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Zolmitriptan nasal spray provides fast relief of migraine symptoms and is preferred by patients: a Swedish study of preference in clinical practice

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Abstract The objectives were to compare patient preference for zolmitriptan nasal spray with their current acute therapies for migraine (by asking whether or not they wished to continue to use zolmitriptan nasal spray), to determine patients' reasons for this choice and to evaluate efficacy of zolmitriptan nasal spray. Patients with an established diagnosis for migraine (IHC criteria) who were already receiving a migraine-specific treatment were enrolled in an open-label, clinical experience study in a clinical practice. Patients were invited to treat up to 6 migraine attacks with 5 mg of zolmitriptan nasal spray. Data from 232 patients were analysed. Most patients (89%) were already using a triptan as migraine treatment. The majority of patients (68.5%) wished to continue using zolmitriptan nasal spray; the most common reason being its fast onset of action. Almost half of the patients (47.8%) wishing to continue with zolmitriptan nasal spray reported few or no adverse events as a motivating reason. Of patients currently using sumatriptan nasal spray, tablet or injection, 90.9%, 74.2% and 70.6%, respectively, wanted to continue using zolmitriptan nasal spray. Most patients are satisfied with, and wish to continue using, zolmitriptan nasal spray.

Key words Zolmitriptan nasal spray • Patient preference

Introduction

Migraine is a paroxysmal disorder characterised by attacks of headache, nausea, vomiting, photo- and phonophobia. It is a common condition that affects 5–17% of the general population and is approximately 2–3 times more common in women than in men [1, 2]. The main goals in the treatment of migraine are to provide patients with highly effective and rapid relief from migraine symptoms during an attack [1, 3].

The selective 5-$HT_{1B/1D}$ receptor agonist or 'triptan' drug class (sumatriptan, zolmitriptan, rizatriptan, naratriptan, almotriptan, frovatriptan and eletriptan) is well-established in the acute treatment of migraine. The selectivity of the triptans for the 5-$HT_{1B/1D}$ receptors make them effective migraine-specific treatments, providing relief from headache and associated symptoms, with a low incidence of adverse effects [4, 5]. All of the currently available oral triptans have broadly comparable efficacy and tolerability. However, some triptans are also available in various other formulations, such as orally disintegrating tablets, nasal sprays or subcutaneous injections. Differences have emerged in the ability of specific formulations to satisfy patient treatment preferences; for example, orally disinte-

grating tablets provide a convenient and discreet treatment option, without the need to swallow liquids. Consequently, when selecting a triptan, consideration should be given to patient choice, as well as to an individual's previous response to therapy [6]. Patient preference and treatment outcomes are thus important factors in providing optimal migraine treatment, as this will ultimately influence compliance [7, 8].

Zolmitriptan, the first of the second generation of triptans, has a higher oral bioavailability and longer plasma half-life than sumatriptan, the first triptan available to patients [5, 9]. Zolmitriptan conventional oral tablets have been available for several years and are established as a fast, effective and well-tolerated acute treatment for migraine [10, 11]. An orally disintegrating tablet formulation, which does not require additional fluid intake, has also been available since the late 1990s. The convenience of this formulation may facilitate earlier intervention [12], an approach that has been shown to result in a better response to therapy among migraine patients in recent studies [13, 14]. Despite this, an oral formulation may not be suitable for the treatment of all migraine attacks, particularly those associated with nausea and vomiting. In addition, gastric stasis is a common feature of migraine attacks, and this can reduce or delay the absorption of orally administered medications [15, 16]. Consequently, a nasal spray formulation of zolmitriptan has been developed in an attempt to overcome the limitations of oral therapy.

Zolmitriptan nasal spray is a single-dose device that delivers 5 mg of zolmitriptan in an aqueous solution (0.1 ml) to one nostril. The nasal spray provides particularly rapid onset of relief of migraine, with a significant headache response compared with placebo being apparent within 10 min of dosing [17]. Importantly, this rapid onset is also observed in patients with pre-treatment nausea. In a dose-ranging study, a complete headache response (defined as a 2-h headache response, no recurrence and no use of escape medication within 24 h) was reported for 49% of attacks in patients receiving zolmitriptan nasal spray 5 mg, compared with 43% of attacks in those receiving the 2.5 mg oral tablet and 14% of attacks in placebo recipients [18]. Clinical studies have shown that the spray is well tolerated, with the majority of adverse events of short duration and mild to moderate intensity [18, 19].

