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Zolmitriptan versus a Combination of Acetylsalicylic Acid and Metoclopramide in the Acute Oral Treatment of Migraine: A Double-Blind, Randomised, Three-Attack Study

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Key Words

Migraine · Zolmitriptan · Acetylsalicylic acid · Metoclopramide · Clinical trial

Abstract

This multicentre, randomised, double-blind study compared oral zolmitriptan 2.5 mg with a combination of oral acetylsalicylic acid 900 mg and metoclopramide 10 mg as acute anti-migraine therapy for 3 migraine attacks. In total, 666 patients took at least one dose of study medication (326 took zolmitriptan and 340 took acetylsalicylic acid plus metoclopramide). The percentage of patients with a 2-hour headache response after the first dose for all 3 attacks (the primary end point) was 33.4% with zolmitriptan and 32.9% with acetylsalicylic acid plus metoclopramide [odds ratio 1.06, 95% confidence interval (CI) 0.77–1.47; p = 0.7228]. For the majority of secondary end points, the two treatments demonstrated comparable efficacy. However, post hoc analysis showed that significantly more patients receiving zolmitriptan were free of pain 2 h after the first dose in all 3 attacks compared with patients receiving acetylsalicylic acid plus metoclopramide (10.7 vs. 5.3%; odds ratio 2.19, 95% CI 1.23–4.03; p = 0.0095). In addition, post hoc analysis showed that the overall 2-hour pain-free response rate was consistently higher with zolmitriptan (34.6%) than with acetylsalicylic acid plus metoclopramide (27.9%) (odds ratio 1.40, 95% CI 1.09–1.78; p = 0.007). Both treatments reduced migraine-associated nausea, vomiting, phonophobia and photophobia. There were no important inter-group differences with respect to the onset of meaningful migraine relief, the frequency of headache recurrence, the usage or efficacy of a second dose of medication or the use of escape medication. However, at the last attack, the proportion of patients who expressed overall satisfaction with the treatment was significantly higher in the zolmitriptan group, i.e. 83.7%, versus 75.0% with acetylsalicylic acid plus metoclopramide (p = 0.0346). Both agents were well tolerated. Adverse events were reported by 40.8% (133/326) of zolmitriptan-treated patients and 29.1% (99/340) of those treated with acetylsalicylic acid plus metoclopramide. The incidence of withdrawals due to adverse events was very low with both zolmitriptan (0.9%) and the combination regimen (1.5%); the latter percentage included 1 patient who withdrew from the study due to phlebitis, which was classified as a serious adverse event. This study showed that zolmitriptan is effective and well tolerated for the acute treatment of moderate to severe migraine. Zolmitriptan was at least as effective as acetylsalicylic acid plus metoclopramide in achieving a 2-hour headache response, but significantly more effective than the combination therapy for other end points, including the 2-hour pain-free response.

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Introduction

Migraine is a chronic, debilitating disorder associated with considerable indirect economic costs to society, as well as reduced quality of life for patients [1–5]. The prevalence of migraine in France [6] and other developed countries [7–10] is estimated to be approximately 15–20% in women and 6% in men.

Conventional therapy for migraine consists of acute treatment to abort attacks and, for patients who suffer 2 or more attacks per month, possible prophylactic therapy. Analgesics such as acetylsalicylic acid or paracetamol or non-steroidal anti-inflammatory agents (NSAIDs) are commonly used for acute therapy. Analgesics are considered moderately effective in the treatment of mild to moderate migraine headaches, while NSAIDs can be effective in moderate attacks [11]. However, NSAIDs have the disadvantages of gastrointestinal intolerability, various contra-indications and drug interactions [12]. In addition, as none of these agents treat the nausea and vomiting often associated with migraine, they are often combined with anti-emetics such as metoclopramide. Concomitant treatment with an anti-emetic has the additional advantage of improving gastrointestinal motility and therefore absorption of the analgesic, which can be impaired by emesis or gastric stasis during an attack. In France, the combination of acetylsalicylic acid and metoclopramide is considered the standard acute oral therapy for migraine, with an approved dosage regimen of 900 mg of acetylsalicylic acid plus 10 mg of metoclopramide [13].

Acute anti-migraine therapy has been advanced in recent years by the development of specific 5-hydroxytryptamine ($5HT_{1B/1D}$) receptor agonists. Unlike traditional analgesics, these agents act specifically upon the serotonergic trigeminovascular system central to the neurovascular theory of migraine pathophysiology [14, 15].

Zolmitriptan is a selective $5\text{-}HT_{1B/1D}$ receptor agonist with inhibitory activity on the trigeminovascular system, both peripherally and centrally [16–18]. This central anti-migraine activity of zolmitriptan may confer additional benefits in migraine therapy [17]. Oral zolmitriptan has proved highly effective in double-blind, placebo-controlled clinical trials, with a 2.5-mg dose exhibiting an optimal balance between efficacy and tolerability [19, 20]. Oral zolmitriptan is rapidly absorbed, with significant migraine relief shown to occur within 45 min compared with placebo [21].

