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Zolmitriptan, a 5-$HT_{1B/1D}$ receptor agonist for the acute oral treatment of migraine: a multicentre, dose-range finding study

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Zolmitriptan is a selective 5-$HT_{1B/1D}$ receptor agonist for acute oral migraine therapy. This randomized, placebo-controlled, parallel-group study investigated the efficacy and tolerability of oral zolmitriptan (5, 10, 15 and 20 mg) in the treatment of single acute migraine attacks. Of 1181 patients randomized, 840 were evaluable for the primary efficacy analysis. Headache response rates (a reduction in headache intensity from severe or moderate at baseline to mild or no pain at 2 hours post-treatment) were similar across the zolmitriptan dose groups (66%, 71%, 69% and 77% for 5 mg, 10 mg, 15 mg and 20 mg, respectively) and were significantly higher than that for placebo (19%; all groups $P < 0.001$). A headache response was reported at 1 hour by 40–50% of zolmitriptan recipients (16% placebo). At 2 hours post dose, 39–47% of zolmitriptan-treated patients were pain-free, compared with 1% of placebo recipients. Headache recurrence occurred in 21–29% (upper 95% CI 37.1) of zolmitriptan-treated patients and in 65% (95% CI 38.3, 85.8) of placebo recipients. Zolmitriptan was well tolerated at each dose. The most commonly reported adverse events were asthenia, dizziness, paraesthesia and feelings of heaviness. Most adverse events were of mild or moderate intensity and were transient. The frequency of adverse events was dose-related. Although, zolmitriptan 5 mg exhibited the most favourable efficacy and tolerability profile, the dose response data suggest that lower doses would also offer significant efficacy. Eur J Neurol 5:535–543 © 1998 Lippincott Williams & Wilkins

Keywords: zolmitriptan, 5$HT_{1B/1D}$ receptor agonist, migraine, dose-range finding

INTRODUCTION

Options for the acute treatment of migraine, a common, debilitating condition associated with a considerable social and economic burden (Stewart *et al.*, 1992; Osterhaus *et al.*, 1992; Rasmussen, 1995), have been expanded in recent years. The introduction of the selective 5-hydroxytryptamine $(5\text{-HT})_{1B/1D}$ receptor agonists, have represented a major advance in therapy (Diener, 1994, Goadsby and Olesen, 1996).

Zolmitriptan is a selective 5-$HT_{1B/1D}$ receptor agonist which, in animal studies, has demonstrated a novel dual

This study was completed before the acquisition of zolmitriptan ('Zomig', 311C90) by Zeneca and was sponsored by Glaxo Wellcome. Zeneca now owns zolmitriptan and is responsible for the worldwide development and marketing of zolmitriptan. 'Zomig' is a trademark of the Zeneca Group of Companies

mechanism of action (Martin, 1997). In common with sumatriptan, the first compound in the class (Dechant and Clissold, 1992), zolmitriptan acts upon peripheral components of the trigeminovascular system (Goadsby and Edvinsson, 1994), producing cranial vasoconstriction (Martin *et al.*, 1997), inhibition of neuropeptide release (Goadsby and Edvinsson, 1994) and blockade of plasma protein extravasation (Martin *et al.*, 1997). Unlike sumatriptan, in the cat, zolmitriptan crosses the blood brain barrier and reduces cranial nociception centrally by inhibiting evoked potentials within the trigeminocervical complex (Goadsby and Hoskin 1996) through activation of specific local receptors (Goadsby and Knight, 1997; Storer and Goadsby, 1998). Zolmitriptan is also able to modify serotonin-dependent central nervous system activities in humans (Proietti Cecchini *et al.*, 1997). Theoretically, this may confer additional benefits in the treatment of migraine (Goadsby and Hoskin, 1996). Zolmitriptan has good oral bioavailability (approximately 40% at doses of 2.5 and 5 mg; Dixon and Warrender, 1997).

