Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Duloxetine and electric shock-like sensations

Introduction

Duloxetine is a combined serotonin and noradrenalin reuptake inhibitor. It is indicated for the treatment of major depressive disorders, diabetic peripheral neuropathic pain in adults and generalised anxiety disorders [1].
It was granted marketing authorisation in 2004 via a Central European Registration Procedure.
Tremor and paraestesia are the most common side effects on the CNS.
In the SPC of duloxetine, it is stated that discontinuation of duloxetine, particularly when abrupt, commonly leads to withdrawal symptoms, including sensory disturbances (including paraesthesia). Hence, it is recommended that gradual discontinuation by dose tapering should be carried out [1].

Electric shock-like sensations are sensory perceptions of short electric low-voltage discharges, usually localized in the brain. In medical terms, it could be interpreted as a sort of 'central paraesthesia'. The sensations last momentary to a few seconds. In literature and on the Internet, the symptoms are described as 'brain zaps', 'brain shocks', 'brain shivers' or 'cranial zings'. In rare cases, the electric shock sensations are observed in the extremities or even in the whole body. The frequency varies from a couple per minute to once per hours. The total duration varies from days to weeks. The shocks are merely sensory and not accompanied by motoric muscle activity. Between the 'shocks' there are no complaints involved [2-6].

Lareb received 3 reports of electric shock sensations following discontinuation of duloxetine. In addition, 3 cases concerned the occurrence of this event during the start of treatment with duloxetine.

So far, electric shock-like sensations during withdrawal are unknown adverse events of duloxetine. For SSRIs, this shock-like phenomena is already known to be associated with discontinuation [2-6]. Lareb has previously reported on shock-like sensations that occurred at the start of SSRI therapy, during therapy and during withdrawal [3].

Reports

On February 24th 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports concerning electric shock sensations and the use of duloxetine. In addition, two reports from the Lareb Monitoring Project (LIM) were received. Out of five reports in total, four were well-documented consumer reports and one from a pharmacist.

Lareb received a total of five reports of electric shock sensations associated with the use of duloxetine. In 2 reports the electric shock sensations occurred following discontinuation of duloxetine. In addition, 2 cases concerned the occurrence of this event during the start of treatment with duloxetine. One patient suffered from electric shock sensations during both start of treatment and when the dose was unintentionally forgotten.
At the time of reporting to Lareb, one patient was recovered, two patients were recovering and in two patients the event was still present.

Table 1. Reports of electric shock sensations associated with the use of duloxetin.

Patient, sex, age	Drug, Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 64652 F, 21-30 years	duloxetine 60 mg daily unknown indication	None	paraesthesia (“tingling and electric shock sensations in extremities”)	3 weeks after dose reduction from 60 mg to 30 mg daily, not recovered
B, 83963 F, 21-30 years	duloxetine 60 mg daily depression	None	electric shock sensation (“electric shock sensations in brain”)	1 day after dose reduction from 60 to 45 mg daily, unknown latency, recovering
C, 109565 F, 21-30 years	duloxetine 60 mg daily anxiety disorder	oxazepam, melatonin, mebeverine	paraesthesia (“electric shock sensations through the head”)	occurred during start of treatment and when dose was unintendedly forgotten, not recovered
D, LIM F, 31-40 years	duloxetine 120 mg daily depression	oxazepam, amitriptylin, ethinylestradiol/ gestodene	electric shock sensation (“voltage in brain during head movements”)	a couple of days after start, recovering after dose reduction
E, LIM M, 31-40 years	duloxetine 60/120 mg daily * depression	lormetazepam, losartan/ hydrochloro thiazid	electric shock sensation (“electric shock sensations in head”)	3 days after start, recovering

Patient A was treated for 11 months with 60 mg duloxetine once daily after which the dose was reduced from 60 to 30 mg.
Patient B was treated for 9 months with duloxetine 30 mg BID. She experienced electric shock sensations one day after each dose reduction and persisted 3 days. Furthermore, she developed an unspecified thyroid disorder during discontinuation of duloxetine.
Patient C experienced electric shocks through the head, particularly, when turning the head and during walking on a solid floor. Sometimes the shocks were painful. The patient had similar electric shock-sensations in the past during withdrawal of paroxetine.
Patient D also experienced anxiety attacks, emotional instability, enhanced memories, myoclones, dry mouth, and fatigue during start of treatment.
Patient E reported two different dosages, i.e. 60 and 120 mg daily (*). Furthermore, she also suffered from headache, insomnia, constipation and restless legs following treatment with duloxetine.

From the available patient data, it is considered if the shock-like sensations could have been caused by concomitant medication or diseases. In the SmPC’s of the concomitant medication, electric shock-like sensations are not described as an adverse drug reaction [7-12]. It is concluded that there were no known or suspected relations between the event and concomitant medical factors.

All of the 5 patients used recommended doses duloxetine.
In four patients, the electric shock sensations were localized in the brain and in one patient in the extremities.
In two patients, the event occurred after dose reduction and in one patient when the dose was unintendedly forgotten; in three patients after start of treatment.

One patient experienced similar symptoms during earlier treatment with paroxetine.
These data suggest a relation between the occurrence of electric shock-like sensations and duloxetine during start of treatment or withdrawal of the drug. Three patients were recovered or recovering at the time of reporting; two were not recovered.

Other sources of information

SmPC

The event electric shock-like sensations is not included in the SmPC of duloxetine [1]. In contrast, it is a known adverse events of the SSRIs and included in those SmPCs (except for Cipramil®, Prozac® and Zoloft®) It is stated in section 4.4. and 4.8. as follows: “Discontinuation of paroxetin (particularly, abrupt) could result in withdrawal symptoms dizziness, sensoric disturbances (including paraesthesia, electric shock sensations and tinnitus)“ [13-19].
In the US SmPC of duloxetine, a more general statement with regard to SSRIs and SNRIs concerning the occurrence of electric shock sensations upon discontinuation is included , i.e.: “During marketing of other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including sensory disturbances (e.g. paraesthesias such as electric shock sensations) Although these events are generally self-limiting, some have been reported to be severe.” [20].

Literature

In 2 articles, the symptom of electric shock sensations after discontinuation of duloxetine is described [21,22]. In the article of Perahia, adverse events following abrupt discontinuation of duloxetine were compared to placebo. The pooled data comprised 6 clinical trials of patients treated for major depressive disorder. It was concluded that abrupt discontinuation of duloxetine reveals similar adverse events profiles compared to SSRIs including the occurrence of electric shock paraesthesias [21]. Pitchot observed this event during discontinuation of duloxetine in a case study [22].

Databases

On February 24th the Lareb database contained 3 reports of shock-like paraesthesia associate with duloxetine. Because the reports of shock-like paraesthesia have been coded in the past under a number of varying MedDRA® terms, the calculation of a reporting odds ratio (ROR) was deemed too unreliable. In addition, 2 reports were obtained from Lareb Intensive Monitoring project (LIM). These LIM reports are collected in a separate data-base.

For the WHO-MedDRA database, the PT ‘paraesthesia’ includes ‘electric shock sensation’, ‘tingling’ ‘tingling sensation’, ‘localized tingling’ and ‘paraesthesia of the scalp’. This database contained 511 reports of paraesthesia and duloxetine. The number of electric shock-like paraesthesia with duloxetine is 12, but a reporting odds ratio could not be calculated, since the WHO database does not allow for statistical calculations of reported reactions on the LLT level in MedDRA. Hence, the WHO-data are not evaluable. The same applies for the Eudravigilance data.

Prescription data

The number of patients treated with duloxetine in the Netherlands is presented in table 4.

Table 2. Number of patients using duloxetine in the Netherlands between 2007 and 2009.

Drug	2007	2008	2009
Duloxetine	18,814	24,057	28,572

Mechanism

The pathophysiology is hypothetical; the assumption is a change in neurotransmitter regulation.
In some cases, the electric shock-like sensations resembles Llermitte's sign: 'sudden electrical pains occurring with neck flexion down the spine and into the extremities'. Llermitte's sign might be related to hyperexcitability of the ascending neurons. With regard to drugs containing serotonine, it is strongly suggested that a local change in (response to) serotonin results in the shock-like reaction. Down-regulation of serotonin 5-HT2 receptors and the desentization of the 5-HT2 transmembrane signalling system and the 5-HT autoreceptors seem to be of concern [1,3-5,21,22].
The mechanism through which SNRIs might induce electric shock-like paraesthesias during withdrawal is likely the same as for SSRIs [5,6,21,22].

Discussion

Lareb received 5 well documented reports with respect to electric shock sensations in the use of duloxetine of which 3 reports concerned this event during withdrawal. In addition, in 2 reports the occurrence was observed during start of treatment. In all cases, the event was not likely to have been caused by other medical factors. There was a positive de-challenge in at least three patients.

In scientific literature, this withdrawal phenomena of duloxetine is described in 2 articles of which data are mainly based on pooled analyses of clinical studies. The pathophysiological mechanism is considered similar to that in SSRIs, i.e. a local change in (response to) serotonine results in the shock-like reaction.

The data from the WHO and Eudravigilance databases are not evaluable as they only specify on Preferred Term level and not on Lower Level Terms.

In the current US SmPC of duloxetine, a general statement concerning electric shock sensations during withdrawal in both SSRIs and SNRIs is included.
In the current European SmPC of duloxetine, a paragraph is included with regard to withdrawal symptoms including sensory disturbances (including paraesthesia) however this term is considered to refer to deviated sensibility, particularly, tingling or pricking sensations of the skin. This statement does not comprise the electric shock-like sensations localized in the brain (or body). This manifestation of electric shock-like sensations is considered a specific adverse event rather than a general paraesthesia. Therefore, the event could be regarded as a separate, particular sign. As it probably concerns similarity with the SSRIs, a statement in the SmPC might be included in accordance with those texts.

Conclusion

Three Lareb reports support the association between electric shock-like sensations and withdrawal of duloxetine. Furthermore, this event was also observed during the start of treatment in additional Lareb reports.
These data illustrate a signal of 'electric shock-like sensations' associated with duloxetine.

- Possible new signal of duloxetine associated with 'electric shock-like sensations'

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