Epileptic convulsions probably induced by desloratadine: a case report

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Received 3 March 2021
Accepted 8 June 2021
Published Online First 28 June 2021

SUMMARY

Desloratadine, a second generation H1-antihistamine, is generally considered to be safe. We found only one article reporting four children with a family or disease history of epilepsy who developed the condition after desloratadine treatment, with all four patients recovering well. Here we describe a healthy boy who developed left-arm convulsions on day 68 after taking desloratadine, at which point the desloratadine treatment was immediately stopped. Investigations were completed on day 83 and the patient was diagnosed with epilepsy. He was prescribed sodium valproate combined with oxcarbazepine, topiramate, lamotrigine and clonazepam for 15 months, which did not control the convulsions. During the following 3 months the patient received sodium valproate combined with lacosamide, and on day 615 the seizures stopped 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. The convulsions continued after the withdrawal of desloratadine; therefore, the pathological mechanism of convulsion and the treatment plan need further research.

BACKGROUND

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 causing an increase in the use 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 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 paediatrics using pharmacovigilance data from the WHO database found several significant drug reaction associations, including between levocetirizine and epilepsy.[8] 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 the condition after desloratadine treatment.[9] Here we describe a case of a healthy boy who developed left-arm convulsions after repeated exposure to desloratadine.

CASE PRESENTATION

A healthy 8-year-old boy with no family or disease history of epilepsy or febrile 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 (containing desloratadine 2.5 mg, administered orally, once daily) (day 0, desloratadine started) plus fluticasone propionate cream (proper amount applied to skin, once daily). The 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, and the antiallergy programme was again a dry suspension of desloratadine (containing desloratadine 2.5 mg, administered orally, once daily). The patient fully complied with the doctor's advice when the urticaria was serious, and reduced the dosage when the urticaria was mild. After 2 months (day 68), he first developed epileptic convulsions of his left arm that appeared one to three times a day, with each episode lasting about 30 s. The boy and his father came to consult the pharmacist about whether the convulsions were caused by drugs. The pharmacist carefully took a medical history and speculated that the epileptic convulsions were caused by an ADR to desloratadine; this was because the boy had never experienced limb convulsions before taking the antiallergic drug and he had no family history, nor had he taken any other drug therapy, and that seizures caused by desloratadine had been reported. The pharmacist suggested that the dry suspension of desloratadine should be discontinued immediately (on day 68, desloratadine treatment was stopped).

INVESTIGATIONS

The patient was taken to the hospital to see a doctor about his epileptic convulsions. On admission, his

To cite: Han X, Zan X, Xiong F, *et al*. *Eur J Hosp Pharm* 2023;**30**:e17.

physical features and development were normal, the findings of laboratory examinations were normal (including routine blood, electrolyte and biochemical tests), no abnormality was found on MRI scan, and three electroencephalogram (EEG) recordings (two lasting for 4 hours and one 24-hour recording) also produced normal findings (day 83, investigations completed, and the second and third EEGs were examined on day 180 and day 345, respectively). The only abnormality detected was convulsions of the left arm, and they did not improve, with the left arm being affected almost every day. After 2 weeks of convulsions, the patient was diagnosed with epilepsy and was prescribed sodium valproate (VPA, 500 mg, twice daily) and oxcarbazepine (0.45 g, twice daily) (day 83, antiepileptic drugs started).

TREATMENT

The patient's convulsions were not controlled by sodium valproate and oxcarbazepine. The pharmacists recommended monitoring the blood concentration of these drugs: the serum concentrations of valproate and metabolites of oxcarbazepine were 81 g/mL (normal range 50–100 µg/mL) and 20.02 g/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 patient's left arm was twitching. Eight months later he was prescribed VPA combined with topiramate, lamotrigine and clonazepam successively for 7 months, which also did not control the convulsions; instead they became aggravated, with the left arm now exhibiting convulsions seven or eight times a day.

OUTCOME AND FOLLOW-UP

During the following 3 months the patient received VPA (500 mg, twice daily) combined with lacosamide (100 mg, twice daily) and no further convulsions occurred (day 615, seizures stopped). At the follow-up, his father reported that the boy's memory was not as good as it had been previously. The patient now receives VPA (250 mg, twice daily) combined with lacosamide (100 mg, twice daily) and no further convulsions have occurred.

DISCUSSION

There had been no family or disease history of epilepsy or febrile convulsions in this patient, and the boy denied taking any other medications. Except for convulsions of the left arm, the physical and laboratory examinations were normal, the MRI was normal, and the 24-hour EEG 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[10] (table 1). Our patient scored 6 on this scale, which indicates a probable ADR, and so his convulsions were probably related to the taking of desloratadine.