The dose response curve must be profiled during the development of any new drug, in order that the dose offering the best balance between efficacy and tolerability can be determined. A comprehensive clinical trial programme (reviewed by Schoenen and Sawyer, 1997) was conducted to investigate the dose-response profile of zolmitriptan. The first zolmitriptan double-blind study demonstrated that 5 mg and 25 mg doses were effective and well tolerated, while a 1 mg dose appeared to have lower efficacy (Visser *et al.*, 1996a).

Data are presented here from a study that investigated the efficacy and tolerability of zolmitriptan doses between 5 and 20 mg.

METHODS

Selection of patients

Patients were recruited at 54 trial centres in 14 countries. Each trial centre obtained appropriate regulatory and ethical committee approvals prior to entering patients. All patients gave written informed consent prior to participation, which was conducted in accordance with the Declaration of Helsinki and conformed to Good Clinical Practice.

Patients aged 18–65 years, with migraine (with or without aura) according to the International Headache Society definitions (Headache Classification Committee of the IHS, 1988), were eligible for inclusion. Patients were required to have suffered from migraine for at least 1 year, with an age of onset less than 40 years, an attack frequency of between 1 and 6 per month and no more than 6 days of non-migraine headaches per month. Exclusion criteria included, a history of coronary artery disease or other vascular disease; Prinzmetal angina; renal or hepatic disease; neurological or psychiatric disease; hypertension (usual systolic blood pressure $\geqslant$ 160 mmHg or diastolic blood pressure $\geqslant$ 95 mmHg).

Study design

This was a double-blind, placebo-controlled, parallel-group study. Eligible patients were randomized to receive either placebo or 5 mg, 10 mg, 15 mg or 20 mg zolmitriptan (in a ratio of 1:2:2:2, respectively) by assigning the next medication pack in the computer-generated numerical sequence for each centre. Randomization was blocked and stratified by centre. One dose of study medication was dispensed to treat a single migraine headache. All tablets were identical in appearance. During a screening visit, patients were instructed on the use of a standard diary card to record efficacy and tolerability data.

Patients were instructed to take study medication within 12 weeks of randomisation to treat a migraine headache of moderate or severe intensity within 6 hours of headache onset. Patients were required to have been free from a migraine for 72 hours prior to study treatment and not to have taken sumatriptan or ergotamine-derivatives within the previous 72 hours or analgesics within the previous 24 hours. Patients were allowed to take certain concomitant prophylactic medication (excluding medications that were considered psychoactive or active at 5-HT receptor sites). The use of escape medication 2 hours after administration of study medication was also permitted if patients did not obtain adequate relief of their migraine symptoms. Ergotamine-derivatives or sumatriptan were not allowed as escape medication within 12 hours of taking study medication. Patients were asked to return to clinic for a follow-up visit as soon as was practical after completion of their diary card.

Efficacy and tolerability assessments

Patients rated the intensity of their headache before and after study treatment on a scale of severe, moderate, mild or no pain. The primary efficacy endpoint was headache response (a reduction in headache intensity from severe or moderate to mild or no pain) at 2 hours post treatment. Secondary efficacy endpoints included: headache response at 1 hour; pain free response at 1 and 2 hours; and reduction in associated migraine symptoms (nausea, photophobia and phonophobia) at 1 and 2 hours. Recurrent headache (headache of moderate or severe intensity occurring within 24 hours of treatment in patients who obtained a headache response at 2 hours) was also recorded, as well as the percentage of patients that used escape medication. Additionally,

whether a patient achieved a complete response (headache response at 2 hours not followed by recurrence within 24 hours post treatment) was assessed.

A physical examination, which included measurement of blood pressure, was conducted prior to randomization. Before randomization and at follow up, 12-lead electrocardiographs (ECGs) were recorded. Routine haematology, biochemistry and urinalysis laboratory tests were also performed. Patients recorded all adverse events, irrespective of their relationship to trial medication, in their diary card at 1, 2 and 24 hours post treatment. These and any other adverse events occurring prior to the follow-up visit were reviewed with the investigator.