This study compared zolmitriptan with the combination of acetylsalicylic acid and metoclopramide as acute oral anti-migraine therapy. The efficacy of the agents in the treatment of 3 migraine attacks was assessed in order to examine the consistency of efficacy in the clinical setting.

Methods

Study Population

Male and female patients aged 18–65 years were recruited at centres throughout France. All patients had an established diagnosis of migraine [22] with symptoms of at least 1 year's duration and an age of onset < 50 years. Patients had to have experienced between 1 and 6 attacks per month with headache of moderate to severe intensity for the 3 months prior to inclusion in the study. Patients were required to comply with all trial procedures, including the completion of diary cards, and to be able to distinguish non-migraine headaches from typical migraine without aura. All patients provided written, informed consent.

Patients with basilar, ophthalmoplegic or hemiplegic migraine headache were excluded. Other exclusion criteria were: non-migraine headache on more than 10 days per month over the preceding 6 months; pregnancy, lactation or inadequate contraception in female patients; a recent history of repetitive, prolonged use of analgesics for the acute treatment of headache; ischaemic heart disease, vascular spasms or electrocardiogram evidence of clinically significant arrhythmias or Wolff-Parkinson-White syndrome; uncontrolled hypertension (systolic blood pressure 160 mm Hg or diastolic blood pressure 95 mm Hg); gastric or peptic ulcer disease; haemorrhagic disease; any condition in which intestinal stimulation could constitute a risk (e.g. gastrointestinal haemorrhage or intestinal obstruction or perforation); known or suspected phaeochromocytoma; use of monoamine oxidase inhibitors, oral anticoagulants, serotonin uptake inhibitors or methotrexate; serious adverse events during treatment with other $5HT_{1B/1D}$ receptor agonists; salicylate hypersensitivity; a history of tardive dyskinesia with neuroleptics; a recent history of alcohol or drug abuse; any medical or psychiatric condition in which the study medications could create an additional risk for the patient, and receipt of an investigational drug in the 30 days before screening. Patients could only enter the trial once.

The trial was designed and conducted in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki.

Study Design

This was a multicentre, double-blind, parallel-group study. Using a computer-generated randomisation list, eligible patients were randomised to receive zolmitriptan 2.5 mg or acetylsalicylic acid 900 mg plus metoclopramide 10 mg. Patients were initially supplied with study medication for the treatment of 1 attack. Patients took one dose of study medication (consisting of active treatment and double-dummy placebo) for the treatment of a moderate or severe migraine headache within 6 h of the start of headache (or within 6 h of waking if the headache was present on awakening), provided they had been free from any previous migraine for at least 24 h.

Patients could take a second dose of study medication between 2 and 24 h after the first dose if the headache persisted or recurred. Patients who did not experience adequate symptomatic relief 2 h after the second dose could take prescribed escape medication.

Patients recorded on a diary card the details of the migraine at baseline, the treatment taken, the therapeutic response and their satisfaction with the study therapy (poor, fair, good or excellent). Patients were required to return to the study centre within 15 days of treating the first attack. Medication and diary cards were provided for the treatment of 2 further attacks. Within 15 days of the third attack, patients returned to the study centre. Patients were withdrawn from the study if they did not experience a migraine attack within 2 months of randomisation.

Zolmitriptan was supplied as 2.5-mg oral tablets and the acetylsalicylic acid plus metoclopramide combination as oral sachets containing 900 mg of acetylsalicylic acid and 10 mg of metoclopramide. Blinding was maintained using a double-dummy technique. Escape medication (analgesic, anti-emetic or sedative) was prescribed by the investigator on trial entry. The use of acetylsalicylic acid as escape medication was restricted to a maximum of 1 g because of its use in one treatment arm. If additional analgesia was required, paracetamol was used. Acute anti-migraine therapies were used for migraines not treated with trial medication, but sumatriptan and ergot derivatives were not permitted within 24 h before the treatment of an attack with study medication or for 12 h after a second dose of study medication. Preparations of intranasal or injectable dihydroergotamine and combinations of ergotamine plus caffeine (with or without cyclizine) were specifically prohibited. Long-term prophylactic migraine treatments were permitted provided they were kept consistent throughout the study.

Efficacy

The primary efficacy end point was the proportion of patients with a headache response 2 h after the first dose of trial medication in all 3 attacks. Headache response was defined as a reduction in headache severity from severe or moderate at baseline to mild or none. In the few patients who entered the study with mild headaches at baseline, a response was considered as a headache that remained mild or was absent 2 h after the first dose, as patients treating a mild attack to prevent the development of a moderate or severe attack would regard success as a positive response.

