

1.1. Selective serotonergic vasoconstrictors (triptans) and pain re-activation – an update

Introduction

Selective serotonergic vasoconstrictors (triptans) are indicated for *the acute treatment of migraine with or without aura in adults*. The subcutaneous formulation of sumatriptan and the nasal formulation of zolmitriptan are also indicated for *acute treatment of cluster headache*. Triptans activate the 5HT(1B/1D) receptors and have low affinity for 5-HT(1A), 5-HT(5A) and 5-HT(7) receptors. They exert their effect by stimulating vasoconstriction in the basilar artery and in the blood vessels of the dura mater, this action is presumed to result in the relief of migraine (and cluster headaches) [1].

Among the triptanes, sumatriptan (Imigran[®]) was granted marketing authorization in the 1991, followed by naratriptan (Naramig[®]), zolmitriptan (Zomig[®]), rizatriptan (Maxalt[®]), almotriptan (Almogran[®]), eletriptan (Relpax[®]) and frovatriptan (Fromirex[®]).

The current observation describes the association between triptans and pain re-activation in 19 patients. A previous report regarding this association in 8 patients has been sent to the Medical Evaluation Board in 2002 [2].

Reports

Lareb received 19 reports of re-activation of pain associated with the use of triptans, in a period from July 18, 1996 till January 15, 2015. The reports are listed in Table 1.

Table 1. Reports of pain re-activation associated with the use of triptans

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
*A 24509 M, 31-40 Physician	sumatriptan sc 12 mg/ml migraine	verapamil temazepam	pain burning	unknown no change unknown
*B 24967 F, 21-30 Physician	sumatriptan 100mg migraine	psyllium ethinylestradiol/cypro teron	leg pain	unknown withdrawn recovered
*C 26265 F, 51-60 Physician	sumatriptan sc 12 mg/ml migraine		tendon pain	2 hours no change unknown

*D 27177, F, 21-30, General Practitioner	sumatriptan 50 mg migraine		abdominal pain nausea hyperhidrosis	15 minutes, drug withdrawn recovered
*E 32001 F, 41-50 Physician	sumatriptan 100 mg migraine	loratadine fluconazole	burning skin	1-2 hours no change recovered
*F 34255 M, 41-50 Physician	zolmitriptan 1.25 mg migraine		joint ache	hours withdrawn recovered
*G 34473 F, 41-50 Physician	naratriptan 5 mg migraine		cramp legs	hours no change recovered
*H 37073 M, 51-60 Pharmacist	sumatriptan sc 12 mg/ml	flurazepam naproxen diazepam salbutamol cimetidine	burning skin	unknown no change recovered
I 38151 F, 51-60 Pharmacist	sumatriptan 50 mg migraine	alendronate	bone pain	1 hour not changed recovered
J 43432 F, 41-50 Pharmacist	sumatriptan sc 12 mg/ml migraine	metropolol atorvastatine	pain trauma activated	hours discontinued recovered
K 44919 F, 31-40 Consumer	sumatriptan sc 12 mg/ml migraine	medroxy- progesterone	pain trauma activated	unknown discontinued recovered

L 45295	sumatriptan 50 mg b.i.d. if necessary	cimetidine	postoperative pain	5,5 year
F, 51-60	migraine	tibolon		unknown
Pharmacist	atenolol 25 mg o.d.		periphereal vascular disease	not recovered
	unknown			7 years
				unknown
				unknown
M 49513	sumatriptan sc 12 mg/ml	tamsulosine	pain trauma activated	unknown
M, 51-60	migraine	diclofenac		unknown
Pharmacist				recovered
N 56409	sumatriptan 50 mg migraine	ethinylestradiol/desog estrel	leg pain	3 hours
F, 41-50				withdrawn
Pharmacist				recovered
O 112764	rizatriptan 10 mg o.d.		abdominal pain lower	1 day
F, 31-40				withdrawn
Consumer				recovered
P 134936	sumatriptan sc 12 mg/ml		pain during injection	minutes
F, 51-60	migraine			unknown
Pharmacist				unknown
Q 162108	rizatriptan 10 mg migraine	zolpidem	pain trauma activated	1 hour
F, 51-60				no change
Physician				recovered
R 174800	sumatriptan 50 mg		paraesthesia upper limb	1 hour
F, 61-70			pain in extremity	dose reduced
Consumer				not recovered
S 187493	sumatriptan 75 mg od migraine	paracetamol naproxen	pain trauma activated	15 minutes
F, 51-60				withdrawn
Consumer				recovered