Statistical analysis

The trial was designed to detect a statistically significant difference between a 2-hour headache response rate of 35% for placebo and 55% for zolmitriptan (88% power, with a two-sided error rate of 0.05). It was estimated that 90 placebo patients and 180 patients per zolmitriptan arm (i.e. a total of 810 patients) would be required.

For the primary endpoint of headache response, a logistic regression model was used to evaluate the dose-response relationship, using dose level as a continuous variable. The variables of gender, age, presence of pre-treatment aura and the baseline headache intensity were included in the model. The model was also used to compare each zolmitriptan treatment group with the placebo group, adjusting by the same specified variables and using dose level as a categorical variable.

All categorical efficacy endpoints, including headache response, were summarised as proportions of responses and presented with 95% confidence intervals based on Pratt's approximation of the exact confidence interval.

RESULTS

Patient population

A total of 1181 patients were randomized. Of these, 951 were known to have treated a migraine attack with study medication. The majority (184) of the remaining patients did not take study medication and 46 patients did not provide follow-up data.

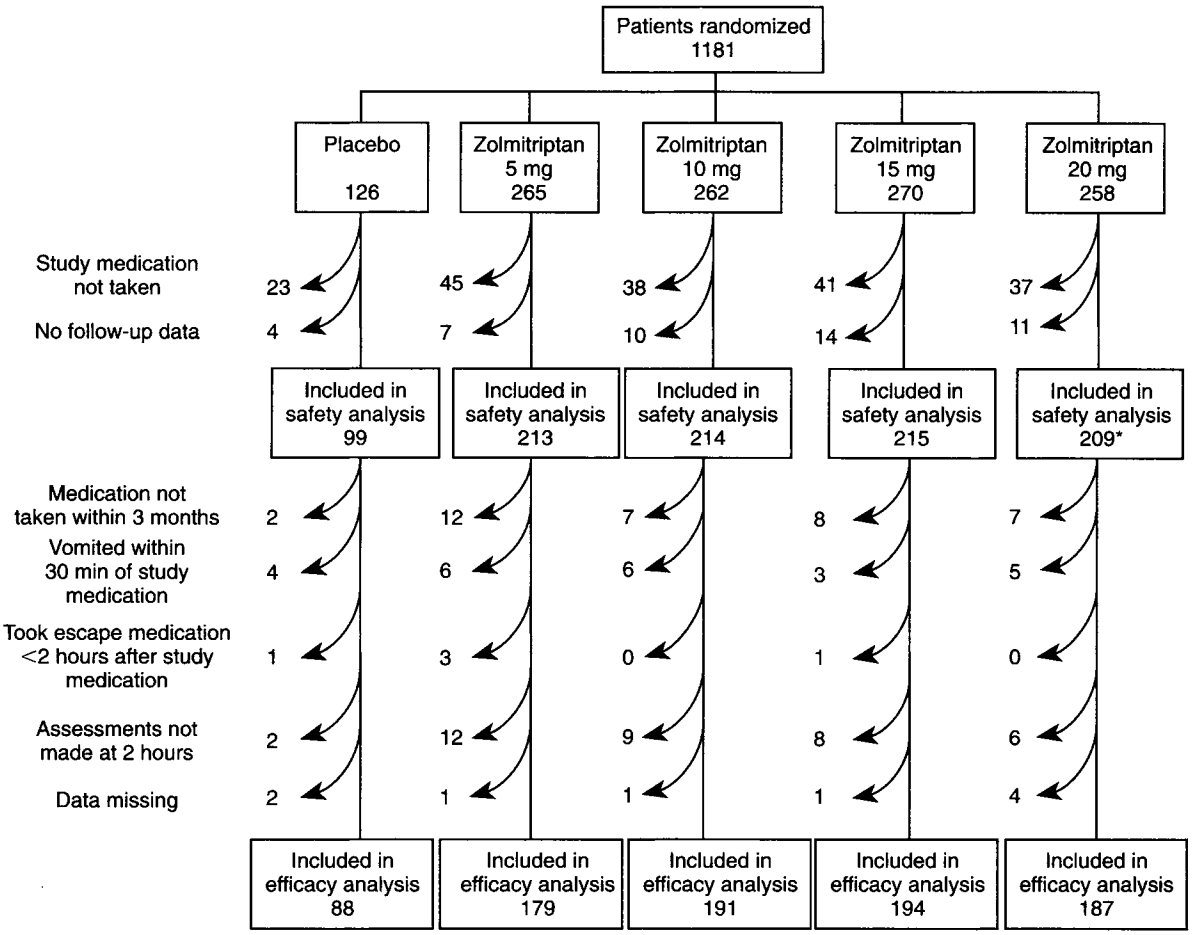
Eight hundred and forty patients were included in the primary per protocol efficacy analyses. An additional efficacy analysis using all available data was performed on the primary endpoint. This gave similar results to the per protocol analysis and so is not presented here. The demographic and migraine history details of these patients were similar across the treatment groups (Table 1), as were the characteristics of the migraine attacks treated with study medication (Table 2). The observed predominance of female patients is consistent with the epidemiology of migraine in the general population (Stewart *et al.*, 1992; Rasmussen, 1995). Of the 951 patients who took study medication, 950 were included in the tolerability evaluation (safety data was not available for one patient). The reasons for excluding patients from the efficacy analyses are shown in Fig. 1.

