Brief Communication

Activation of Pain by Sumatriptan

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Objective.—To demonstrate that sumatriptan may induce activation or aggravation of pain at sites of inflammation caused by trauma or disease.

Methods.—Case reports from the national pharmacovigilance centers of 2 countries, The Netherlands and New Zealand, are presented. These reports come from programs that use 2 methodologies to monitor drugs for adverse reactions: spontaneous reporting and a prospective observational cohort study. The potential mechanisms for pain production by sumatriptan are discussed in detail.

Results.—Thirteen case reports of activation of pain by sumatriptan following injury and 8 associated with inflammatory diseases are presented. Most patients had one or more positive rechallenges. This type of reaction occurred at a higher rate with the subcutaneous formulation than with the oral preparation. Pain mostly was severe but short-lasting; pain was prolonged in some patients with inflammatory disease.

Conclusions.—A strong association has been demonstrated between the use of sumatriptan and the production of pain at sites of inflammation, and there is a plausible pharmacological mechanism for this reaction. Pain activation may be a class effect of the selective serotonergic agonists used in the treatment of migraine.

Key words: sumatriptan, pain activation, pharmacovigilance, pharmacology, migraine, prescription event monitoring

Abbreviations: NL The Netherlands, NZ New Zealand

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Sumatriptan has been widely used in the treatment of migraine and cluster headache. This article presents a series of cases from 2 countries where the use of sumatriptan was followed by exacerbation of pain at sites of previous injury or inflammatory disease. The characteristics of these events are presented, and a possible mechanism is described in detail.

METHODS

The observations presented are from The Netherlands (NL) and New Zealand (NZ). In NZ, sumatriptan was studied in the Intensive Medicines Monitoring Programme (IMMP) for 8 years, beginning in 1991. This was a noninterventional, prospective, observational, cohort study of 14951 patients using prescription event monitoring (PEM).[1,2] Prescription records were received from community and hospital pharmacies throughout the country. Questionnaires were sent to the prescribers every 6 months for each individual patient for as long as they continued to have prescriptions dispensed. If the patient had not returned to see their doctor by the time a questionnaire was received, the doctor or nurse contacted the patient by telephone in order to complete the questionnaire. There were 26309 questionnaires sent with a response rate of 83% (n = 21836).[3] Each report of an adverse event was reviewed by a physician. Both the oral (100-mg and 50-mg tablets) and subcutaneous (6 mg) formulations were available by prescription only. More injections than tablets were prescribed because only the injections were subsidized. The ratio of use of injections to tablets was 1.8:1.

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The Netherlands Pharmacocovigilance Centre, Lareb maintains the spontaneous adverse drug reaction reporting system in NL on behalf of the Dutch Medicines Evaluation Board. Both physicians and pharmacists report to the system on a voluntary (ie, noninterventional) basis.

RESULTS

In NZ, the ratio of women to men who were dispensed sumatriptan was 3.6:1. There were 2356 reports describing 3978 adverse events. The female to male ratio of patients sustaining these events was 5.6:1. Amongst these, there were 9 reports of aggravation or activation of pain at sites of previous injury (Table 1). Between June 1991 and July 2002, NL Pharmacovigilance Centre received from physicians and pharmacists 162 spontaneous reports describing 237 adverse events associated with the use of sumatriptan. The female to male ratio was 5.5:1, almost identical to that in NZ. Included in these were 4 additional reports of aggravation or activation of pain at sites of previous physical injury for a total of 13 such reports from the 2 countries (Table 1).

All of the above events (Table 1) occurred over a period of up to 4 weeks following injury, with the exception of the event in report 13. This occurred several years following surgery for varicose veins. The types of trauma were varied and included superficial injury of the skin, deep muscle injury, fracture, and surgery (Table 1). Eleven of these 13 events occurred with use of the subcutaneous formulation. Time to onset of the pain was rapid. Pain was sometimes severe and lasted up to 2 hours. Six of the 13 patients with pain following trauma were subject to re-exposure with sumatriptan and had recurrence of symptoms (ie, a positive rechallenge).