* cases were already described in the report in 2002

In the reports below is described in detail to show the relation of symptoms with previous trauma, surgical inventions or inflammatory diseases.

Patient A

A 31-40-year-old man regularly uses sumatriptan injections. When he has a superficial wound, it starts to ache smart after use of sumatriptan. At the moment he has many grazes after a fall. Soon after administration of sumatriptan by injection the injuries smarted intensively for several hours.

Patient B

After intake of sumatriptan, a 21-30-year-old woman experienced pain in a leg, which was operated for varicosis several years ago. She recovered the same day. The same reaction had occurred in the past after use of sumatriptan. After use of rizatriptan, she experienced no problems.

Patient C

A 51-60-year-old woman experienced aggravation of tendinitis related pain, about two hours after injection of sumatriptan). Only the tendons already affected were involved.

Patient D

A 21-30-year-old woman experienced, within 15 minutes after oral intake of sumatriptan, abdominal pain, exactly like the pain she felt five years ago during pancreatitis. She recovered within an hour, no lab tests were performed.

Patient E:

A 41-50-year-old woman had a partially sun-burned skin on her back. The next day she took sumatriptan and 1-2 hours hereafter she experienced aggravation of pain in the burned parts of the skin, lasting for several hours.

Patient F

A 41-50-year-old man had a fissure of his fibula. He used 1.25 mg of zolmitriptan for migraine two days and nine days thereafter. On both occasions he experienced aggravation of the joint-ache. Once the fracture consolidated and the pain

decreased, the aggravation of pain after intake of zolmitriptan also diminished.
Patient recovered.

Patient G

A 41-50-year-old woman experienced severe cramps (during 5 hours) in her recently operated leg after oral intake of 5 mg of naratriptan. A positive re-challenge was seen, up to three times. The patient had no problems after intake of 2.5 mg of naratriptan. Patient recovered.

Patient H

A 51-60-year-old man experienced severe burning of the skin, on parts which had previously been exposed too long to the sun. This lasted for several hours.

Patient I

A 51-60-year-old woman is known with osteoporosis and rheumatoid arthritis. One hour after intake of sumatriptan for migraine, she experienced stiffness and pain in her bones. Patient recovered.

Patient J

A 41-50-year-old female had a knee operation with a bad healing wound in her lower leg. After subcutaneous injection of sumatriptan for migraine, she experienced a violent pain in this wound. The pain lasted for several hours. A positive re-challenge was observed.

Patient K

A 31-40-year old woman had a sun burned skin. Soon after subcutaneous injection of sumatriptan she experienced aggravation of pain with a stinging sensation in this sun-burned area, lasting for about two minutes. Re-administration resulted in similar symptoms.

Patient L

Patient had used sumatriptan for seven years. Two years ago she had a hand operation. Since that moment, she suffers from hand pain. In that year also atenolol had been started, which she had used for two years now. During the last two to three times of sumatriptan use, she noticed painful blue swollen fingers in her operated hand. Outcome is unknown. She will start with zolmitriptan.

Patient M

A male of 51-60 years had used sumatriptan injections for nine years. Recently he had a varicose operation of his left leg. After injection of sumatriptan for migraine in his other leg, he experienced pain, stinging and numbness on the varicose operation location. After one hour, the pain decreased.

Patient N

A 41-50-year-old woman experienced severe pain in one varicose leg, three hours after intake of sumatriptan for migraine. She had to lie down, because of the leg pain. The leg pain disappeared the following day.