TABLE 1. Patients' demographic characteristics and migraine histories

Characteristic	Zolmitriptan dose				
	Placebo ($n = 88$)	5 mg ($n = 179$)	10 mg ($n = 191$)	15 mg ($n = 194$)	20 mg ($n = 188$)
Sex					
Female	67 (76%)	146 (82%)	163 (85%)	164 (85%)	161 (86%)
Male	21 (24%)	33 (18%)	28 (15%)	30 (15%)	27 (14%)
Mean age (years) ± SD	39.5 ± 10.7	39.7 ± 10.5	39.9 ± 10.7	41.6 ± 10.4	39.4 ± 10.4
Mean weight (kg) ± SD	69.4 ± 13.5	68.0 ± 12.4	66.3 ± 9.9	67.6 ± 13.2	64.1 ± 10.9
Mean age at migraine onset (years) ± SD	19.2 ± 9.3	18.1 ± 8.5	19.3 ± 8.9	20.4 ± 9.2	20.2 ± 8.8
Mean number of migraine attacks per month ± SD	2.8 ± 1.4	2.8 ± 1.4	2.9 ± 1.5	2.9 ± 1.5	2.8 ± 1.3
Mean number of days of non-migraine headaches per month ± SD	1.4 ± 1.9	1.3 ± 1.7	1.5 ± 2.0	1.6 ± 1.9	1.5 ± 2.0
Usual type of migraine					
With aura	15 (17%)	31 (17%)	32 (17%)	30 (15%)	21 (11%)
Without aura	61 (69%)	119 (66%)	126 (66%)	130 (67%)	141 (75%)
Mixed	12 (14%)	29 (16%)	33 (17%)	34 (18%)	26 (14%)

TABLE 2. Characteristics of the treated migraine attacks

Characteristic		Zolmitriptan dose			
	Placebo ($n = 88$)	5 mg ($n = 179$)	10 mg ($n = 191$)	15 mg ($n = 194$)	20 mg ($n = 188$)
Preceding aura	18 (20%)	30 (17%)	34 (18%)	24 (12%)	22 (12%)
Headache severity					
Moderate	45 (51%)	99 (55%)	115 (60%)	111 (57%)	117 (62%)
Severe	43 (49%)	80 (45%)	76 (40%)	83 (43%)	71 (38%)
Associated symptoms					
Nausea	52 (59%)	111 (62%)	134 (70%)	120 (62%)	118 (63%)
Photophobia	67 (76%)	139 (78%)	150 (79%)	152 (78%)	145 (77%)
Phonophobia	60 (68%)	132 (74%)	145 (76%)	144 (74%)	138 (73%)



*Safety data not available for an additional patient.