Preference, efficacy and tolerability data obtained from use in a clinical practice setting provide important information on zolmitriptan nasal spray, to supplement those data obtained from clinical trials. Therefore, the aim of this study was to explore whether patients wished to continue to use zolmitriptan nasal spray or their current therapy in the acute treatment of migraine and to analyse which factors influenced this choice, and also to provide efficacy and tolerability data in this clinical practice setting.

Methods

This study was an open-label study conducted at the Gothenburg Migraine Clinic in Sweden between 1 February 2002 and 30 April 2003. Female and male patients with an established diagnosis of migraine according to International Headache Society criteria were recruited. The vasty majority of patients were receiving migraine-specific treatment at the time. Dissatisfaction with, or failure to respond to, current therapy was not a requirement for inclusion in the study.

Patients visiting the clinic for a follow-up visit or for renewal of prescription were invited to use zolmitriptan nasal spray 5 mg to treat up to 6 consecutive acute attacks of migraine, to see if treatment efficacy was improved compared with current therapy. The individual attack frequency decided the period of time needed to complete the study, but in the vast majority of patients the feedback was obtained within three months. A large emphasis was placed on instructing (written and oral) patients on the correct technique of administering zolmitriptan nasal spray. Zolmitriptan was prescribed in the usual manner with patients paying the usual fees to fill a prescription.

Patients were, as usual, instructed to treat early on in the headache phase of the migraine attack. Patients were allowed to take more than one dose of zolmitriptan nasal spray to treat recurrent symptoms but no more than two doses per 24 h.

Data were collected using a patient questionnaire. The first part of the questionnaire was distributed when patients received the initial prescription for zolmitriptan nasal spray. In this section, patients were asked to provide details of migraine history. Patients were also asked about onset and duration of efficacy of zolmitriptan nasal spray, migraine recurrence, and the nature of any adverse events.

After patients returned the first part of the questionnaire to the clinic, the investigator telephoned the patient and conducted a short telephone interview to complete the second part of the questionnaire. This preference section of the questionnaire was to be completed after patients had treated up to 6 migraine attacks with zolmitriptan nasal spray. In the second part of the questionnaire patients were asked to indicate whether zolmitriptan nasal spray was better than, similar to, or not as good as current medication, and whether or not they wanted to continue using zolmitriptan nasal spray, and reasons for wanting to continue or discontinue were ascertained. A number of possible reasons for continuing or not continuing were suggested in the questionnaire (Fig. 1). Patients could give more than one reason and were prompted to suggest alternative reasons.

The results of the questionnaire were assessed for the treatment group as a whole, and according to previous triptans used. Data are presented here for the overall treatment group and for a subset of patients who were previously treated with sumatriptan, as this was the largest subgroup of patients, and sumatriptan is currently the most commonly used specific anti-migraine treatment in Sweden. In the second part of the questionnaire, patients also rated the overall effect of zolmitriptan nasal spray using a 10-point graded analogue scale (where 0=worst possible effect and 10=best possible effect) to assess headache pain.

The primary endpoint was whether patients wanted to continue treatment with zolmitriptan nasal spray or current treatment.

Would you like to continue to use zolmitriptan nasal spray?

If yes, why? (>1 choice allowed)
1. Complete relief of migraine pain
2. Complete relief of migraine-associated symptoms
3. Fast onset
4. Didn't make me tired/sleepy/drowsy
5. Had a long duration of efficacy
6. Only needed one dose for migraine relief
7. No recurrence
8. Fast return to normal activity
9. Few or no adverse advents (e.g. unusual (bad) taste, sweating, fatigue/drowsiness, chest tightness)
10. Other…

If no, why? (>1 choice allowed)
11. Poor relief of migraine pain
12. Poor relief of migraine-associated symptoms
13. Slow onset
14. Made me tired/sleepy/drowsy
15. Had a short duration of efficacy
16. Too many doses needed for migraine relief
17. Recurrence
18. Did not give a fast return to normal activity
19. Adverse advents (e.g. unusual (bad) taste, aggression, joint pain, bad mood/depression)
20. Other…

Fig. 1 The second part of the patient questionnaire, completed after treating up to 6 attacks with zolmitriptan nasal spray

Secondary endpoints included:
- reasons for wanting to continue zolmitriptan nasal spray treatment,
- rating of overall effect of zolmitriptan nasal spray,
- speed of onset of efficacy,
- duration of action, and
- adverse events.

Statistical methods

No formal statistical analyses were performed, as this was an open assessment of a single treatment (zolmitriptan nasal spray). Results are presented using descriptive statistics.

