November 2003

Emotional disinhibition by sumatriptan and zolmitriptan

Introduction

Sumatriptan (Imigran®, 16-05-1991) and zolmitriptan (Zomig®, 25-09-1997) are licenced at the Dutch market for the *acute treatment of migraine attacks*[1,2]. Sumatriptan is also approved for the *acute treatment of cluster headaches*. The most frequently occurring adverse drug reactions are paraesthesia, dizziness, fatigue/asthenia, nausea and an oppressed feeling [1,2].

Euphoria, depersonalisation and emotional lability are labelled in the Summary of Product Characteristics (SPC) of eletriptan (Relpax®), but not in the SPCs of the other triptans [3].

The pain sensitive areas of the cranial cave are the blood vessels and vasculature of the dura mater. In humans, a migraine attack is provoked by vasodilatation and oedema of the cranial and intracranial vessels. Sumatriptan and zolmitriptan stimulate the $5HT_{1D}$-receptor in the cranial and intracranial arteries, which leads to vasoconstriction. The vasculature of the dura mater is also innervated by the trigeminal nerve. Triptans inhibit the activity of the trigeminal nerve peripherally and possibly also centrally by decreasing the release of calcitonin-gene related peptide (CGRP) and Vasoctive Intestinal Peptide (VIP) and substance P [1,2,4].

Reports

In September 2003, the Lareb database contained six reports concerning disinhibitive behaviour associated with the use of a triptan. Five of these reports refer to sumatriptan and one to zolmitriptan.

Table 1. reports of disinhibition associated with the use of triptans

Patient, Sex, age	Drug	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A F, 44	Sumatriptan 20 mg nasal inhalations	-	Euphoria with overrated selfconfidence	One hour after administration Recovered
B F, 29	Sumatriptan 100mg po	Propranolol, lynestrenol	Strengthened emotions	Unknown Not recovered, drug continued
C F, 31	Sumatriptan 100mg po	Ethinylestradiol + levonorgestrel	Restlessness, aggression, agitation, extremely energetic	Several hours after administration Recovered
D F, 26	Zolmitriptan 2,5mg po	Ethinylestradiol + levonorgestrel	Psychiatric disinhibition	Unknown Recovered
E F, 28	Sumatriptan 100mg po	-	Speech disorder, mood disorder, feeling of chest pressure, chills	Several hours after administration Recovered
F F, 44	Sumatriptan 6mg sc	Clonidine	Emotional lability	One hour after administration; Unknown

Patient A, a 44-year-old female started the use of sumatriptan nasal inhalations for treatment of a migraine attack. One hour after taking the first dose, she experienced euphoria and she overestimated her own capacities (unsafe behaviour in traffic and unadjusted behaviour while at work). These feelings lasted for six hours. She took sumatriptan three more times and developed euphoria and overrating of her capacities on all these occasions. The woman did not use any concomitant medication. The characteristics of this report and the other five reports are listed in table 1.

Other sources of information

Literature

A search in Pubmed does not provide case reports on disinhibition during treatment with triptans. One article does describe a dysphoric reaction, similar to marijuhana intoxication after subcutaneous use of sumatriptan, lasting for three hours [5]. However, as is specified in the paragraph *Mechanism*, several investigations have been published on the effects of serotonin on behaviour. Apparently, serotonin plays a critical role in the aggressive and impulsive behaviour.

Databases

With respect to the Lareb database, the reported complaints of disinhibition and emotional disorders are too diverse to calculate an Reporting Odds Ratio (ROR).
The database of the WHO Monitoring Centre contains a total number of 10,153 reported adverse drug reactions on sumatriptan. Of the reports 32 refer to euphoria, which results in a ROR of 3.7 (95%-CI = 2.6–5.3). The database contains 629 associations for zolmitriptan, of which 1 concerns euphoria. This association is reported twice on rizatriptan. Because of these small numbers a ROR cannot be applied.

Mechanism

Zolmitriptan equally binds the $5HT_{1B}$- and the $5HT_{1D}$-receptor. Sumatriptan preferably binds the $5HT_{1D}$-receptors, but only with a 2 to 20 fold selectivity over $5HT_{1B}$-receptor. The $5HT_{1B}$-receptors are amongst others found in the substantia nigra. They serve as autoreceptor on the presynaptic nerve ending, where they modulate the firing rate of the neuron [4,6].

Serotonin plays a critical role in aggression and impulsivity, whereas reduced serotonergic activity has been associated with impulsive behaviour. Rapid tryptophan depletion, which will lead to lowering of the 5-HT level in the brain, results in a more impulsive or disinhibited response style [4,7]. Moreover, knock out-mice lacking the $5HT_{1B}$ receptor are used for the investigation of impulsivity and aggressive behaviour [8]. Since triptans are agonists for the presynaptic autoreceptor 5-HT1B/D, they inhibit release of serotonin from the nerve ending and deplete for serotonin.

Conclusion

Treatment with sumatriptan and zolmitriptan, and possibly other triptans, may result in disinhibition and self-overrating. These kind of feelings may be harmful in traffic and certain activities at work. The reports found in the Lareb database indicate causality of this association. Pharmacologically, this relation is supported by investigations on the effects of serotonin depletion, which leads to impulsive behaviour.

References
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