, affected by allergic rhinitis, experienced severe obsessive-depressive thinking, mixed anxiety depression, and excessive crying episodes 9 days after the beginning of the treatment with oral levocetirizine at the therapeutic dose (5 mg/day). Immediately after the onset of symptoms, the parents and pediatrician have closely monitored the patient; they reported that the child has manifested a dramatic change in mood, inactivity, and withdrawal from typical pleasurable activities (e.g., leave the house) and feelings of hopelessness with low mood and depression. According to the pediatrician's decision, therapy was maintained for 7 more days. Since symptoms did not disappear, the treatment was discontinued; thus, the patient has improved, and the ADRs were definitively resolved in about 12 days.

The patient received no other concomitant drug or herbal treatment. Moreover, the patient was in overall good health and had never suffered from psychiatric disorders. In view of the medical history, the positive dechallenge, and the temporal association, a diagnosis of iatrogenic events was made. A probable association was also confirmed by the causality assessment scale of Naranjo.

To define better, this association we carried out an analysis of data in five international pharmacovigilance DBs, the largest publicly available repositories of ADR reports and medication errors spontaneously submitted by health-care professionals, patients, and manufacturers. We extrapolated and included in our analysis all reports to date in which levocetirizine is indicated as suspected drug in the onset of at least one symptom combined with the system organ class (SOC) "Psychiatric disorders." ADRs were detected using the Medical Dictionary for Regulatory Activities code at the Preferred Term level.

By the analysis of the international pharmacovigilance DBs [Table 1], we retrieved 1625 reports (equal to 4274 ADRs) related to levocetirizine use in the general population (duplicated reports were excluded from our analysis); of these, 268 (433 ADRs) reported at least one symptom combined with the SOC "psychiatric disorders" (16.4%). 228 (524 ADRs) were reports involving pediatric patients (0 <18); of these, 52 (81 ADRs) reported at least one psychiatric symptom (22.8%).

The percentage of psychiatric ADRs we retrieved in the pediatrics was higher than in adult patients (22.8 vs. 16.4) suggesting that they have a higher tendency to manifest these clinically relevant disorders. This could be explained by the known differences in the pharmacokinetic of levocetirizine between children and adults in that the C_{max} and area under the curve values were found to be about 2-fold greater in children aged 6–11 years (in a single-dose pharmacokinetic study, in 14 children) than those reported in healthy adult subjects who also received a 5 mg dose in a cross-study comparison.^[4]

Levocetirizine administration, resulting in an increased histamine availability, may contribute to the onset of psychiatric events in children. In the oxidative deamination, route diamine oxidase uses molecular oxygen to deaminate oxidatively histamine to imidazole acetaldehyde; thus, imidazoleacetic acid (IAA) is oxidized to imidazole acetic acid and subsequently ribosylated for efficient transport. Recent studies support a role for IAA-ribotide in modulating synaptic transmission in the hippocampus, the area involved in the emotional control and behavior modulation.^[5]

Histamine stimulates prostaglandins (PG) biosynthesis through H₁-receptors leading to the release of PGE₂ and

Table 1: Total number of reports of levocetirizine-induced psychiatric disorders, according to international pharmacovigilance databases

Pharmacovigilance DBs (period of observation)	Number of reports (ADRs)	Number of psychiatric reports (ADRs); percentage of total reports	Number of pediatric reports (ADRs)	Number of psychiatric reports (ADRs); percentage of total pediatric reports	Psychiatric ADRs (0<18) (number of report)
FDA Adverse Event Reporting System (2004-2014)	519 (2067)	134 (240); 25.8	54 (187)	20 (46); 37	Abnormal behavior (4), nightmare (4), fatigue (3), asthenia (3), suicidal ideation (3), mixed allucinations (3), insomnia (2), hypersomnia (2), depression (2), agitation (2), aggression (2), psychomotor hyperactivity (2)
New Zealand Suspected Medicine Adverse Reaction Search DB (2000-2016)	4 (7)	1 (1); 25	0	-	-
Canada Vigilance ADR DB (1965-2016)	0	-	-	-	-
Australian database of Adverse Event Notifications (1971-2016)	2 (5)	0	0	-	-
Eudravigilance DB (2005-2016)	1100 (2195)	133 (192); 12	174 (337)	32 (35); 18.3	Disorientation (5), agitation (5), suicide attempt (3), hallucination visual (3), insomnia (2), confusional state (2), anxiety (2), hallucination (2), abnormal behavior (1), aggression (1), autism spectrum disorder (1), disturbance in social behavior (1), hallucination auditory (1), irritability (1), mood swings (1), nightmare (1), sleep disorders (1), suicidal ideation (1), tension (1)
Total	1625 (4274)	268 (433); 16.4	228 (524)	52 (81); 22.8	

ADRs=Adverse drug reactions, DBs=Databases, FDA=Food and Drug Administration

PGI2. Levocetirizine may cause a reduction in the production of PG sustained by H1-receptors leading to an imbalance in PG synthesis, an event that has been associated with the pathogenesis of psychotic symptoms since PGE2 reduces the levels of dopamine in the CNS.^[6]

The ability for H1-antihistamines to cross the blood–brain barrier (BBB) depended on their relative affinity to P-glycoprotein (PgP). Interestingly, levocetirizine is a weak PgP substrate although the clinical implications of these findings are to be established, a decreased efflux from the BBB causing an increase in the cerebral concentration of the drug may have contributed to the psychiatric symptoms.

The mechanism of action of levocetirizine is consistent with its ability to induce psychiatric ADR as the one we

observed. The analysis of the DBs suggests that this is not an uncommon occurrence and the need to monitor its use in pediatric settings.

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Conflicts of interest

There are no conflicts of interest.

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