Results

A total of 276 patients were recruited and 232 patients completed the study and provided feedback. As shown in Table 1, 89% of patients were female, the mean age was 43 years (range 13–74 years), the mean age at migraine onset was 19 years (range 4–50 years) and patients had a mean attack frequency of four attacks per month. The majority of patients experienced migraine without aura (59%).

Of the 232 patients who completed the study and provided feedback, 89% received triptan therapy for the acute treatment of migraine attacks prior to study entry (Table 2). The majority of patients who had been treated with a triptan prior to study entry used sumatriptan (87%; Table 2), with an approximately equal number of patients receiving sumatriptan injection, tablet and nasal spray formulations (n=51, 62 and 55, respectively); some patients received >1 drug and/or formulation.

Table 1 Baseline characteristics of 232 patients using zolmitriptan nasal spray for the acute treatment of migraine

Characteristic	
Gender	
Female, n (%)	206 (89)
Male, n (%)	26 (11)
Mean age (years)	43 (range, 13–74)
Type of migraine, n (%)	
Without aura	138 (59)
With aura	16 (7)
With and without aura	78 (34)
Mean age of onset (years)	19 (range, 4–50)
Mean attack frequency (attacks/month)	4 (range, 0–12)
Duration of migraine (years)	24 (range, 2–57)

Table 2 Current therapy for the acute treatment of migraine prior to trying zolmitriptan nasal spray

Current treatment	Patients (%)* n=232
Triptans	206 (89)
Ergots	10 (4)
NSAIDs	19 (8)
Other	43 (19)
Current triptan therapy	**Patients (%)* n=204†**
Sumatriptan	177 (87)
Zolmitriptan	35 (17)
Rizatriptan	23 (11)
Naratriptan	12 (6)
Eletriptan	6 (3)

*Each patient can be represented in more than one treatment group
†206 patients indicated previous use of triptans, but only 204 patients detailed the actual triptan taken

Patient preference for treatment

Overall treatment group

After using zolmitriptan nasal spray for the acute treatment of up to 6 migraine attacks, 116 patients (50.0%) considered zolmitriptan nasal spray to be better than current therapy. In total, 159 patients (68.5%) expressed a wish to continue using zolmitriptan nasal spray. Reasons for this included: a fast onset of action (75.5% of patients), only one dose required (58.5%), complete pain relief (56.0%), fast return to normal activities (52.2%), a long duration of action (49.7%) and few or no adverse events (47.8%) (Fig. 2).

When asked to rate the overall effect of zolmitriptan nasal spray using the visual analogue scale, the mean score for those patients wishing to continue using zolmitriptan nasal spray was 8.0, whereas the mean score for those not wishing to continue using zolmitriptan nasal spray was only 2.9.

In terms of onset of efficacy, 22.4% and 56.5% of patients reported headache relief within 15 and 30 min of administration, respectively, increasing to 77.6% within the first 60 min (Fig. 3). Only 10.3% of patients reported no headache relief. Over the period following treatment, headache relief was maintained (headache relief at 2 h with no recurrence for 24 h) in 37.5% of patients who used a single dose of zolmitriptan nasal spray. Over the series of migraine attacks treated with zolmitriptan nasal spray, 22% of patients reported that migraine symptoms always recurred, with 45% reporting this sometimes. However, recurrence did not seem to be a particular issue for most patients, with 59% of patients stating the reason for wishing to continue with zolmitriptan nasal spray as "number of doses needed" and 26% stating (lack of) "recurrence".

Patients previously treated with sumatriptan

Of the 55 patients who were using sumatriptan nasal spray prior to study entry, 36 (65.5%) considered zolmitriptan nasal spray to be better compared with their previous experience, and 50 (90.9%) wished to continue using zolmitriptan nasal spray. While the most common reason for wanting to continue with zolmitriptan nasal spray was the same as in the total group (i.e. a faster onset of action [70.0% of patients]), in this subgroup, few adverse events (58.0%) and the need for only one dose to provide pain relief (56.0%) were the second and third most common reasons (Fig. 4). These percentages are similar to those in the total group (see above).

Similarly, high proportions of patients who had been treated previously with sumatriptan tablets or subcutaneous injection stated that they wanted to continue using zolmitriptan nasal spray (74.2% and 70.6% of patients, respectively). Again, speed of onset was the most common reason given for this choice over both formulations, but complete relief of pain and fast return to normal activities were the second most common reasons influencing this choice over sumatriptan tablet and subcutaneous injection, respectively.