The secondary efficacy end points were: 2-hour headache response rate after the first dose in the first attack; 2-hour headache response rate after the first dose for at least 2 of 3 attacks; pain-free response rate 2 h after the first dose in all 3 attacks; the time to first perceived onset of meaningful migraine relief (MMR; a subjective global assessment of the overall treatment benefit) after the first dose during the last attack, and the patients' satisfaction with the treatment during the last attack. Given the increasing discussion in recent years regarding the importance of the IHS pain-free end point [23–25], a post hoc analysis of the pain-free response after 2 h across all attacks treated was also conducted. If a patient took escape medication or a second dose of study medication within 2 h, they were classed as non-responders.

Other assessments included the proportion of patients responding during each attack according to the migraine sub-type (i.e. migraine with and without aura and menstrual migraine) and patient sub-group (i.e. gender, age and weight), the requirement for escape medication, the proportion of patients with headache recurrence and the effect of study therapy on migraine-associated symptoms (nausea, vomiting, photophobia and phonophobia).

Tolerability

All patients in the intent-to-treat (ITT) population were included in the tolerability assessment. The severity, duration, treatment, outcome and relationship to study medication of all adverse events were recorded by the investigator. Adverse events were considered serious if they resulted in death, were life-threatening, required hospitalisation, produced disability, required medical intervention to prevent permanent impairment or resulted in a congenital abnormality. Patients could withdraw from the study at any time and could be withdrawn by the investigator if deemed necessary.

Sample Size Calculation and Statistical Analysis

The primary end point was the proportion of patients with a 2-hour headache response in all 3 attacks. In a previous study, acetylsalicylic acid plus metoclopramide produced response rates of 45.0, 36.0 and 34.0% in the first, second and third attacks, respectively [26]. It was assumed that 20% of patients would respond in all 3 attacks following treatment with acetylsalicylic acid plus metoclopramide. Thus, the midpoint of these figures (20.0%) was used for the sample size calculation in the current trial. Assuming a clinically relevant difference between treatment groups of 12% (at the 5% significance level and 90% power), 300 evaluable patients were required in each treatment group. Assuming that 20% of patients would be unevaluable [26, 27], the trial therefore required a total of 375 patients to be recruited into each group.

The primary population for analysis was the ITT population, comprising all patients who received at least 1 dose of trial medication. A per-protocol population, comprising all ITT patients who adhered closely to the protocol, was also defined. Binary logistic regression analysis was used to model the proportion of responding patients (in each population) within each treatment group. The model included treatment and baseline headache severity (categorised as either severe – at least 2 of the 3 migraines causing severe pain at baseline – or not severe). The treatment by baseline severity interaction was found to be not significant and so was removed from the model. Using the results of logistic regression, the odds ratios between zolmitriptan and acetylsalicylic acid plus metoclopramide together with 95% confidence intervals (CIs) were computed. In addition, 95% CIs were calculated for the percentage of responders. Statistical significance was defined as $p < 0.05$.

All secondary end points were analysed using the ITT population only. The proportions of patients with a 2-hour headache response to the first dose in the first attack and in 2 of 3 attacks and with a 2-hour pain-free response in all 3 attacks were analysed in the same manner as the primary end point. The times to perceived MMR during the last attack were analysed by survival techniques. The Cox proportional hazards model was used to determine if there was a difference between the treatment groups based upon results of the Wald χ^2 test. The model controlled for baseline severity as described for the primary end point analysis. The patients' satisfaction with the treatment response at the last attack was analysed by logistic regression analysis using the proportional odds model, controlling for baseline severity.

A post hoc statistical analysis was performed to determine the proportions of patients with a pain-free response across the 3 migraine headaches treated, using the generalised estimating equations for binary data. The analysis allowed for the factors of treatment and baseline headache intensity. The estimated treatment odds ratios are presented, together with the 95% CIs and associated p values. Statistical significance was denoted as $p < 0.05$.

Table 1. Summary of patient numbers and reasons for withdrawal

Population	Zolmitriptan group	Acetylsalicylic acid plus metoclopramide group
Patients randomised	356	363
Patients treated		
First migraine attack (ITT)	326	340
Second migraine attack	298	318
Third migraine attack	285	291
Per-protocol population	217	223
Reasons for withdrawal		
Protocol non-compliance	11 (3.1)	9 (2.5)
Withdrew informed consent	9 (2.5)	3 (0.8)
Adverse event	3 (0.8)	5 (1.4)
Patient lost to follow-up	1 (0.3)	1 (0.3)
Other[1]	45 (12.6)	50 (13.8)
Not recorded	2 (0.6)	2 (0.6)

Figures in parentheses represent percentages.

[1] Eighty-eight percent of 'other' reasons were associated with lack of or an insufficient number of migraine headaches or failure to treat migraine headaches with study medication. The remaining 'other' reasons included pregnancy, perceived lack of efficacy of study medication, fear of adverse events, poor compliance, non-availability of patient, stolen medication, new concomitant medications, new medical condition or laboratory abnormality.