Patient O

A 31-40-year-old female with Crohn's disease experienced lower abdominal pain, one day after intake of rizatriptan for migraine. This lasted for two weeks. After a month she took another rizatriptan, resulting in lower abdominal pain in the same location. Years before she had the same experience with the use of ibuprofen.

Patient P

A female of 51-60 years experienced pain in her leg, minutes after administration of sumatriptan subcutaneously. In the past, this leg was operated for varicose. Outcome is unknown.

Patient Q

A 51-60-year-old woman had severe pain in her formerly broken ankle, one hour after intake of rizatriptan for migraine. The pain lasted for 2 weeks. A year before, she had the same experience of pain activation following rizatriptan intake after a wrist fracture and later also after a wrist operation.

Patient R

A woman, aged 61-70, had used sumatriptan for seven years. Recently a neuroma of the brachial plexus had been diagnosed. Pressure or touching of the neuroma results in paresthesia, numbness and pain in the arm and hand. One hour after intake of sumatriptan worsening of this paresthesia and pain in this arm occurred.

Patient S

A 51-60-year-old woman experienced severe pain at the site of a bone fracture, fifteen minutes after intake of sumatriptan 50 mg, 1.5 tablet, for migraine. Naproxen and paracetamol were insufficient for pain relief, therefore patient was treated with oxycodone. Patient recovered. A week later, a positive re-challenge was observed.

Other sources of information

SmPC

Pain re-activation is not mentioned in the SmPCs of sumatriptan (Imigran®), naratriptan (Naramig®), zolmitriptan (Zomig®), rizatriptan (Maxalt®), almotriptan (Almogran®), eletriptan (Relpax®) and frovatriptan (Fromirex®) [1,3-9]. In the SmPC of naratriptan only pain is mentioned, without further description. In the other SmPCs several sites of pain are included. The most extensive description of pain perception as adverse reaction is to be found in the SmPC of frovatriptan, which includes headache, ear pain, eye pain, pharyngolaryngeal pain, abdominal pain, lip pain, pain in the salivary glands, tooth pain, chest pain, back pain, kidney pain, skeletal pain, arthralgia, pain in extremities and pain in breasts [9].

Literature

One publication presents case reports reported to the Pharmacovigilance centres of New Zealand and the Netherlands. Thirteen cases of pain activation and eight cases of aggravation of pain in inflammatory diseases are shown. It is suggested that higher concentrations, as is the case for the subcutaneous formulation, gives a higher rate of pain activation. Pain was mostly severe, but short-lasting, however pain was prolonged in some patients with inflammatory diseases [10]. Furthermore an internet communication from the Belgian Pharmacovigilance Centre can be found. They reported a case of a 19-year-old woman, who experienced in multiple occasions a reactivation of pain in old burns and abrasions shortly after an injection of sumatriptan for migraine [11].

Databases

Table 2. Reports of post-traumatic pain, procedural pain and inflammatory pain with triptans in the databases of the Netherlands Pharmacovigilance Centre Lareb, the WHO- and Eudravigilance (EMA) database [12,13] .

Database	Preferred Terms	Number of reports	ROR (95% CI)
Lareb*	Post traumatic pain	5	580.0 (112.3-2994.7)
	Procedural pain	1**	
WHO	Post-traumatic pain	13	71.7 (40.1-128.3)
	Procedural pain	2**	
	Inflammatory pain***	7	36.3 (16.9-78.0)
Eudravigilance	Post traumatic pain	6	147.3 (62.7 – 346.4)
	Procedural pain	2**	

Database	Preferred Terms	Number of reports	ROR (95% CI)
	Inflammatory pain	1**	

*13 cases have other preferred terms

** numbers too low to calculate the ROR

*** only reports in association with sumatriptan

Prescription data

Table 3. Number of patients using triptans in the Netherlands between 2009 and 2013 [14].

