Epileptic Convulsions Probably Induced by Desloratadine, a Second-Generation H1-Antihistamine

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Abstract

Second-generation H1-antihistamines are generally considered to be safe. Here we describe a healthy boy who developed left-arm convulsions after repeated exposure to a dry suspension of desloratadine combined with Huatengzi granules. The boy had no family or disease history of epilepsy, convulsions, or any other drug therapy. The Naranjo Adverse Drug Reaction Probability Scale was used to determine that the convulsions were probably related to desloratadine. Our findings suggest that desloratadine (a second-generation H1-antihistamine) can cause epileptic convulsions in healthy children, and so clinicians should be vigilant of the possibility of central side effects.

Keywords: desloratadine, second-generation H1−antihistamine, epileptic convulsions

H1−antihistamines are commonly administered to infants and children for allergic diseases. They are also used for other conditions, such as coughs, colds,

anaphylaxis, food-protein-induced gastrointestinal allergy and asthma [1], despite a lack of evidence for their efficacy[2]. The increasing prevalence of allergic diseases is increasing the usage of antihistamines, which are now the most common primary-care medicine prescribed to children[3]. Antihistamines have been reported to be one of the top-three drug types in Italy, with cetirizine being the fourth most common drug prescribed by paediatricians[4]. First-generation H1-antihistamines exhibit poor H1-receptor selectivity and they can cross the blood–brain barrier (BBB), with both of these characteristics resulting in numerous adverse drug reactions (ADRs). In contrast, second-generation H1-antihistamines exhibit high selectivity for the histamine H1 receptor and cannot cross the BBB, and so they are associated with minimal ADRs[5]. This situation has resulted in second-generation H1-antihistamines being widely prescribed, especially by paediatricians. Desloratadine is a frequently administered second-generation antihistamine, and its safety and tolerability have been rated as at least moderate by 99% of patients and physicians [6]. In our hospital, desloratadine is the most common antihistamine prescribed by paediatricians.

Despite the widespread use of second−generation antihistamines in clinical practice over many years, there are few reports on their ADRs. A retrospective, multicentre, observational study found that overdose with a second-generation antihistamine does not have severe effects[7]. A comparative analysis of the safety of H1−antihistamines in children using pharmacovigilance data from the WHO database found several significant drug–reaction associations, including between levocetirizine and epilepsy. However, there have been few reports of epilepsy induced by desloratadine. We found only one article reporting four children with a family or disease history of epilepsy who developed epilepsy after desloratadine treatment[8]. Here we describe a healthy boy who developed left-arm convulsions after repeated exposure to desloratadine combined with Huatengzi granules.

Case Presentation

A healthy 8-year-old boy (28 kg, 128 cm) with no family or disease history of epilepsy or convulsions experienced urticaria after playing with water for a long time.

He had been taken to the hospital to receive treatment for urticaria, and his first antiallergic therapy regimen was a dry suspension of desloratadine (0.25 g, po, qd) plus Huatengzi granules (a Chinese patent medicine, 4 g, po, bid). Pruritus was relieved, but not completely cured, by the administration of these two drugs. No ADR occurred. The boy was subsequently taken two more times to the hospital, at which the antiallergy program was again a dry suspension of desloratadine (0.25 g, po, bid) plus Huatengzi granules (4 g, po, bid). The boy fully complied with the doctor's advice when urticaria was serious, and reduced the dosage when the urticaria was mild. After 2 months, he developed an epileptic twitch of his left arm that appeared one to three times daily, with each episode lasting about 30 seconds. The boy had never experienced limb twitching before taking the antiallergic drugs and had no family history, nor had he taken any other drug therapy. The dry suspension of desloratadine and Huatengzi granules were discontinued immediately.

The boy was taken to the hospital to see a doctor about his epileptic twitch. On admission, his physical features and development were normal, the findings of laboratory examinations were normal (including routine blood, electrolyte and biochemical tests), no abnormality was found in an MRI scan, and three electroencephalogram (EEG) recordings (two lasting for 4 hours and one 24-hours recording) also produced normal findings. The only abnormality detected was convulsions of the left arm, and they did not improve, with the left arm twitching almost every day. After 2 weeks of convulsions, the boy was diagnosed with epilepsy.

The boy's convulsions were not controlled by sodium valproate (VPA, 20 mg/kg/day) and oxcarbazepine (0.45 g, q12h), and his serum concentrations of valproate and metabolites of oxcarbazepine were 81 μg/ml (normal range 50–100 μg/mL) and 20.02 μg/ml (normal range 12–36 μg/mL), respectively. During the 24-hour EEG monitoring period, no epileptic discharge was found in the EEG when the boy's left arm was twitching. Ten months later he was prescribed VPA combined with topiramate and lamotrigine successively for 5 months, but he stopped taking these medicines because of ADRs. He was subsequently prescribed VPA combined with

clonazepam for 2 months, which also did not control the convulsions; instead they were aggravated, with his left arm now twitching seven or eight times daily. During the following 3 months the boy received VPA combined with lacosamide, and no further convulsions occurred. At the follow-up, his father reported that the boy's memory was not as good as it had been previously.

