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Sumatriptan 6 mg subcutaneous as an effective migraine treatment in patients with cutaneous allodynia who historically fail to respond to oral triptans

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Abstract The objective of the study was to assess the efficacy of 6 mg subcutaneous (SC) sumatriptan to treat migraine and the relationship between response of migraine and cutaneous allodynia in a population of migraine patients who historically failed to respond to oral triptan medications. This was an open-label study consisting of patients with migraines who historically failed to respond to oral triptan medications. Forty-three patients were asked to treat three migraine attacks with 6 mg SC sumatriptan. The primary efficacy endpoint was the percentage of patients achieving relief of headache at 2 h. Ninety-one percent of the patients responded to a single dose of SC sumatriptan 6 mg. Fifty percent of all patients were pain-free by 2 h and over 30% had a 24-h sustained pain-free response. When administered within 90 min from the onset of migraine (i.e., during the developing phase of cutaneous allodynia), SC 6 mg sumatriptan proved to be effective despite the occurrence of allodynia in a group of patients, who historically had failed to respond to oral triptan medica-

tions. These findings suggest that the window of opportunity to treat allodynic patients with injectable triptans may be longer (up to 2 h) than with oral triptans (up to 1 h).

Keywords Sumatriptan • Cutaneous allodynia • Control sensitization • Migraine • Migraine treatment

Introduction

Since the initial introduction of triptans, selective serotonin (5-hydroxy-tryptamine, 5-HT) 5-HT_{1B/1D} receptor agonists have become the treatment of choice for the relief of moderate-to-severe migraine attacks [1]. The use of triptans has been associated with reduction in both disability and productivity loss secondary to migraine [2]. The first triptan introduced in the USA was sumatriptan in a 6-mg subcutaneous (SC) injection. There are currently seven triptans available in the USA with several formulations available for delivery including oral tablets, orally disintegrating tablets, nasal sprays and SC injection [3].

Previous studies have demonstrated that 6-mg SC sumatriptan has the highest response rate for any of the available triptans. The US Headache Consortium Guidelines [4] reviewed the results of placebo-controlled trials and reported that the 14 trials of SC sumatriptan 6 mg compared to placebo demonstrate consistent superiority for both headache relief and complete relief at the 1- and 2-h time points. Two other trials compared SC and oral formulations of sumatriptan. These trials demonstrated that SC sumatriptan was significantly more effective than oral sumatriptan at both 2 and 4 h. Response to triptans may depend on the duration [5, 6] and severity of migraine attacks, but also the rapidity of achieving therapeutic concentrations [7]. Improved response to triptan medications may occur through several methods. One of these would be to increase the dose of the oral triptan [8, 9]. Another approach would be to use a SC route of administration of the drug as is available for sumatriptan. This delivery method and agent has the earliest therapeutic drug levels of any triptan. In patients who are non-responders to oral triptan, the use of a SC route of drug delivery can prove effective.

Clinical trials demonstrate that there are several other factors influencing the efficacy of triptans. The development of cutaneous allodynia (central sensitisation) is one of them.

The biology underlying central sensitisation, its development and contribution [10] to the migraine process and subsequent impact on migraine treatment, has become one of the foremost issues in headache research in the past several years. Allodynia does not occur in all patients with migraine. Burstein et al. has estimated that approximately 70% [11] of migraine patients may develop cutaneous allodynia during their attacks. The severity of the patient's migraine attacks, the patient's age and the number of years that they have had their migraines may be contributing factors to the development of allodynia [11]. Burstein and Jakubowski have suggested that in those who develop allodynia there may be a narrow window of opportunity [12] for the patient to be able to achieve pain-free results with oral triptan treatment. Once the allodynia is established, and with this the process of central sensitisation, then it is believed that the patient can only achieve resolution of the throbbing stage [13] of their pain and will not be able to achieve pain-free status for that migraine attack.

Objectives

The objective of this study was to assess the efficacy and tolerability of 6 mg SC sumatriptan in the treatment of migraine pain in a recidivist population of migraine patients who historically failed to respond to oral triptan medications for acute migraine treatment. Additionally, we attempted to assess the relationship between response to treatment and symptomatic cutaneous allodynia in this population.

Methods

This was an open-label study. Patients were selected from a population consisting of those with migraine who historically had failed to achieve relief from an oral triptan in at least 2 out of 3 attacks. Subjects were screened for a history of migraine headache with or without aura fulfilling the criteria of the International Headache Society [14]. They were required to be in good health with no concomitant cardiovascular disease or other significant medical or psychiatry illness that would affect their ability to make use of the study medication. They were required to either not be using daily preventive medications or to have a stable regimen of preventive medications for at least one month prior to study enrollment. By definition, the patients must have used triptans in the past and had a history of having been unable to achieve relief from their headache pain in at least two out of three attacks. They were required to be naïve to the use of SC sumatriptan. Subjects underwent a brief physical examination and were instructed in the use of the study medication and the completion of their headache diaries. They were provided with adequate medication to treat three headache attacks. They were instructed to return to the clinic for the end study visit upon completion of the treatment of three headaches or if they had adverse events necessitating withdrawal from the study or if they wished to withdraw from the study for other reasons.