In addition, there were 6 reports from NZ and 2 from NL of exacerbation of pain in a variety of inflammatory diseases such as rheumatoid arthritis and colitis (Table 2). One patient (report 8) felt abdominal pain exactly like the pain experienced 5 years previously with pancreatitis. As with the reports of pain following trauma, most of these episodes were severe. In general, the pain lasted longer than the episodes following trauma. The patient with colitis had exacerbations lasting around 10 days. Only 2 of these events occurred with use of the oral formulation. One patient (report 7) had the injection followed by a 100-mg tablet (interval unknown). Time to onset of pain following treatment was rapid in all those in whom this was recorded. Six of the 8 patients listed with inflammatory conditions had positive rechallenges.

In NZ, the number of patients who had received injections was 10733 and the tablets, 6151. There

Table 1.—Activation of Pain by Sumatriptan at Sites of Previous Trauma*

Report	Sex/Age, y	Dose	Type of Injury	Time Since Trauma	Duration to Onset	Duration of Pain	Postive Rechallenge
1 NZ	F 43	6 mg SC	Hysterectomy	2 Weeks	Rapid	1 Hour	0
2 NZ	F 43	6 mg SC	Hematoma	1–2 Weeks	Rapid	Unknown	0
3 NZ	F 47	6 mg SC	Sunburn	Unknown	Immediate	30 Minutes	Several
4 NZ	M 59	6 mg SC	Minor cuts	Same day	5 Minutes	2 Hours	0
5 NZ	F 52	6 mg SC	Fractured humerus	4 Weeks	Unknown	2 Hours	3
6 NZ	F 47	6 mg SC	Knee surgery	2 Weeks	5 Minutes	45 Minutes	2
7 NZ	F 53	6 mg SC	Sunburn	Unknown	Unknown	Unknown	Unknown
8 NZ	M 50	6 mg SC	Sunburn	Unknown	Unknown	1 Hour	0
9 NZ	F 55	6 mg SC	Soleus muscle tear	Unknown	Unknown	Unknown	2
10 NL	M 54	6 mg SC	Sunburn	1 Day	Immediate	Unknown	0
11 NL	F 48	100 mg PO	Sunburn	1 Day	Rapid	1–2 Hours	0
12 NL	M 39	6 mg SC	Abrasions	Unknown	Rapid	Hours	Several
13 NL	F 26	100 mg PO	Varicose veins surgery	Several years	Unknown	Unknown	1

*NZ indicates New Zealand; SC, subcutaneous; NL, The Netherlands; PO, by mouth.

Table 2.—Activation of Pain by Sumatriptan at Sites of Inflammation*

Report	Sex/Age, y	Dose	Condition	Duration to Onset	Duration of Pain	Positive Rechallenge
1 NZ	F 30	6 mg SC	Flare of psoriasis	5–10 Minutes	Few minutes	Several
2 NZ	F 34	100 mg PO	Rheumatoid arthritis	1 Hour	24 Hours	Several
3 NZ	F 46	6 mg SC	Shoulder-arm pain	Unknown	Unknown	Several
4 NZ	M 51	6 mg SC	Rheumatoid arthritis	20 Minutes	2 Days	Several
5 NZ	F 37	6 mg SC	Colitis	5 Minutes	10 Days	Several
6 NZ	F 34	6 mg SC	Sacroiliac pain	Unknown	"All day"	1
7 NL	F 56	6 mg SC + 100 mg PO	Tendinitis	2–3 Hours	Unknown	Unknown
8 NL	F 28	50 mg PO	Chronic pancreatitis	15 Minutes	1 Hour	0

*NZ indicates New Zealand; SC, subcutaneous; PO, by mouth; NL, The Netherlands.

were 14 reports (trauma plus disease cases) associated with injections and 1 with tablets; ie, 1.3 reports per 1000 patients of pain activation with the subcutaneous form and 0.2 reports per 1000 patients with the oral formulation. This difference is significant (relative risk, 8.0; 95% confidence interval, 1.1 to 61.0).

COMMENTS

Case Characteristics and Reaction Terms.—The reports from NZ and NL present a compelling case for recognition of pain activation as an adverse reaction associated with sumatriptan. Time to onset of the pain in most cases was consistent with the pharmacological action of the drug. In all cases where patients were known to have been rechallenged with sumatriptan, pain recurred. As a result of the NZ reports, the World Health Organization (WHO) Collaborating Centre for the International Monitoring of Adverse Drug Reactions (Uppsala Monitoring Centre) has added the terms *pain trauma activated* and *pain inflammation activated* to the WHO Adverse Reactions Terminology (WHOART).

