

1.1. Serotonin Reuptake Inhibitors and shock-like paraesthesias: an update

Introduction

In an earlier quarterly report, we discussed nine reports of shock-like paraesthesias associated with the use of serotonin reuptake inhibitors (SRIs). [1] Because since our quarterly report of 2002, new additional cases have been reported, an update is given on the association between shock-like paraesthesias and serotonin reuptake inhibitors (SRIs), and the serotonergic acting antidepressants mirtazapine and venlafaxine.

Specific Serotonin Re-uptake Inhibitors have been approved for marketing in the Netherlands since the introduction of fluvoxamine (Fevarin®) [2] in 1985. Since then the following drugs have been introduced: fluoxetine (Prozac®) [3], paroxetine (Seroxat®) [4], sertraline (Zoloft®) [5], venlafaxine (Efexor®, an unselective serotonin re-uptake inhibitor) [6], citalopram (Cipramil®) [7], escitalopram (Lexapro®) [8] and duloxetine (Cymbalta®) [9]. The serotonin re-uptake inhibitors (SRIs) are approved for the treatment of one or more of the following indications: depressive episodes, obsessive-compulsive disorders, panic disorders, obsessive compulsive disorder, bulimia nervosa, diabetic neuropathic pain, social and generalized anxiety. Mirtazapine is an antidepressant drug that mainly acts through inhibition of pre-synaptic α_2 - and 5-HT₂-receptors and stimulates noradrenergic and serotonergic transmission. [10]

Paraesthesias are mentioned as general adverse drug reaction in the SmPCs of citalopram, sertraline, venlafaxine, escitalopram and duloxetine. All SmPCs mention paraesthesias as one of the symptoms when treatment is discontinued. The SmPCs of fluvoxamine, citalopram, escitalopram and paroxetine specify shock-like sensations as withdrawal symptom. The SmPCs of duloxetine, fluoxetine, sertraline and venlafaxine do not mention shock-like sensations at all.

Reports

In MedDRA shock like paraesthesias are coded with the Lower Level Term 'shock-like sensations' under the Preferred Term 'paraesthesias'. In this analysis, all reports on 'shock-like sensations' were included. Also all reports on 'paraesthesias' were included if they described 'shock-like sensations' in the clinical information.

From January 2002 to August 2008, a total of 33 reports on 'shock-like paraesthesias' were received by the Netherlands Pharmacovigilance Centre Lareb. Of these, 12 were reported by consumers, 11 by pharmacists, four by specialists, three by general practitioners, two by the Pharmaceutical Industry and one by another health professional. Most reports were received on venlafaxine (13), paroxetine (11), fluoxetine (3), mirtazapine (3), citalopram (2), and sertraline (1). We found no indication for a relation with demographic characteristics of the patients who experienced shock-like paraesthesias. Some reports were received when the drug was started (n=6, latency some hours to some day). Most shock-like sensations were reported due to missing a dose (n=7), when the dose was reduced (n=2), or as withdrawal symptom when the drug was stopped (n=15, latency 1 day to 2 weeks after discontinuation). Eight patients reported shock-like paraesthesias during drug therapy. At the time of reporting to Lareb, five patients were recovered, in 13 patients the outcome was unknown or not reported and 15 patients were not recovered. Patients and health care providers used similar expressions for the reactions, such as 'sort of electric shocks through the head'. The shocks were most frequently localized in the head, but also electric shocks to the extremities, and through the whole body were mentioned.

Other Sources of Information

Literature

In our quarterly report in 2002, we reviewed the literature on this association: shock like paraesthesias have been associated with start and discontinuation of SSRIs. [11,12] Since January 2002, several case reports have been published on the association for escitalopram [13], venlafaxine [14], duloxetine [15]. Also SSRIs (including venlafaxine) and shock-like reactions are mentioned in handbooks, such as Micromedex. [16] There are no reports published on mirtazapine and shock-like reactions. An analysis has been published about the discussion about electric

shock sensations - by patients often described as 'brain shivers' - on the internet. [17] On many internet sites patient experiences of this ADR are described, yet psychiatrists seemed unfamiliar with these patient-led terms. [17] Shock-like paraesthesias have not been reported for other antidepressant drugs, such as the tricyclic anti-depressants.

Databases

As this ADR is typically mentioned for central acting serotonergic drugs, no statistical analysis has been performed. Shock-like sensations have been reported on 12 other drugs, and calculated RORs have no added value.

The database of the WHO Monitoring Centre contains reports on the WHO-art term electric shock. For this association, we found the following number of reports and RORs: paroxetine (n=139, ROR=143, 95%CI =102-202), citalopram (n=47, ROR=22.6, 95% CI=7.0-73), escitalopram (n=24, ROR=2716, 95% CI=359-20526), sertraline (n=47, ROR=5.3, 95%CI=1.3-21.6) and venlafaxine (n=132, ROR=6.3, 95%CI=12.9-26.4). These association was highly significant, yet this ADR has also been reported little for other drugs.

Mechanism

The pathophysiology of drug-induced shock-like paraesthesias is still unclear, but in some cases resembles Llermitte's sign: 'sudden electrical pains occurring with neck flexion down the spine and into the extremities'. [11] Llermitte's sign might be related to hyperexcitability of the ascending neurons. [11] The cases strongly suggest that the shock-like reaction is related to a local change in (the response to) serotonin. Down-regulation of serotonin 5-HT₂ receptors and the desensitization of the 5-HT₂ transmembrane signaling system and the 5-HT autoreceptors seem to be of concern. [18] As mirtazapine also influences the 5-HT₂ signaling, a related mechanism for mirtazapine induced electric shock sensations is suggested.

Conclusion

Since the previous quarterly report in January 2002, 33 additional cases of electric shock paraesthesias in association with SRIs, venlafaxine and mirtazapine were reported to Lareb. Shock-like paraesthesias were reported at the start of SRI therapy, during therapy and during withdrawal. The association was reported by consumers and professionals, and additional case reports have been published.

References

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This signal has been raised on December 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbq-meb.nl/cbq/en/default.htm or the responsible marketing authorization holder(s).