Several studies have indicated that the central histaminergic neuron system plays a crucial role in inhibiting seizures by stimulating histamine H1 receptors.[11] 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.[12] 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.[13] H1 receptor antagonists can induce convulsions in both healthy children and patients with epilepsy.[11] 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 the 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.[14] 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 normalised. Our patient with no history of epilepsy experienced intermittent convulsions over 15 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 18 month follow-up. These findings might be related

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 causes (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 known 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 confirmed by any objective evidence?	+1	0	0	+1
				Total	6

Definite, ≥9; Doubtful, ≤0; Possible, 1–4; Probable, 5–8.

to the demonstrated synergistic or additive anticonvulsant effects of lacosamide when administered in combination with VPA.[15] The exact mechanism of action of lacosamide is not yet clear, although it has been found in vitro that lacosamide stabilises hyperexcitable neuronal membranes by selectively enhancing the slow inactivation of voltage-gated sodium channels. However, as the convulsions carried on for 18 months after stopping desloratadine, it cannot be concluded that the child's epilepsy was not iatrogenic at all; therefore, the pathological mechanism of convulsions needs further research.

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. The convulsions continued after the withdrawal of desloratadine; therefore, the pathological mechanism of convulsion and the treatment plan need further research.

Learning points

⇒ Desloratadine, a second generation H1-antihistamine, is generally considered to be safe, but it can cause epileptic convulsions in healthy children.
⇒ The adverse effect occurring in this case was probably due to a mutation of the multidrug resistance gene 1 impairing the effect of P-glycoprotein on efflux pumps.
⇒ The convulsions continued after the withdrawal of desloratadine; therefore, the pathological mechanism of convulsion and the treatment plan need further research.

Acknowledgements We would like to thank our patient and the family for their patience in replying to our questions during the follow-up.

Contributors XN completed the literature review and the case presentation; XH wrote the article; XZ reviewed the literature and collected the clinical data; FX followed up the patient; LP revised the article. All authors read and approved the final manuscript and its submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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REFERENCES

1 Fitzsimons R, van der Poel L-A, Thornhill W, *et al*. Antihistamine use in children. *Arch Dis Child Educ Pract Ed* 2015;100:122–31.
2 De Bruyne P, Christiaens T, Boussery K, *et al*. Are antihistamines effective in children? A review of the evidence. *Arch Dis Child* 2017;102:56–60.
3 Helms PJ, Ekins Daukes S, Taylor MW, *et al*. Utility of routinely acquired primary care data for paediatric disease epidemiology and pharmacoepidemiology. *Br J Clin Pharmacol* 2005;59:684–90.
4 Piovani D, Clavenna A, Bonati M, *et al*. Review of Italian primary care paediatricians identifies 38 commonly prescribed drugs for children. *Acta Paediatr* 2014;103:e532–7.
5 Kalpaklioglu F, Baccioglu A. Efficacy and safety of H1-antihistamines: an update. *Antiinflamm Antiallergy Agents Med Chem* 2012;11:230–7.
6 Berger WE. The safety and efficacy of desloratadine for the management of allergic disease. *Drug Saf* 2005;28:1101–18.
7 Verdu E, Blanc-Brisset I, Meyer G, *et al*. Second-generation antihistamines: a study of poisoning in children. *Clin Toxicol* 2020;58:275–83.
8 Motola D, Donati M, Biagi C, *et al*. Safety profile of H1-antihistamines in pediatrics: an analysis based on data from VigiBase. *Pharmacoepidemiol Drug Saf* 2017;26:1164–71.
9 Cerminara C, El-Malhany N, Roberto D, *et al*. Seizures induced by desloratadine, a second-generation antihistamine: clinical observations. *Neuropediatrics* 2013;44:222–4.
10 Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.
11 Yokoyama H, Iinuma K. Histamine and seizures. *CNS Drugs* 1996;5:321–30.
12 Yawata I, Tanaka K, Nakagawa Y, *et al*. Role of histaminergic neurons in development of epileptic seizures in EL mice. *Mol Brain Res* 2004;132:13–17.
13 Kukko-Lukjanov T-K, Lintunen M, Jalava N, *et al*. Involvement of histamine 1 receptor in seizure susceptibility and neuroprotection in immature mice. *Epilepsy Res* 2010;90:8–15.
14 Chen C, Hanson E, Watson JW, *et al*. P-Glycoprotein limits the brain penetration of nonsedating but not sedating H1-antagonists. *Drug Metab Dispos* 2003;31:312–8.
15 Hoy SM. Lacosamide: a review in focal-onset seizures in patients with epilepsy. *CNS Drugs* 2018;32:473–84.