Patients were encouraged to initiate treatment with the study medication as early as possible in the migraine regardless of pain severity or duration of the attack. Forty-three patients were enrolled. They were provided diaries to record information on their treated migraine attacks. Among the information gathered in the diaries were symptoms of cutaneous allodynia recorded by the patients at 15, 30, 45 min, and 1, 1.5, 2, 3 and 4 h. The symptoms collected to describe cutaneous allodynia included discomfort associated with: wearing a necklace or closed neck shirt and tie, wearing a ring or bracelet, wearing glasses or earrings, taking a shower, shaving or applying makeup, brushing or combing hair. The amount of discomfort caused by the allodynic symptoms were rated using a 1–4 scale (where 1 is mild discomfort, 2 – mild-to-moderate discomfort, 3 – moderate and 4 – severe discomfort).

A final diary entry was made 24 h from the onset of treatment. The primary efficacy endpoint was the percentage of patients achieving relief from headache at 2 h. Relief was defined as reduction of the pain severity from mild, moderate or severe pain to none, or from moderate or severe pain to mild pain.

Based on the demographics of the study subjects, correlations were made between the occurrence of cutaneous allodynia and migraine.

The study was conducted in accordance with the Good Clinical Practice procedures, the Declaration of Helsinki, and the US code of federal regulations concerning informed patient consent. Patients meeting all of the enrolment criteria were provided with a written informed consent approved by a nationwide independent institutional review board.

Results

Of the 50 patients providing informed consent, 43 patients took at least one dose of study medication. Four patients terminated the study before treating all three headaches. One discontinued secondary to multiple adverse events, and three withdrew consent for other reasons. Additionally, one patient had unreliable data, which was not included in the data analysis, and one patient withdrew due to SAEs without using study medication and provided no outcome data. Five patients failed to treat any attacks.

The subjects, who were almost exclusively Caucasian females, had an age range from 25 to 56 years, with a mean age of 43 years, similar to other migraine trials. All the patients had a long history of migraine headaches, ranging from seven to 43 years with a mean of 21.7 years.

The primary efficacy endpoint was the percentage of patients achieving relief from their headache at 2 h after using 6 mg SC sumatriptan (Table 1). Thirty-nine of 43 (91%) patients treating the first headache achieved relief of their headache at 2 h. Similar results were found for the second and third attacks treated. Eighty-two percent (35 patients) of the second attacks were relieved by 2 h and 72% (31 patients) of the third attacks had also responded by the 2-h endpoint.

Forty of the 43 patients (93%) had at least one attack with at least one allodynic symptom at baseline. The mean number of allodynic symptoms per attack was 2.7.

Approximately 50% of all treated headache attacks produced pain-free outcomes by 2 h. Additionally, over 30% of all attacks resulted in a 24-h sustained pain-free response. Migraine-associated symptoms declined from baseline in a similar pattern to the response of the headache intensity.

While over one-half of the patients experienced adverse events, chest symptoms and injection site reactions occurred in only about one-fourth of all patients.

As had been suggested in previous studies, as patients age they are more likely to have allodynic symptoms. We found that there was a slow gradual trend with age being somewhat more likely to increase the likelihood development of allodynia (Fig. 1). Similarly, we found that the number of years that an individual experienced migraine correlated with an increased likelihood of the individual developing allodynic symptoms (Fig. 2). The impact of duration of migraine may have been greater than the effect