Discussion and Conclusion

The boy developed convulsions after taking desloratadine dry suspension and Huatengzi granules at the same time, and the seizures caused by desloratadine had been reported[8] but Huatengzi granules hadn't been reported. There had been no family or disease history of epilepsy or convulsions, the patient denied taking any other medications. The physical examination except for convulsions of the left arm and laboratory examination were normal, the MRI was normal ，and the EEG of 24 hours was normal. We decided to substantiate the diagnosis further by using the Naranjo ADR Probability Scale, which is used to determine the likelihood of an ADR being due to the implicated drug or other factors[9] (Table 1). Our patient scored 6 on this scale, which indicates a probable ADR, and so his convulsions was probably related to the taking of desloratadine.

Table 1 Naranjo Adverse Drug Reaction probability score

No.	Item	Yes	No	Do not know	Score
1	Are there previous conclusive reports of this reaction?	+1	0	0	+1
2	Did the adverse reaction event appear after the suspected drug was administered?	+2	-1	0	+2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	0
4	Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5	Are there alternative cause(other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6	Did the reaction reappear when a placebo was given?	-1	+1	0	0
7	Was the drug detected in the blood(or other fluids) in concentrations knows to be toxic?	+1	0	0	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9	Did the patient have a similar reaction to the same or similar drugs at any previous exposure?	+1	0	0	0
10	Was the adverse event confimed by any objective evidence?	+1	0	0	+1
				Total	6

Definite:≥9 ; Probable: 5-8 ; Possible: 1-4 ; Doubtful: ≤0

Several studies have indicated that the central histaminergic neuron system plays a crucial role in inhibiting seizures by stimulating histamine H1 receptors [10]. In the hereditary temporal lobe epilepsy mouse model, various treatments were able to significantly increase histamine levels in the brain. Intraperitoneally injecting the H1-antagonist diphenhydramine increased seizure episodes in mice[11]. H1 receptors play a crucial role in regulating both the intensity and duration of seizures, and they also affected the degree of neuronal damage induced by seizures in immature mice[12]. H1 receptor antagonists can induce convulsions in both healthy children and patients with epilepsy[10]. Disorders associated with H1-antihistamines in the central nervous system (CNS) have been attributed to the BBB, and second-generation H1-antihistamines are highly selective for the histamine H1-receptor, do not cross the BBB, and have minimal ADRs[5].

One potential mechanism for lowering the CNS exposure to second-generation H1-antagonists and consequently the associated CNS-related side effects is P-glycoprotein (P-gp)-mediated efflux. P-gp is encoded by multidrug resistance gene 1 (human MDR1 and rodent mdr1a and mdr1b), and is present in various normal tissues, including the intestinal epithelium, liver bile canaliculi, and the brain endothelium. There have been numerous reports of P-gp in the brain endothelium increasing the efflux of xenobiotics with diverse structures from the brain, thereby reducing undesirable CNS effects[13]. P-gp substrates including second-generation H1-antagonists such as loratadine, cetirizine, and desloratadine can reduce CNS exposure and the associated side effects. This led to speculation that a mutation of multidrug resistance gene 1 impairs the effects of P-gp on efflux pumps, resulting in greater CNS exposure and the consequent side effects for second-generation H1-antihistamines such as desloratadine.

All epilepsy symptoms induced by desloratadine in the four reported children with a family history of epilepsy gradually disappeared after drug withdrawal or antiepileptic treatment, and their EEGs normalized. Our patient with no history of epilepsy experienced intermittent convulsions over 17 months, with VPA treatment successively combined with oxcarbazepine, topiramate, lamotrigine and clonazepam resulting in no response, indeed even aggravating the convulsions. The patient was free of convulsions while on treatment with lacosamide and VPA at the 20-month follow-up. These findings might be related to the demonstrated synergistic or additive anticonvulsant effects of lacosamide when it is administered in combination with VPA[14]. The exact mechanism of action of lacosamide is not yet clear, although it

has been found in vitro that lacosamide stabilizes hyperexcitable neuronal membranes by selectively enhancing the slow inactivation of voltage-gated sodium channels.

While second-generation H1-antihistamines are highly selective and do not cross the BBB, attention still needs to be paid to the possibility of ADRs. The present findings suggest that the second-generation H1-antihistamine desloratadine can cause epileptic convulsions not only in children with a history of epilepsy, but also in healthy children. Therefore, clinicians should be vigilant of the possibility of central side effects, and parents need to help doctors to detect ADRs early in order to reduce their risk.

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Xiaojing Nie completed the literature review and the case presentation; Xiaonian Han wrote the article; Xin Zan collected the clinical data; Fengmei Xiong followed up the patient; Lirong Peng revised the article. All authors read and approved the final manuscript and its submission.

Data Availability Statement

The data about adverse drug reactions are available from the corresponding author upon reasonable request.

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239

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244

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