Results

A total of 778 eligible patients from 169 centres were screened, of whom 719 from 164 centres were randomised. Of these patients, 666 received at least 1 dose of trial medication: 326 received zolmitriptan and 340 received acetylsalicylic acid plus metoclopramide (the ITT population). A total of 226 patients (109 on zolmitriptan, 117 on acetylsalicylic acid plus metoclopramide) had protocol violations or deviations leading to exclusion of data. Thus, 440 patients (217 on zolmitriptan, 223 on acetylsalicylic acid plus metoclopramide) composed the per-protocol population. The patient numbers in each group throughout the trial and the reasons for withdrawal are summarised in table 1.

The treatment groups were comparable with respect to the patients' demographic characteristics and migraine headache histories (table 2). Typically, most of the patients were female. In each group, >95% of patients were Caucasian. In both groups, patients had experienced approximately 3 migraine headaches per month in the 3 months preceding trial entry and more than 80% of patients reported migraine-associated symptoms.

Approximately half of the patients in each treatment arm had previously been treated with acetylsalicylic acid plus metoclopramide, with a good or fair response being reported by roughly 55% of those in each group. Approximately 80% of patients had previously received or were currently receiving treatment with acetylsalicylic acid or NSAIDs alone, with a good or fair response reported in approximately 45% of patients in both groups. Approximately 10% of patients had experience with sumatriptan in both the oral and subcutaneous formulation.

Efficacy

Headache Response. The percentage of patients with a 2-hour headache response after the first dose in all 3 attacks was 33.4% (109/326) in the zolmitriptan group and 32.9% (112/340) in the acetylsalicylic acid plus metoclopramide group (fig. 1). The difference between the groups was not statistically significant. Similar results for this (primary) end point were observed in the per-protocol population. There were also no statistically significant differences between the groups in the proportions of patients who responded after the first dose in the first attack or in 2 out of 3 attacks (table 3). The 2-hour headache response rate with zolmitriptan was consistent across all 3 attacks at 61.8–67.1% (overall 65.0%), compared with 60.1–70.1% (overall 66.0%) for acetylsalicylic acid plus metoclopramide (fig. 1).

Pain-Free Response. More patients in the zolmitriptan group were free of pain 2 h after the first dose in all 3

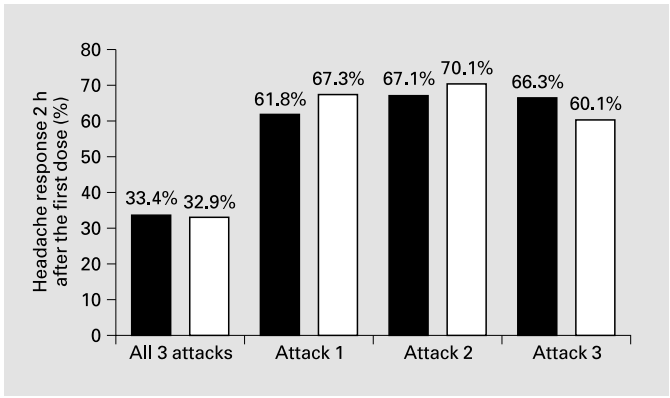

Fig. 1. Two-hour headache response rates after the first dose of zolmitriptan 2.5 mg (black bars; n = 326) or acetylsalicylic acid 900 mg plus metoclopramide 10 mg (white bars; n = 340) in all 3 attacks and for attacks 1–3.

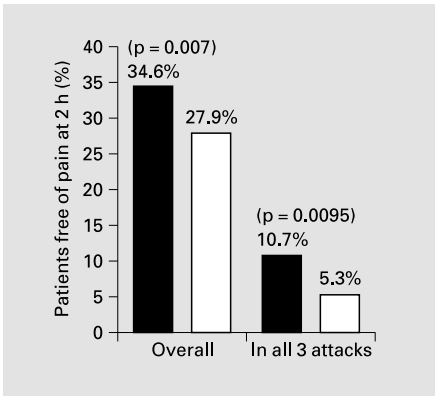

Fig. 2. Two-hour pain-free response rates after the first dose of zolmitriptan 2.5 mg (black bars; n = 326) or acetylsalicylic acid 900 mg plus metoclopramide 10 mg (white bars; n = 340) overall and in all 3 attacks (post hoc analysis).