Two of the reports presented concerned patients who had not had pain at the site of recurrence for several years. In report 13, the patient had previous surgery for varicose veins and pain occurred at this site following 100 mg of oral sumatriptan (Table 1). Low-grade subclinical chronic pancreatitis seems a likely explanation for the pain described in report 8 (Table 2). This pain mimicked that of an acute attack 5 years previously.

Antimigraine Mechanism.—Serotonin (5-hydroxytryptamine [5-HT]) is involved as a neurotransmitter at many sites in the central nervous system and periphery where it stimulates 5-HT receptors and receptor subtypes. The antimigraine effect of sumatriptan is ascribed to 2 main effects. Stimulation of the 5-HT_{1B} receptor leads to the first effect: vasoconstriction of the cranial arteries. The blood supply to the meninges (assumed to be increased during migraine) is thereby reduced. The other effect is due to stimulation of presynaptic 5-HT_{1D} receptors. These receptors are located on the endings of the primary nociceptive nerve fibers in the peripheral and central nervous system. Since sumatriptan does not (easily) pass the blood-brain barrier, it primarily activates peripheral 5-HT_{1D} receptors. This inhibits neurogenic inflammation by inhibiting the release of the neuropeptides CGRP (calcitonin gene-related peptide), VIP (vasoactive intestinal peptide), and substance P.[4,5]

Possible Mechanism for Pain Activation.—The above mechanisms of action for sumatriptan explain the reduction of the pain of migraine but not the phenomenon of pain activation at other sites. The mechanisms involved in the treatment of migraine pain may, in fact, contribute indirectly to the phenomenon of pain activation. Serotonin is a major component of the inflammatory chemical milieu and contributes to the pain of tissue injury via actions on multiple receptor subtypes.[6] It is known to be involved with pain sensitizing at inflammatory sites and in pain processing.[5]

The binding of sumatriptan with the 5-HT_{1B} and 5-HT_{1D} receptor subtypes may disrupt the physiological balance between serotonin and its 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-HT_7 receptors which have been demonstrated to increase pain.[7] The 5-HT_7 receptor occurs in peripheral sensory neurons, and it has been demonstrated that sumatriptan displays moderate binding affinity for this receptor.[8] It is suggested that high concentrations of sumatriptan may enhance neurogenic inflammation through activation of the 5-HT_7 receptor and that this may explain the relatively common pain experienced at the site of injection. It may also help to explain the pain activation or aggravation documented in this article.

Greater Effect of Injection.—The higher rate of pain activation with the subcutaneous formulation of sumatriptan could be explained by a greater intensity of effect than with the oral formulation. The maximum plasma concentration of sumatriptan after subcutaneous administration is higher than with the oral formulation where irregular absorption with multiple peaking is not uncommon.[9] It can therefore be expected that the injection will result in higher concentrations of sumatriptan at receptor sites, including 5-HT_7.

Lack of Reference to Pain Activation.—The Dutch Summary of Product Characteristics and the NZ data sheets for sumatriptan describe "pain" as an adverse event, but not in terms of aggravation or activation of pain.[10,11] Solomon et al describe 2 cases of pain activation in the skin, but we are not aware of other reports.[12] In particular, we have not found any reports of aggravation or activation of inflammatory disease. This latter type of reaction is of clinical importance in patients with inflammatory diseases such as rheumatoid arthritis or colitis.

Possible Class Effect.—Pain activation seems likely to be a class effect of the selective serotonergic agonists because of the pharmacological action. In addition, NL Pharmacovigilance Centre has received 2 other similar case reports, one of aggravation of pain associated with zolmitriptan following fracture of the fibula and one concerning severe leg pain with the use of naratriptan following recent surgery. Both cases showed recurrence of symptoms upon re-exposure to the respective drugs.

Clinical Relevance.—The above case series of pain activation make it advisable that prescribers should warn patients with recent injury that pain may occur at the site of injury following the use of sumatriptan. Perhaps more importantly, patients with inflammatory diseases should be warned of the possibility of activation of pain, even if the disease seems quiescent.

CONCLUSION

A plausible association has been demonstrated in 2 countries of pain activation at sites of previous trauma or inflammatory disease with the use of sumatriptan. It is more frequent with the subcutaneous than the oral formulation, but the reported incidence is low. This syndrome is of clinical importance particularly in patients with inflammatory disease. It seems likely that pain activation is a class effect of the selective serotonergic agonists used in the treatment of migraine.

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