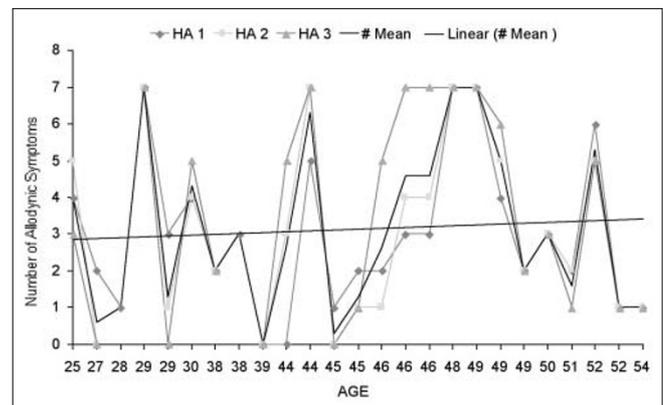


Fig. 1 Relationship between age and allodynic symptoms

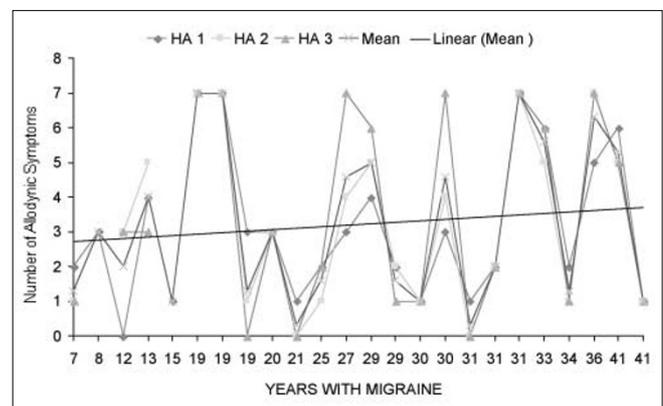


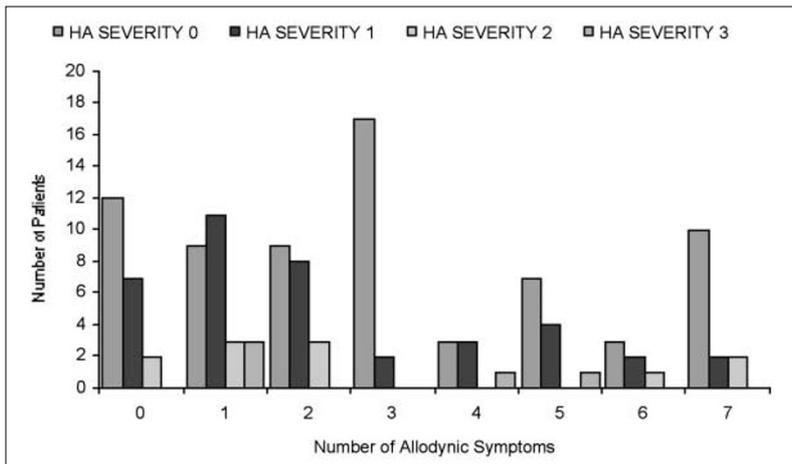
Fig. 2 Relationship between years of migraine and allodynic symptoms

Table 1 Response parameters by headache treated

Parameters	First headache	Second headache	Third headache
2-h headache relief	39 (91%)	35 (82%)	31 (72%)
2-h pain-free	24 (56%)	21 (49%)	22 (51%)
24-h sustained pain-free	14 (32%)	14 (32%)	15 (35%)
Mean time to response (min)	56	62	53
Mean time from headache onset to treatment	93	89	82

Table 2 Baseline headache severity allodynia (occurrence and mean number of symptoms per attack)

Baseline headache severity	Total number	Number with allodynia	Total number of allodynic symptoms	Mean number of allodynic symptoms per attack
1	9	8	22	2.5
2	75	55	157	2.09
3	40	40	160	4.0

**Fig. 3** Two-hour pain-free status and number of allodynic symptoms at baseline**Table 3** Change in headache pain and allodynia symptoms

Time point/relative change in headache pain	Relative change in allodynia (% of patients)		
	↓	No change	↑
15 min			
Decreased pain	15	11	0
No change in pain	24	50	10
Increased pain	0	4	8
30 min			
Decreased pain	38	19	2
No change in pain	24	28	7
Increased pain	0	1	4
1 h			
Decreased pain	76	29	1
No change in pain	4	7	3
Increased pain	1	1	1
2 h			
Decreased pain	83	25	3
No change in pain	4	6	2
Increased pain	0	0	0

of the patient's age on the development of allodynia. Baseline headache severity did not correlate with allodynia (Table 2).

The headache response was independent of the number of allodynic symptoms the patient experienced at baseline (Fig. 3). The vast majority of patients who were allodynic

at baseline were pain-free by 2 h. However, in nine of the treated attacks that were free of allodynia at baseline, patients failed to achieve a pain-free response by 2 h.

We examined the symptoms of cutaneous allodynia reported by patients associated with their headaches. When both the number that reported allodynic symptoms and their

relative intensity are considered and correlated with the change in the headache severity (Table 3), we found that the pain of migraine began to decline prior to the decline in allodynia. During the first 15–30 min after treatment, allodynia may increase despite decreasing migraine pain.