Table 2. Demographic characteristics and migraine headache histories of the ITT population

Characteristic	Zolmitriptan group (n = 326)[1]	Acetylsalicylic acid plus metoclopramide group (n = 340)
Mean age ± SD, years	41.6 ± 10.0	40.9 ± 10.7
Number of patients aged		
18–40 years	144 (44.2)	160 (47.1)
41–60 years	172 (52.8)	166 (48.8)
>60 years	9 (2.8)	14 (4.1)
Gender		
Male	53 (16.3)	47 (13.8)
Female	273 (83.7)	293 (86.2)
Mean weight ± SD, kg	64.2 ± 13.3	63.0 ± 11.1
Mean age of migraine onset ± SD, years	22.6 ± 9.3	21.9 ± 8.9
Mean number of migraine headaches per month in previous 3 months ± SD	3.1 ± 1.4	2.9 ± 1.4
Mean number of non-migraine headaches per month in previous 6 months ± SD	2.5 ± 2.8	2.5 ± 2.9
Migraine with aura	64 (19.6)	55 (16.2)
Migraine without aura	155 (47.5)	165 (48.5)
Migraine with and without aura	106 (32.5)	120 (35.3)
Duration of untreated headache		
0–12 h	28 (8.6)	40 (11.8)
>12–24 h	91 (27.9)	99 (29.1)
>24–48 h	96 (29.4)	104 (30.6)
>48–72 h	89 (27.3)	83 (24.4)
>72 h	21 (6.4)	14 (4.1)
Migraine-associated symptoms		
Nausea	286 (87.7)	293 (86.2)
Vomiting	137 (42.0)	143 (42.1)
Photophobia	294 (90.2)	304 (89.4)
Phonophobia	283 (86.8)	300 (88.2)

Figures in parentheses represent percentages. SD = Standard deviation.

[1] Data for 325 patients shown for most criteria; data for 1 patient in the zolmitriptan group were not recorded.

attacks when compared with the acetylsalicylic acid plus metoclopramide group (10.7 vs. 5.3%), the difference being statistically significant (odds ratio 2.19, 95% CI 1.23–4.03; p = 0.0095) (fig. 2). In addition, a post hoc analysis indicated that the overall 2-hour pain-free response rate was 34.6% (313/905) with zolmitriptan, compared with 27.9% (264/945) with acetylsalicylic acid plus metoclopramide (odds ratio 1.40, 95% CI 1.096–1.783; p = 0.007).

Two-Point Headache Severity Reduction. Post hoc analysis showed that the percentage of patients with a reduction in headache severity of at least 2 points following the first dose of study therapy was higher with zolmitriptan compared with acetylsalicylic acid plus metoclopramide, both overall (39.2 vs. 31.9%) and at each attack (35.0–41.7 vs. 27.6–34.4%).

Migraine and Patient Sub-Types. Of the migraine attacks in women, 33.4% (136/407) in the zolmitriptan group and 33.8% (156/461) in the acetylsalicylic acid plus metoclopramide group were associated with menses. Zolmitriptan produced a 2-hour headache response in a higher proportion of these attacks (75.0%, 102/136) as compared with acetylsalicylic acid plus metoclopramide (66.0%, 103/156), both overall and at each attack (fig. 3), although statistical analysis was not performed on the results from these sub-groups. The overall frequency of migraine with aura was 23.8% (216/907) in the zolmitriptan group and 23.1% (218/943) in the acetylsalicylic acid plus metoclopramide group. The overall 2-hour headache response rates were similar in the two groups: 68.1% (147/216) with zolmitriptan and 66.1% (144/218) with acetylsalicylic acid plus metoclopramide. No clinically relevant effect of age, gender or weight was observed on the 2-hour

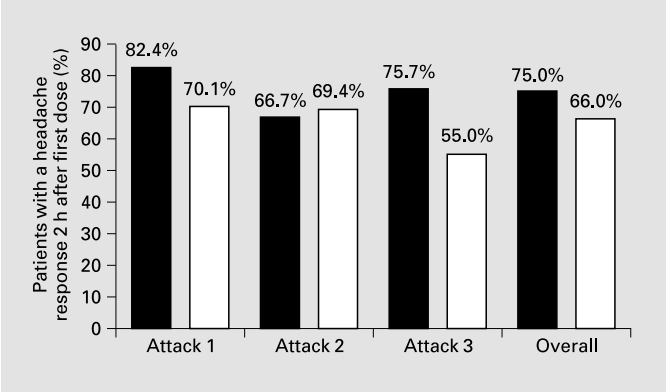

Fig. 3. Two-hour headache response rates in patients with migraine associated with menses after the first dose of zolmitriptan 2.5 mg (black bars; n = 136) or acetylsalicylic acid 900 mg plus metoclopramide 10 mg (white bars; n = 156) in each attack and overall.