FIGURE 1. Flow diagram to show patient accountability.

Efficacy

The 2-hour headache response rates for each dose of zolmitriptan (66%, 71%, 69%, 77% for 5, 10, 15 and 20 mg, respectively) were significantly higher than placebo (19%, $P < 0.001$). A smoothed regression curve for zolmitriptan 5–20 mg was drawn to determine the optimum dose of zolmitriptan (Fig. 2). A substantial percentage of patients (44%, 40%, 42% and 50% of those treated with 5, 10, 15 and 20 mg doses, respectively) experienced a headache response 1 hour

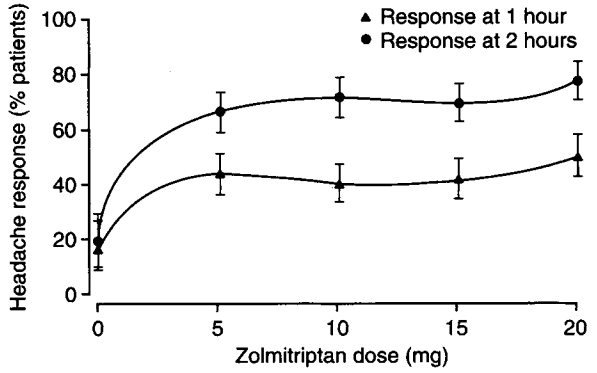


FIGURE 2. Lagrange interpolated curve for rates of headache response (severe or moderate headache improved to mild or no pain) at 1 and 2 h after administration of zolmitriptan (error bars indicate 95% confidence intervals.

after treatment with zolmitriptan (16% with placebo). The dose-response relationship for this endpoint closely followed that for 2-hour headache response (Fig. 2).

The efficacy of zolmitriptan was not influenced by patients' gender or age. A higher response rate was seen in those patients with a moderate pretreatment headache (71–82% zolmitriptan, 22% placebo), compared to those with a severe pretreatment headache (59–69% zolmitriptan, 16% placebo). However, the treatment benefit (treatment response minus placebo response) was similar for headache of moderate (49–60%) and severe (43–53%) intensity. Fifteen percent of patients were taking concomitant prophylactic migraine medication during the study period. The main classes of prophylactic agents were β-blockers (principally propranolol, metoprolol and atenolol) and calcium channel blockers (principally felodipine and nifedipine). There was a slightly higher 2-hour headache response to zolmitriptan within each treatment group (approximately 10%) in those patients taking migraine prophylaxis, although the number of patients was small.

At 1 hour post dose, 9–13% of the zolmitriptan patients were completely pain-free, compared with none of those in the placebo group. At 2 hours this percentage increased to 39–47% in the zolmitriptan group versus 1% in the placebo group (Table 3). The dose-response relationship observed with pain-free response was similar to that seen with headache response.

Headache recurrence (Table 3) was reported by 65% (95% CI 38.3, 85.8) of patients in the placebo group (median time to recurrence was 4.5 h), compared with 26% (95% CI 18.6, 35.2), 28% (95% CI 20.6, 36.3), 21% (95% CI 14.4, 28.8) and 29% (95% CI 21.7, 37.1) of those treated with 5, 10, 15 and 20 mg zolmitriptan, respectively (median time to recurrence was 12.7–16.4 h). Escape medication was taken by 81% of patients in the placebo group, compared with 53%, 50%, 42% and 41% of patients in the zolmitriptan 5, 10, 15 and 20 mg groups, respectively. Of the patients who took escape medication, 47% of zolmitriptan recipients took it for persistent headache compared with 82% of patients in the placebo group. A further 27% of zolmitriptan-treated patients took escape medication for recurrent headache compared with 11% in the placebo group. The low use of escape medication for recurrent headache in the placebo group is not surprising since to qualify for recurrent headache an initial headache response has to occur. A low initial headache response was seen for placebo. Of the patients who took escape medication, 19% of zolmitriptan recipients and 14% of placebo recipients took it for mild pain. A small number of these patients were