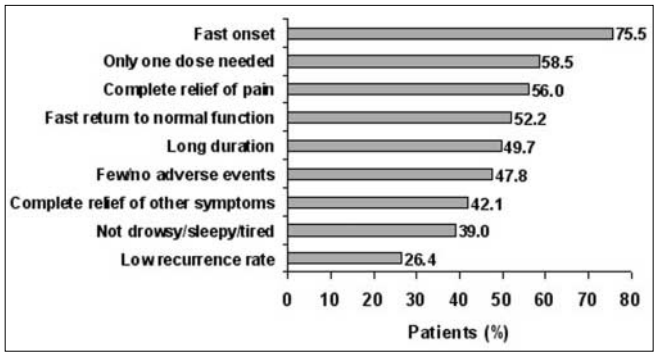

Fig. 2 Patients' reasons for wishing to continue using zolmitriptan nasal spray for the acute treatment of migraine attacks (n=159)

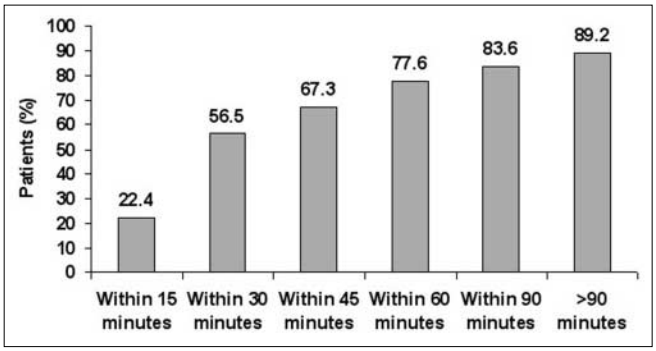

Fig. 3 Onset of efficacy (cumulative frequency) in 232 patients receiving zolmitriptan nasal spray for the acute treatment of migraine attacks

Patients previously treated with non-triptan medications

Among the 43 patients previously treated with a non-triptan medication, 28 (65.1%) wished to continue using zolmitriptan nasal spray. Within this patient subgroup, the most common reason for wishing to continue with zolmitriptan nasal spray was again its fast onset of action (85.7%), followed by the need for only one dose to provide pain relief (71.4%) and fast return to normal activities (57.1%).

Tolerability

Adverse events were reported by 118 patients (50.9%) using zolmitriptan nasal spray at some time during the course of this study. A total of 172 adverse events were recorded, with the six most common being: tiredness/drowsiness (36 events;

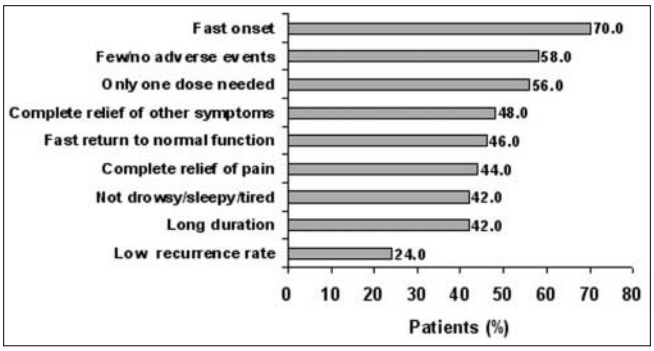

Fig. 4 Patients' reasons for wishing to continue using zolmitriptan nasal spray (patients currently using sumatriptan nasal spray) (n=55)

15.5% of patients), unusual (bad, bitter) taste (31 events; 13.4% of patients), throat discomfort (25 events; 10.8% of patients), nausea (14 events; 6.0% of patients), dizziness (8 events; 3.4% of patients) and allodynia/skin sensitivity (8 events; 3.4% of patients). None of the adverse events were considered to be serious, but they did have an impact on the patients' choice of continuing treatment. Of the 73 patients who did not wish to continue using zolmitriptan nasal spray, 33 (45.2%) stated adverse events as one of the contributory reasons. Conversely, of the 159 patients who wished to continue using zolmitriptan nasal spray, 76 (47.8%) stated few or no adverse events compared with current therapy as a contributory reason for wishing to continue.

Discussion

The present study explores patient preference for zolmitriptan nasal spray compared with their usual acute migraine therapy, by asking whether they wanted to continue to use this new formulation of zolmitriptan. The majority of patients (89%) used a triptan before study entry; 86.8% of triptan users had been treating with at least one formulation of sumatriptan. The most important finding of this study is that almost 70% of migraine patients expressed a wish to continue using zolmitriptan nasal spray rather than current therapy. A fast onset of action was the most important factor in choosing to continue using zolmitriptan nasal spray. The fast onset of action of zolmitriptan nasal spray has also been documented in clinical trials [17, 18, 20]. These new results confirm those of previous studies, which indicated that a faster onset of action is the main reason for preference of one anti-migraine treatment over another [21, 22].

Assessment of preference data for the subset of patients who were using sumatriptan formulations as current anti-migraine treatment prior to study entry also produced interesting results. Over 90% of patients currently using sumatriptan nasal spray wanted to continue using zolmitriptan nasal spray, with speed of action, few or no adverse events and only one dose needed being the most common reasons. For patients using sumatriptan tablets and subcutaneous injection prior to study entry, over 70% in each subgroup wished to continue using zolmitriptan nasal spray. In addition, almost two-thirds of patients previously treated with non-triptan medications wished to continue using zolmitriptan nasal spray.

Overall, adverse events were reported by 118 patients (50.9%) using zolmitriptan nasal spray during this study. The most commonly reported adverse events were tiredness/drowsiness, unusual taste and throat discomfort. This adverse event profile is consistent with that reported in the clinical development programme. For example, in a clinical trial in which 236 patients received zolmitriptan nasal spray 5 mg, the proportion of patients reporting at least one adverse event was 49.2% [18].

The underlying reasons for wishing to continue using zolmitriptan nasal spray in preference to sumatriptan nasal spray are not certain, but it is possible that this may be due to variations in the pharmacokinetics and pharmacodynamics of the two drugs [23]. For example, following intranasal administration of zolmitriptan nasal spray 5 mg or sumatriptan nasal spray 20 mg, it can be calculated that in both cases approximately 0.5–0.7 mg is absorbed across the nasal mucosa. The initial efficacy of zolmitriptan is, however, expected to be better, as the affinity of zolmitriptan for the 5-HT_{1B} receptor and the $5HT_{1D}$ receptor is 5 and 8 times higher, respectively, than that of sumatriptan. In addition, plasma concentrations of the active metabolite of zolmitriptan 183C91, which is about 5 times more potent than the parent compound, start to build up after approximately 30–60 min [23]. Hence, although the plasma concentrations of the two drugs are similar, zolmitriptan would be expected to have a greater efficacy for any given concentration, due to this higher receptor affinity.

In terms of possible taste tolerability differences between the two drugs, this is likely to be due to the absolute quantity of drug passing from the nasal cavity via the nasopharynx to the gastrointestinal tract. Zolmitriptan nasal spray is administered as a 5 mg dose compared with a 20 mg dose for sumatriptan nasal spray. For both drugs, approximately 0.6 mg is absorbed through the nasal mucosa. Thus, the most likely explanation for a possible taste tolerability difference is that almost all (19.4 mg) of the administered sumatriptan is cleared from the nasal cavity to the pharynx and throat, and then swallowed. In contrast, only 4.4 mg of zolmitriptan (about 5 times less) travels via the same route, and thus is associated with better taste tolerability than sumatriptan. Needless to say, these assumptions have to be assessed in a direct comparative RCT. Based on these considerations, however, it is anticipated that zolmitriptan nasal spray will have a superior efficacy profile and better taste acceptance than sumatriptan nasal spray [23].

Having tested zolmitriptan nasal spray up to six times, about 30% of patients did not wish to continue treatment with this new formulation of zolmitriptan. This highlights the individual nature of response and patient preferences with acute migraine therapy, and the need for tailored therapy. For example, patients have traditionally favoured the oral route of administration for anti-migraine medications [6], and therefore may prefer to continue using a familiar formulation. Others may be accustomed to using sumatriptan subcutaneous injection, which has demonstrated fast and high efficacy [24].

When prescribing medication for patients with migraine, physicians should respect patients' treatment preferences and select drugs that most closely meet patients' needs. Patients are more likely to be compliant and satisfied with treatment if preferences and expectations are taken into account. By increasing the number of available delivery formulations it is possible to better match the patients' needs and preferences to a specific migraine therapy. Zolmitriptan nasal spray is particularly useful for patients who have an inconsistent response to oral medication, who do not have immediate access to liquids or those for whom oral formulations do not provide sufficiently fast relief. Accordingly, the advantages of zolmitriptan nasal spray make it a very useful treatment choice for optimal migraine management.

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