Table 3. Comparative efficacy of zolmitriptan and acetylsalicylic acid plus metoclopramide

End point	Patients, %		Odds ratio[1]	95% CI	p value
	zolmitriptan group (n = 326)	acetylsalicylic acid plus metoclopramide group (n = 340)			
2-hour headache response after first dose in all 3 attacks	33.4	32.9	1.06	0.77–1.47	0.7228
2-hour headache response after first dose in the first attack	60.4	66.5	0.81	0.58–1.11	0.1871
2-hour headache response after first dose in at least 2 attacks	62.6	64.7	0.94	0.68–1.30	0.7096
Pain-free response 2 h after first dose in all 3 attacks	10.7	5.3	2.19	1.23–4.03	0.0095
Time to first perceived onset of MMR at the last attack					
< 30 min	1.8	4.1	–	–	–
30–59 min	18.7	22.4	–	–	–
60–119 min	34.0	30.9	–	–	–
≥ 120 min	45.4	42.6	–	–	–
Satisfaction with treatment response at last attack					
Poor	16.3	25.0	–	–	–
Fair	24.5	19.1	–	–	–
Good	35.9	38.5	–	–	–
Excellent	23.3	17.4	–	–	–
Fair, good or excellent	83.7	75.0	1.35	1.02–1.77	0.0346

[1] All odds ratios are zolmitriptan to acetylsalicylic acid + metoclopramide.

Table 4. Effect of therapy on migraine-associated symptoms

Symptom	Patients, %			
	zolmitriptan group (n = 326)		acetylsalicylic acid plus metoclopramide group (n = 340)	
	pre-dose	2 h post-dose	pre-dose	2 h post-dose
Nausea	56.6–65.6	26.5–34.2	54.7–61.3	25.5–30.2
Vomiting	9.6–12.6	5.4–6.8	9.4–11.3	3.8–5.5
Photophobia	76.5–78.6	36.8–43.8	77.7–82.1	36.8–42.3
Phonophobia	73.2–77.4	36.6–43.8	76.7–79.5	39.0–40.9

Table 5. Usage and efficacy of a second dose of study medication

End point	Zolmitriptan group (n = 326)	Acetylsalicylic acid plus metoclopramide group (n = 340)
All attacks treated with a second dose, %	53.6 (487/909)	55.4 (526/949)
Reason for second dose		
Persistent pain, %	36.5 (332/909)	38.0 (361/949)
Recurrence, %	17.1 (155/909)	17.4 (165/949)
Median time to second dose over all attacks, min	135	140
Attacks with 2-hour headache response[1] after second dose, %	65.4 (313/479)	64.9 (339/522)
Range over 3 attacks	60.8–70.2	63.3–68.5
Attacks with 2-hour pain-free response after second dose[2], %	28.2 (135/479)	25.2 (132/523)
Patients with 2-hour pain-free response after second dose (range over 3 attacks), %	24.9–32.1	20.7–29.9

[1] Headache response includes those patients with mild headache at baseline which remained mild at the 2-hour time point.
[2] Some patients who took a second dose of study medication did not record their pain intensity at the 2-hour time point.

headache response rates following the first dose in either group, although the number of patients aged >60 years was small.

Meaningful Migraine Relief. There were no statistically significant differences between the groups in terms of the time course of MMR perception during the last attack (table 3). Just over half of the patients in the zolmitriptan (54.5%) and the acetylsalicylic acid plus metoclopramide groups (57.4%) reported a time to first perceived onset of MMR of <120 min. Overall, patients reported MMR (within 2 h) in 55.3% (502/907) of attacks treated with zolmitriptan and 60.2% (569/945) of those treated with acetylsalicylic acid plus metoclopramide. These percentages were generally consistent between attacks 1–3. Kaplan-Meier plots indicated that the overall median time to onset of MMR was similar with zolmitriptan (98 min) and acetylsalicylic acid plus metoclopramide (90 min).

Migraine-Associated Symptoms. Migraine-associated symptoms, particularly photophobia, phonophobia, nausea and vomiting, were commonly reported by patients prior to study therapy. The two treatments produced similar improvements in these symptoms in each of the 3 attacks (table 4). Notably, zolmitriptan was as effective against nausea as the combination regimen containing the anti-emetic metoclopramide.

Headache Recurrence. Overall, headache recurrence was reported by 23.1% of patients treated with zolmitriptan and 24.2% of those who received acetylsalicylic acid plus metoclopramide.

Second Dose. Data on the use and efficacy of a second dose of study medication for persistent or recurrent migraine are summarised in table 5. A similar proportion of attacks were treated with a second dose in the zolmitriptan and acetylsalicylic acid plus metoclopramide groups (53.6 vs. 55.4%). This proportion was generally consistent over the 3 attacks in both groups (49.8–56.4 vs. 53.2–57.7%). In the zolmitriptan group, a second dose was used for persistent pain in 36.5% of attacks, whereas headache recurrence was cited as the reason in 17.1% of attacks. The corresponding figures were comparable in the acetylsalicylic acid plus metoclopramide group. The median time to the taking of a second dose was also similar in the two groups. Following a second dose of study medication, a 2-hour headache response was reported over the 3 attacks by 60.8–70.2% and 63.3–68.5% of patients in the zolmitriptan and acetylsalicylic acid plus metoclopramide groups; corresponding overall values were 65.4 and 64.9%, respectively. The 2-hour pain-free response rate following a second dose of study medication was slightly higher with zolmitriptan (overall rate 28.2%) than with acetylsalicylic acid plus metoclopramide (overall rate 25.2%).

Use of Escape Medication. Overall, patients took escape medication in 25.2% of attacks in the zolmitriptan group and 26.9% of attacks in the acetylsalicylic acid plus metoclopramide group. In the zolmitriptan group, this proportion decreased over time at each successive attack, ranging from 30.2 to 17.5% from the first to the third attack. In contrast, the proportion using escape medication remained relatively constant in the acetylsalicylic acid plus metoclopramide group at 23.6–29.6%.

Patient Satisfaction. Compared with the acetylsalicylic acid plus metoclopramide recipients, a lower proportion of zolmitriptan-treated patients regarded the therapy in each attack to be poor (overall rate 15.0 vs. 19.9%) and a higher proportion reported therapy to be excellent (overall rate 21.4 vs. 16.8%). The proportion who expressed overall satisfaction with the treatment (as defined by the satisfaction at the last attack, described as fair, good or excellent) was significantly higher in the zolmitriptan group than the acetylsalicylic acid plus metoclopramide group, i.e. 83.7 versus 75.0%, respectively ($p = 0.0346$). Although the assumption of proportional odds did not hold, a binary test performed for satisfaction being poor versus fair, good or excellent was also statistically significant in favour of zolmitriptan.

Tolerability

Both treatments were well tolerated. Adverse events were reported by 40.8% (133/326) of zolmitriptan-treated patients and 29.1% (99/340) of those treated with acetylsalicylic acid plus metoclopramide. However, there were no differences between the groups regarding the incidence of serious adverse events (1.8 vs. 1.5%) or withdrawals due to adverse events (0.9 vs. 1.5%) or not due to adverse events (11.7 vs. 12.9%).

Table 6. Percentage of patients with >2% incidence of adverse events in either group

Adverse event	Zolmitriptan group (n = 326)	Acetylsalicylic acid plus metoclopramide group (n = 340)
Vertigo	6.7	3.5
Somnolence	5.5	5.0
Paraesthesia	4.3	1.5
Asthenia	5.2	4.7
Tightness	3.7	0.6
Chills	2.8	0.9
Nausea	3.4	3.2
Abdominal pain	2.8	5.0
Dizziness	2.8	0.6
Dry mouth	2.5	0.6
Tremor	1.2	2.1
Diarrhoea	1.2	2.1

Adverse events reported were typical for each regimen (table 6). Certain adverse events, such as paraesthesia, dizziness and tightness, were reported more commonly with zolmitriptan, whereas others such as abdominal pain and diarrhoea were more common with acetylsalicylic acid plus metoclopramide.

All adverse events leading to withdrawal were considered to be related to study therapy. Of the 3 patients who withdrew from zolmitriptan treatment due to adverse events, 1 had dizziness, 1 had somnolence and the other had dizziness and vasodilatation. The adverse events causing withdrawal in 5 patients (which included a serious adverse event) in the acetylsalicylic acid plus metoclopramide group were diarrhoea (2 patients), palpitations plus asthenia (1 patient), anxiety plus dry mouth (1 patient) and phlebitis (1 patient). The case of phlebitis was the only serious adverse event considered to be drug related.

Discussion

This randomised, double-blind trial was designed to compare zolmitriptan, a relatively new therapeutic option, with the oral combination therapy of acetylsalicylic acid plus metoclopramide in the acute oral treatment of migraine. Importantly, each drug was assessed in the treatment of 3 separate migraine attacks. This minimised the placebo effect, which can be considerable in migraine [25], and allowed evaluation of the consistency of the treatments' efficacy. Each drug was used at recommended dosages and hence the results are applicable to the clinical setting. In analysing the results, we used the ITT population (all patients who took trial medication) to minimise any potential bias due to drop-outs.

In double-blind, placebo-controlled, single-attack studies, oral zolmitriptan 2.5 mg has produced 2-hour headache response rates of 59–65% [19, 21, 28]. The consistently high response rates observed across the 3 attacks treated with zolmitriptan in the current trial (61.8–67.1%) are therefore in accordance with previous findings. However, the primary end point in this trial was the percentage of patients in whom a 2-hour headache response was obtained in all 3 attacks. Although the response rate for this rigorous end point was high for zolmitriptan (33.4%), the high response rates with acetylsalicylic acid plus metoclopramide produced a non-significant difference between the groups. A previous study of this combination regimen reported 2-hour headache response rates of 45.0, 36.0 and 34.0% in the first, second and third attacks, respectively [26]. Based on these data, we estimated that the proportion of patients responding in all 3 attacks would be approximately 20%; however, it was actually 32.9%. As the treatment groups were generally naïve to $5HT_{1B/1D}$ receptor agonists and were mainly good responders to acetylsalicylic acid plus metoclopramide, this selection bias may have contributed to the unusually high response rate observed for the combination regimen. Further, these results suggest that this study may not have selected patients that resemble clinical groups to whom the results should be applied.