TABLE 3. Efficacy of zolmitriptan compared with placebo

Endpoint	Zolmitriptan dose									
	Placebo ($n = 88$)		5 mg ($n = 179$)		10 mg ($n = 191$)		15 mg ($n = 194$)		20 mg ($n = 187$)	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Headache response										
1 h	16	9,26	44	37,52	40	38,48	42	35,49	50	42,57
2 h	19	12,29	66	59,73	71	64,78	69	62,76	77	71,83
Pain free										
1 h	0	0,4	10	6,16	9	5,14	13	8,19	12	8,18
2 h	1	0,6	39	32,47	39	32,47	43	36,51	47	40,54
Headache recurrence	65	38,86	26	19,35	28	21,36	21	14,29	29	22,37
Median time to recurrence (hours) [range]	4.5 [2.8–21.0]		15.2 [3.6–23.4]		16.4 [3.8–23.7]		12.7 [2.0–24.0]		16.1 [3.0–24.0]	
Complete response	7	3–14	49	41–56	51	44–59	55	47–62	55	47–62

included in the number that took additional escape medication for the development of recurrent headache. In addition, a further 8% of zolmitriptan-treated patients took escape medication even though they had no pain 2 hours post-dose and did not have recurrent headache.

The mean time for use of escape medication was 4 hours in the placebo group and 7, 10, 8 and 9 hours in those treated with zolmitriptan 5, 10, 15 and 20 mg, respectively. The rates of complete response (Table 3) associated with zolmitriptan were similar across the dose groups (49%–55%) and higher than that in the placebo group (7%).

Zolmitriptan also relieved non-headache symptoms of migraine. There was a 41–50% reduction in the percentage of zolmitriptan-treated patients who reported photophobia at 2 hours post treatment compared to baseline (17% reduction on placebo). Similar improvements were observed for phonophobia. There was also a trend for zolmitriptan to reduce the percentage of patients with nausea, with a 30–39% decrease at 2 hours from baseline, versus a 25% reduction by placebo.

Tolerability

Diary cards were used as an aid to help patients document all adverse experiences occurring within 1, 2 and 24 hours post dose, irrespective of their relationship with study medication. All zolmitriptan doses were well tolerated, although the frequency of adverse events was dose-related. Overall, 61% of patients in the 5 mg zolmitriptan group and 75%, 79%, and 76% of those in the higher dose groups (10, 15 and 20 mg, respectively) reported at least one adverse event (34% in the placebo group). The most commonly reported adverse events were asthenia, dizziness, paraesthesia and feelings of heaviness (Table 4). The incidence of chest-related adverse events i.e. tightness, pain, heaviness, and pressure was low (Table 5). Most of the adverse events were mild or moderate in intensity, not serious, transient and resolved without intervention.

One serious adverse experience was reported. A 35-year-old female patient with pre-existing Wolff-Parkinson-White syndrome (WPW) experienced an episode of tachycardia (estimated at 200 beats/minute) 30 minutes after taking 5 mg zolmitriptan. Her heart rate spontaneously converted to sinus tachycardia (rate approxi-

TABLE 4. Percentage of patients with most frequent adverse events >5% in any group reported within 24 h of treatment with zolmitriptan or placebo (regardless of relationship with study medication)