Drug	2009	2010	2011	2012	2013
Sumatriptan	104,020	108,790	111,180	110,490	109,820
Naratriptan	8,340	8,107	7,849	7,371	6,794
Zolmitriptan	11,677	11,810	11,591	11,163	10,529
Rizatriptan	73,786	78,300	80,616	79,571	76,715
Almotriptan	5,135	5,124	4,916	4,720	4,239
Eletriptan	4,816	5,227	5,635	6,037	6,383
Frovatriptan	8,388	9,723	10,830	11,430	11,345
Total	202,550	212,250	217,520	216,030	211,790

Mechanism

Stimulation of the 5-HT_{1B} receptor leads to vasoconstriction of the cranial arteries. Stimulation of the presynaptic 5-HT_{1D} receptors is primarily on the endings of the primary nociceptive nerve fibers in the peripheral nervous system. This inhibits neurogenic inflammation by inhibiting the release of the neuropeptides CGRP, VIP and substance P.

Serotonin is a major component of the inflammatory chemical milieu and contributes to the pain of tissue injury via actions on multiple receptor subtypes. [15]. It is known to be involved with pain sensitizing at inflammatory sites and in pain processing [16]. The binding of triptans with the 5-HT_{1B} and 5-HT_{1D} receptor subtypes may disrupt the physiological balance between serotonin and receptors. This disruption might increase the susceptibility to pain mediated through activation of excitatory receptors such as the vascular 5-HT_{2B} and the neuronal 5-HT₇ receptors which have been demonstrated to increase pain [17]. The 5-HT₇ receptor occurs in peripheral sensory neurons and it has been demonstrated that sumatriptan displays moderate binding affinity for this receptor [18]. It

is suggested that high concentrations of sumatriptan may enhance neurogenic inflammation through activation of the 5-HT₇ receptor [10].

Discussion and conclusion

Lareb has received 19 reports of pain re-activation in association with triptans. The lower level term 'pain trauma activated' or 'post procedural pain' was only used in a small number (6) of cases. Additional 13 cases were found by word-mining. Initial pain in patients involved inflammations or inflammatory diseases (skin, intestinal tract, bones), injuries (skin, tendons, bones) or pain after surgical procedures. Re-activation of pain following use of triptans developed in almost all cases within hours (minutes to 1 day) after administration, which is consistent with the pharmacological action of these drugs. In nearly all patients, the resolution of pain was within hours (minutes to 1 day) after administration. In one patient with Crohn's disease (O) complaints of abdominal pain lasted for 2 weeks, which is in line with the experienced pain in inflammatory diseases [10]. In eight patients a positive re-challenge was observed. In seven cases pain reactivation occurred after subcutaneous administration of sumatriptan, in all other cases an oral formulation was used. In a single patient (G), a dose relationship was suggested, because no problems were encountered with a lower dose of naratriptan. Surprisingly in one patient (B) no reaction on rizatriptan occurred, although on multiple occasions he had experienced a reaction after administration of oral sumatriptan 100 mg.

The association of pain-reactivation in relation to triptans was supported by the WHO database and Eudravigilance database. It should be noted that the lower level terms 'pain trauma activated' (preferred term 'post-traumatic pain') and 'pain inflammation activated' (preferred term 'inflammatory pain') were added to the WHO adverse reaction terminology (WHOART) only in the early years of this millennium, after the detection of this association by case reports in New Zealand and the Netherlands. No word-mining exercise could be performed in the WHO or Eudravigilance database. Therefore, it is expected that perhaps more cases of pain re-activation might be present in the WHO or Eudravigilance database with different coded terms. The publication of the cases from New Zealand and the Netherlands [10] has not been confirmed by other publications on this association; only an internet communication could be retrieved.

Still it is of importance to acknowledge the possible role of triptans in a patient with pain re-activation. Moreover in patients with inflammatory diseases such as rheumatoid arthritis or colitis, it could mimic an exacerbation of the disease.

- Pain re-activation should be mentioned in the SmPC of triptans

References

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This signal has been raised on July 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl