Can high-dose loratadine cause seizures – adverse drug reaction or interaction?

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Introduction:

Loratadine and other non-sedating antihistamines are being used at two to four times the recommended maximum daily dose for the treatment of urticaria. They are generally considered safe although seizures have been reported.

Seizures are not listed as an adverse effect or following overdose in the product information for loratadine in Australia but are included in the product information in the USA.

Objective:

To describe a case of loratadine induced seizures and the risks associated with using above maximum doses.

Case details:

Presentation (Admission 1):

A 64-year-old Caucasian male presented to emergency with a grand mal seizure in **September 2016** following three recent seizures.

Past Medical History:

Epilepsy (diagnosed at age 16), angina, MI (2011), GORD, osteoporosis, urticarial rash (July 16).

Antiepileptic medications:
Phenytoin 100 mg mane, 200 mg nocte
Lacosamide 200 mg BD

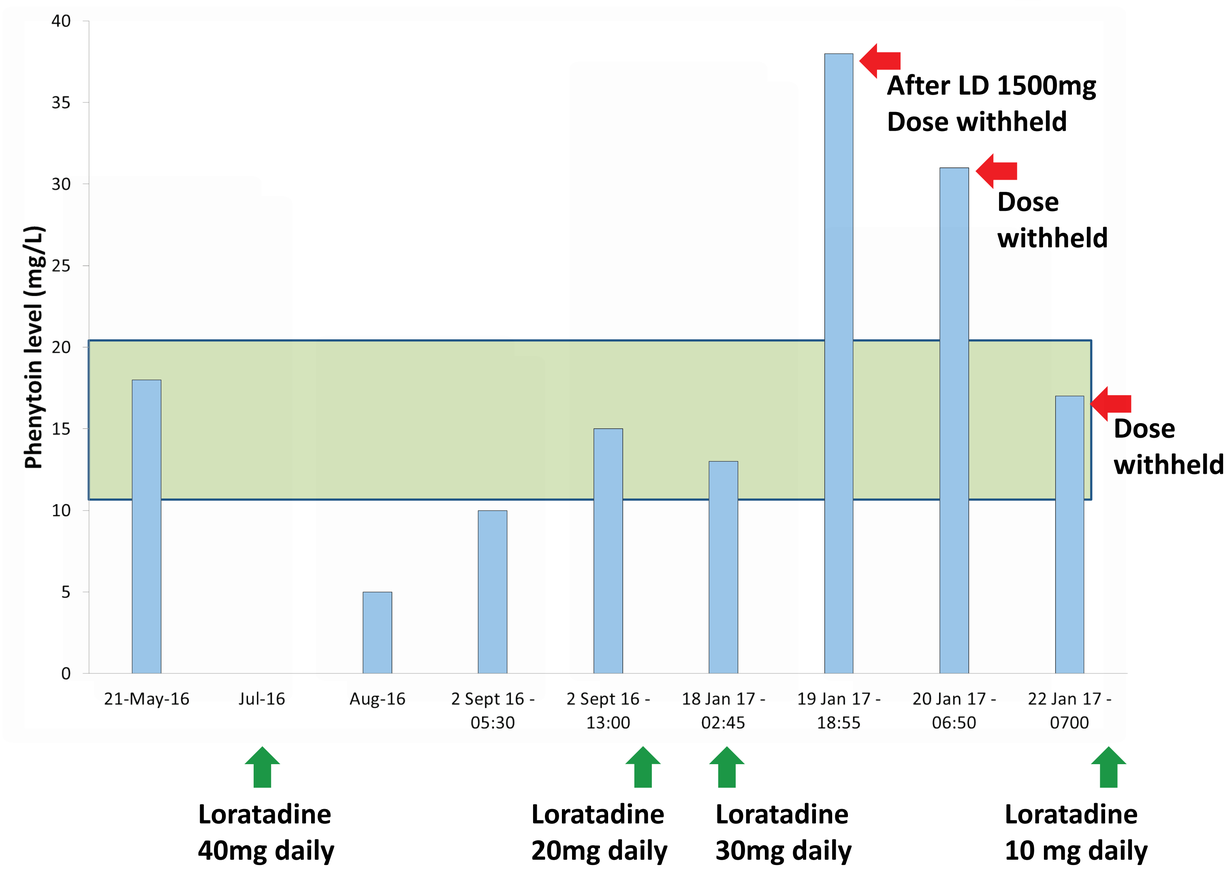
For treatment of his urticarial rash he was treated with loratadine 40 mg daily PRN and a short course of prednisone.

On admission his phenytoin level was 10 mg/L but had reported a sub-therapeutic level of 5 mg/L four weeks earlier. His seizures were treated with a loading dose of phenytoin IV 600 mg and his level the following day was 15 mg/L.

Interventions:

His wife had noticed an increase in his seizure frequency since starting loratadine and prednisone for his urticarial rash. The pharmacist investigated the possibility of loratadine induced seizures or an interaction between phenytoin and either loratadine or prednisone. No interaction was found resulting in decreased phenytoin levels but an association of loratadine with seizures was documented in the medical notes and communicated to the medical team.

His loratadine dose was reduced to 20 mg daily. Clobazam 10 mg twice daily was given for two days, his phenytoin dose was increased to 400 mg daily and he was discharged on same medication.



Presentation (Admission 2):

He continued to have three to four seizures per month until re-admitted to hospital with status epilepticus in **January 2017**. His phenytoin level was 13 mg/L and he continued to take loratadine at an increased dose of 30 mg daily prn.

On admission he was given a loading dose of phenytoin (1500 mg) and levetiracetam (2 g). Later in the evening he was very drowsy and had a fall. A phenytoin level the following evening was 38 mg/L and the dose was withheld until discharge three days later when it was 17 mg/L. His lacosamide dose was increased to 450 mg daily while his phenytoin dosage remained unchanged from admission.

Interventions:

His phenytoin levels were reported to vary considerably despite stable long term dosing.

The association of loratadine and seizures was re-investigated and documented in the medical notes. The dose of loratadine was reduced to 10 mg daily prn and no subsequent admissions due to seizures have occurred to date.

Discussion:

Adverse Drug Reaction:

A literature search found numerous adverse event reports documenting loratadine induced seizures (see Table one). There was one published report of a 37 year-old male with no history of seizures who had two grand mal seizures, three hours apart, after taking loratadine 25 mg daily for three days.[1]

Table One: Loratadine induced seizures adverse drug reaction (ADR) reports

Source	No. reports	No. (%) total ADRs	Comments
Health Canada[1] (2002)	9	3.6%	15 of 20 cases (included data for cetirizine and fexofenadine) had prior history of seizures or on antiepileptic medication.
FDA[2] (Apr 2000)	43 (26)	1.05% (0.6%)	A causal association was likely or possible in 26 of the 43 cases reported.
FDA[3] (Dec 2016)	52	0.31%	In all cases, seizures occurred within one month of starting loratadine. Causality not assessed on this site.
TGA DAEN[4] (Jul 2017)	4	0.49%	Sole suspected drug in all reports. Loratadine was only drug taken in two reports, in combination with pseudoephedrine in one report and with three other antiepileptics in the other report.

The mechanism for loratadine induced seizures is thought to be due to its effect on histamine as agents that deplete brain histamine have been shown to potentiate experimental convulsions.[5]

Drug interaction:

No published reports of an interaction between loratadine and phenytoin were found. There have been five reports (out of 30 on combination) to the FDA of a decreased phenytoin level which occurred in those aged 60 years or older.[6] Loratadine and phenytoin are both substrates of the CYP450 3A4 isoenzyme. Phenytoin is an inducer of this isoenzyme while loratadine has not been reported to induce or inhibit this isoenzyme at the normal therapeutic dose of 10 mg daily. Loratadine and phenytoin are both highly protein bound; 98% and 90% respectively. Loratadine may displace phenytoin from albumin resulting in an initial increase in free phenytoin, followed by increased clearance and lower total phenytoin levels. The effect of loratadine at three to four times the recommended maximum dose on the CYP450 3A4 isoenzyme is unknown.

Phenytoin can reduce the efficacy of corticosteroids but no reports of an interaction between phenytoin and prednisone resulting in decreased phenytoin levels. Dexamethasone has been reported to both increase and decrease phenytoin levels.[7]

Conclusion:

This case highlights the risk of seizures associated with use of up to four times the maximum daily dose of loratadine and the possibility of high-dose loratadine interacting with phenytoin contributing to loss of seizure control. The pharmacist had an important role in identifying and managing this patient's medication related issues.

References:

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