Mei 2002

Selective serotonergic vasoconstrictors in suspected association with pain activation.

Introduction

Zolmitriptan, naratriptan and sumatriptan belong to the group of selective serotonergic vasoconstrictors: they activate the $5HT_{1B}/_{1D}$-receptor and have low affinity for $5HT_{1A}$-receptors [1-3]. Imigran® (sumatriptan) was approved for the Dutch market in 1991 for treatment of all symptoms of migraine with and without aura. Zomig® (zolmitriptan) was approved in 1997 for acute treatment of migraine with or without aura. Naramig® (naratriptan) was approved in 1998 for acute treatment of migraine associated headache with or without aura.

Reports

Lareb received 6 case reports concerning the *aggravation* of existing pain and 2 reports of *activation* of pain at sites of previous injury in suspected association with the use of these products.

Lareb received several reports of aggravation of pain in recently injured parts of the body: five in suspected association with use of sumatriptan, one with naratriptan. Two of these reports concerned patients (a 54-year-old man and a 48-year-old woman) with a partially sunburned skin, who experienced aggravation of pain, lasting for several hours, in the burned parts of the skin within 15 minutes after the use (respectively oral and subcutaneous) of sumatriptan. The man in question also used propranolol and diclofenac, the woman loratidine and fluconazol.
A 39-year-old man had many grazes after a fall. Soon after administration of sumatriptan by injection the injuries smarted intensively for several hours. Concomitant medication used was verapamil and temazepam, when needed.
A 56-year-old woman experienced aggravation of tendinitis-related pain about 2 hours after injection of sumatriptan (no concomitant medication). Only the tendons already affected were involved.
A 46-year-old man, who had a fissure of his fibula, subsequently used 1.25 mg of zolmitriptan for migraine 2 days and 9 days, respectively (no concomitant medication). On both occasions he experienced aggravation of the joint ache. Once the fracture had consolidated and the pain decreased, the aggravation of pain after intake of zolmitriptan also decreased. Patient recovered fully.
Finally, Lareb received a report on a 50-year-old woman who experienced severe cramps (during 5 hours) in her recently operated leg after oral intake of 5 mg of naratriptan. A positive rechallenge was seen, up to three times. The patient had no problems after intake of 2.5 mg of naratriptan. No concomitant medication was used and the patient fully recovered.

Lareb also received two reports of pain activation at sites of previous injury in association with the use of sumatriptan, which pain experiences were similar to those experienced earlier.
The first report describes a 28-year-old woman who experienced abdominal pain (within 15 minutes after oral intake of sumatriptan) exactly like the pain she had felt 5 years ago during pancreatitis. The patient did not use concomitant medication. She recovered within an hour and no lab tests were performed.
The other report concerns a 26-year-old woman who experienced pain in the leg that had been operated upon for varicosis several years ago. She used an oral contraceptive and a laxative as concomitant medication. She recovered the same day.

Other sources of information

SPC

The Dutch Summary of Products Characteristics of zolmitriptan does not describe the phenomenon described above. For sumatriptan and naratriptan 'pain' in general is described as adverse event but not in terms of aggravation or (re)activation of pain [1-3].

Literature

No case reports of pain activation were found in literature.
However, Black and Caldwell described an increase in the sensitivity of the skin associated with the use of sumatriptan in 1994 [4]. Two of the patients in the Lareb database also experienced an increase in the sensitivity of the skin.

Databases

On March 1st 2002 the Lareb database contained a total of 33 reports of adverse events in association with zolmitriptan, one of which can be described as pain activation. For sumatriptan 6 out of 254 reports refer to pain activation, for naratriptan 1 out of 20. It is difficult to search the WHO database for reports of activation of pain since this adverse event is not coded as such yet.

Mechanism

The anti-migraine property of zolmitriptan, sumatriptan and naratriptan is ascribed to two effects. The first effect is the vasoconstriction that is realised in the cranial arteries. The blood supply to the meninges (assumed to be increased during migraine) is reduced. The other –suggested– effect is the not only peripheral but also central inhibition of the activity of the trigeminal nerve by inhibition of release of the neuropeptides CGRP (calcitonin gene-related peptide), VIP (Vasoactive intestinal peptide) and Substance P.
Serotonin is a major component of the inflammatory chemical milieu and contributes to the pain of tissue injury via an action on multiple receptor subtypes[5]. Activation of the $5HT_{1B}/_{1D}$-receptor might therefore increase the susceptibility of pain. Another of the well-known ADRs of the 5HT agonists is the occurrence of chest pain. The pathophysiological mechanism of this chest pain is not fully elucidated but may be caused by arterial spasm. It is not known if a similar mechanism might be involved in the reactivation of existing pain.

Conclusion

An association is assumed between the use of selective serotonergic vasoconstrictors and activation of pre-existing pain: patients experience aggravation of existing pain or activation of injury-related pain as was experienced years previously.

References
1. Dutch Summary of Products Characteristics of Zomig, http://www.cbg-meb.nl, October 1999.
2. Dutch Summary of Products Characteristics of Imigran, http://www.cbg-meb.nl, July 2000.
3. Dutch Summary of Products Characteristics of Naramig, http://www.cbg-meb.nl, June 2000.
4. Black P, Caldwell J. Skin sensitivity to sumatriptan. *N Z Med J*. 1994 Jan 26;107:20-1.
5. Zeitz K; Guy N; Malmberg A; Dirajlal S; Martin W; Sun L; Bonhaus D; Stucky C; Julius D; Basbaum A. The 5-HT3 subtype of serotonin receptor contribute. *J Neurosci*. 2002; 22:1010-9