In contrast, stratifying patients according to migraine disability would ensure that only patients with a need for triptan therapy would be included in the trial. Indeed, a recent study comparing treatment strategies has shown that stratifying patients according to their treatment needs is significantly more effective than a step care approach whereby patients only received zolmitriptan if treatment with acetylsalicylic acid plus metoclopramide failed [29]. Implicit in these results is that zolmitriptan is significantly more effective than acetylsalicylic acid plus metoclopramide in the treatment of patients with moderate to severe migraine-induced disability. However, in the present study, as patients were predominantly good responders to acetylsalicylic acid plus metoclopramide, they therefore may not have represented target patients from clinical practice, i.e. those with a need for high-end therapy.

Another consideration is that the results may indicate that a 2-hour headache response is not the most appropriate end point for capturing the benefits of triptans compared with other medications. Indeed, a previous study comparing sumatriptan with acetylsalicylic acid plus metoclopramide also failed to show a statistically significant difference between the treatments with respect to the 2-hour headache response [30]. Furthermore, dosing schedules that reflect clinical practice (i.e. early intervention) may be of greater relevance and may demonstrate increased benefit of triptans compared with other medications, as response rates to triptans have previously been shown to be higher for the treatment of mild headache [31]. Most patients seek relief prior to 2 h, and this study did not address efficacy end points at earlier times, so comparisons of the relative onset of action are not possible. However, previous data have indicated that zolmitriptan has a significant effect relative to placebo by 45 min after the dose, with some patients achieving benefit within 30 min [21].

End points that have greater relevance to the patient, such as pain-free status, patient satisfaction and consistency of efficacy across multiple attacks, may be more appropriate than the traditional end point of 2-hour headache response. In the present study, the overall pain-free response was significantly higher with zolmitriptan than with acetylsalicylic acid plus metoclopramide (34.6 vs. 27.9%; $p = 0.007$). Furthermore, the consistency of this effect was significantly higher for patients treated with zolmitriptan, according to the percentage of patients free of pain 2 h following the first dose of study medication in all 3 attacks (10.7 vs. 5.3%; $p = 0.0095$). This stringent end point is more sensitive to large improvements in the patient's condition and as such is highly clinically relevant.

The clinical importance of the efficacy data favouring zolmitriptan is confirmed by the significantly higher proportion of patients who expressed satisfaction with zolmitriptan (83.7%) compared with the combination regimen (75.0%; $p = 0.0346$). These results contrast with those previously reported for sumatriptan 100 mg versus acetylsalicylic acid plus metoclopramide, where no significant be-

tween-group differences were observed for pain-free status or patient satisfaction [30].

This study adds to previous evidence that zolmitriptan is consistently effective in the treatment of migraine with aura and migraine associated with menses [31, 32, 33]. Indeed, zolmitriptan appeared to be more effective than acetylsalicylic acid plus metoclopramide in patients with migraine related to menses. Zolmitriptan was associated with a 2-hour headache response in a higher proportion of cases of migraine associated with menses compared with acetylsalicylic acid plus metoclopramide, both overall and at each attack. In addition, the efficacy of zolmitriptan was unaffected by age, weight or gender.

Both study treatments reduced the symptoms of nausea, vomiting, photophobia and phonophobia commonly associated with migraine. Approximately half of the patients with these symptoms were free of them 2 h after treatment. Particularly notable is the observation that zolmitriptan showed similar efficacy to acetylsalicylic acid plus metoclopramide in the reduction of nausea and vomiting, despite the inclusion of a specific anti-emetic in the combination regimen.

The tolerability profiles of both study drugs were consistent with previous findings, and no new safety issues associated with either drug were identified. Both treatments were well tolerated, with a very low frequency of withdrawals due to adverse events (0.9% with zolmitriptan and 1.2% with acetylsalicylic acid plus metoclopramide). The type of adverse events experienced more frequently in the zolmitriptan group (e.g. paraesthesia and tightness) are recognised class-related events [34, 35]. Abdominal pain is often reported with acetylsalicylic acid use, and diarrhoea is an adverse event known to be associated with metoclopramide, and hence the greater frequency of these events in the comparator arm is to be expected (5.0 and 2.1%, respectively, for acetylsalicylic acid plus metoclopramide vs. 2.8 and 1.2%, respectively, for zolmitriptan). No extrapyramidal symptoms, which can occur with metoclopramide use, were reported in this study.

In conclusion, zolmitriptan is an effective and well-tolerated option for acute anti-migraine therapy. Although evaluation using the primary end point in this study was inconclusive, other end points such as freedom from pain, now identified as more clinically relevant end points, showed zolmitriptan 2.5 mg to be significantly better than the standard analgesic-anti-emetic combination of acetylsalicylic acid and metoclopramide.

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