Seventy-two of the 123 treated attacks led to a pain-free outcome at 2 h. Of those 72 attacks, 28% of the time the patient was allodynia-free at baseline. By 2 h, 92% of the patients had become allodynia-free. That means, however, that in 72% of the attacks the patient already had developed allodynic symptoms at baseline and was still able to achieve a pain-free outcome by 2 h. Only 8% of the pain-free patients at 2 h maintained allodynic symptoms. With an oral triptan, once a patient has become allodynic, we would expect the patient to merely improve but not achieve a pain-free outcome. Of those patients who obtained partial relief of their migraine at 2 h, 85% had allodynia at baseline. For these patients nearly half continued to experience allodynia at 2 h.

Discussion

In a group of patients who historically had failed to respond to oral triptans, 6 mg SC sumatriptan proved to be highly efficacious and well tolerated. Approximately 80% of these patients responded to a single dose of 6 mg SC sumatriptan. Roughly half of the patients were pain-free by 2 h, with approximately a third of the patients having a 24-h sustained pain-free response. The mean time to response was one hour. The efficacy results were consistent across all three treated headaches.

Migraine-associated symptoms declined in a similar fashion to the pain. The percentage of patients with resolution of the migraine-associated symptoms ranged between 50% and 70%, consistently across the three attacks. Half of the patients experienced adverse events with about 1.8 adverse events per patient; only one patient withdrew from the study because of adverse events directly related to the study medications.

In this group of patients who lacked consistency in response to oral triptans, we found a consistent response to the study medication with over 2/3 of patients responding to all three treated headaches.

Previous studies by Burstein et al. [11, 12] have suggested that when allodynia is measured with sensory testing (QST) the presence of allodynia diminishes the ability to become pain-free with triptans. The use of QST to examine cutaneous allodynia is important for our understanding of migraine and its treatment.

Burstein's work has also suggested that factors such as age, numbers of years with migraine and migraine severi-

ty also influence the development of cutaneous allodynia in an individual. This population of migraine patients tended to verify several concepts that have previously been suggested. That is that both the ageing migraine sufferer as well the patient who has experienced migraine over more years are both more likely to have symptoms of cutaneous allodynia than their younger, more briefly afflicted, counterparts are.

Fifty-eight percent of 124 evaluable headaches produced a pain-free response by 2 h. Of these, 52 attacks, or 72% of the pain-free attacks, were associated with allodynia at baseline. By 2 h however, only 8% of these attacks still had persisting allodynia. These results would seem to provide a level of contradiction to the previous work by Burstein. This contradiction may exist for any one of several reasons given the nature of the study.

Similar results were also achieved in a study conducted by Linde et al. [15].

One of the major difficulties in a study such as this is the design of the questionnaire. At the time of the study, a clinical questionnaire to correlate patient-related symptoms of allodynia to the laboratory-verified QST findings of allodynia did not exist. The availability of such a tool now would improve the reliability of the data obtained in a similar study.

Seventy-two percent of the aborted attacks were classified allodynic at the time of treatment. These findings could be interpreted in several ways: (1) it may suggest that allodynia is an all-or-none phenomenon and, as such, the presence of allodynia does not interfere with the ability to abort the pain by SC sumatriptan; (2) it may suggest that early allodynia (i.e., developing phase) differs mechanistically from late allodynia (established phase) and that allodynic attacks were aborted because treatment was issued during the developing, rather than the established, phase of allodynia and central sensitisation. According to Burstein et al., the developing phase of allodynia (which lasts 20–120 min after onset of migraine) is mediated by an activity-dependent central sensitisation whereas the established phase of allodynia (which starts about 4 h after onset of migraine) is mediated by an activity-independent central sensitisation. In view of the second interpretation, one would propose that 50% of the patients, although allodynic at the time of treatment, were only at the developing phase whereas the other 50% had already reached the established phase of allodynia. Since the time for treatment was within 90 min in the majority of patients, we cannot favour one of these two options over the other. Only a study in which treatment is initiated no earlier than 4 h after onset of migraine, using a verified tool for recognising allodynia in the clinic, and studying subjects who report themselves to be allodynic, will be able to distinguish between these options.

In conclusion, in a population of patients who have historically failed to respond to oral triptans, sumatriptan 6 mg SC injection proved to be effective and capable of producing a pain-free response in over 50% of patients despite the occurrence of allodynic symptoms at baseline and moderate or severe pain. We found evidence in this population that the number of symptoms of cutaneous allodynia increased with increasing age and the number of years that an individual suffered from migraine attacks. The response of the patients to resolution of their

migraine headache pain and resolution of allodynic symptoms, while tending to occur in a simultaneous fashion, could in fact have resolution of migraine headache pain in advance of resolution of cutaneous allodynia reduction.

The use of an alternative approach to treatment of migraine with a more highly reliable delivery such as the SC delivery of the sumatriptan should be considered in those patients who have had a history of inconsistent or non-response to migraine specific treatments.

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