Adverse event	Zolmitriptan dose				
	Placebo ($n=99$) %	5 mg ($n=213$) %	10 mg ($n=214$) %	15 mg ($n=215$) %	20 mg ($n=209$) %
Asthenia	5	8	14	17	22
Dizziness	6	11	10	13	16
Paraesthesia	2	9	12	10	18
Heaviness – other than chest or neck	1	6	9	17	16
Somnolence	2	8	12	9	13
Nausea	1	8	6	15	10
Warm sensation	3	6	8	9	6
Dry mouth	1	2	8	9	6
Vertigo	0	2	2	5	8

TABLE 5. Incidence of chest-related adverse effects

Adverse event	Zolmitriptan dose				
	Placebo ($n=99$) %	5 mg ($n=213$) %	10 mg ($n=214$) %	15 mg ($n=215$) %	20 mg ($n=209$) %
Chest tightness	0	1	1	4	0
Chest pain	1	1	2	1	3
Chest heaviness	0	0	0	1	1
Chest pressure	0	0.5	3	1	1

mately 100 beats/minute) after approximately 90 minutes. No sequelae were reported and this was considered a typical WPW episode for this patient.

No consistent changes in ventricular rate were observed in any zolmitriptan dose group compared to placebo. Review of 12-lead ECGs by a central cardiologist (blinded to treatment allocation) showed there were no clinically significant changes in post-treatment ECGs relative to baseline in any patient. Furthermore, there was no evidence that any clinical chemistry, haematology or urinalysis laboratory tests were affected by zolmitriptan administration.

DISCUSSION

The data presented show that zolmitriptan is a highly effective acute treatment for migraine, supporting the results of an earlier placebo-controlled inpatient study (Visser *et al.*, 1996a). In addition, the study characterizes the upper range of the zolmitriptan anti-migraine dose-response curve in more detail.

These data indicated that further studies were required to define the optimal dose, i.e. although a slightly higher response rate was produced by the highest dose (20 mg), efficacy gains at doses over 5 mg were marginal. A quadratic curve fitted through the 2-hour headache response values suggests that the shoulder of the dose-response curve may be around 2.5 mg (Fig. 2). These data led to the design of a large outpatient study of zolmitriptan where 1, 2.5, 5 and 10 mg doses were studied (Rapoport *et al.*, 1997). This subsequent study demonstrated a similar 2-hour headache response rate with zolmitriptan 5 mg (67%) and 2.5 mg (65%), while both doses were significantly superior to the 1 mg dose (53%) and to placebo (34%).

In the present study, the efficacy of zolmitriptan was not influenced by patients' gender or age. Moreover, the drug was effective in the treatment of headaches of both moderate and severe intensity.

The speed of onset of headache action is an important criterion for anti-migraine therapies from the patient's perspective (Göbel *et al.*, 1997). In this study, a substantial percentage of patients treated with zolmitriptan (40–50%) reported a headache response 1 hour after zolmitriptan treatment. Although these data were not formerly analysed, they support another published study where zolmitriptan provided statistically significant headache response within 1 hour post dose (Rapoport *et al.*, 1997). In addition to headache response, zolmitriptan also proved effective in this trial according to the more rigorous endpoints of pain-free response and complete response. The dose-response relationships observed using these measures were similar to those for 2-hour headache response, with doses over 5 mg providing little if any incremental benefit. The percentage of patients who experienced headache recurrence was lower in the zolmitriptan groups than in the placebo group and was slightly lower than reported in the dose-range finding study by Rapoport *et al.* (1997) at the 5 and 10 mg doses. Zolmitriptan also treated the non-headache migraine symptoms.

When determining the optimal dose of a drug, efficacy considerations must be viewed in conjunction with the tolerability dose-response profile. In the present study, zolmitriptan was administered at doses up to eight times the ultimate therapeutic dose (2.5 mg). Nevertheless, the drug was well tolerated, with the majority of adverse events reported being mild or moderate in intensity, transient and self-limiting. The spectrum of adverse events seen was similar to that in other studies with zolmitriptan (Edmeads and Millson, 1997) and also a comparative study with sumatriptan (Diener and Klein 1996; Schoenen *et al.* 1996).

Administration of zolmitriptan, even at the highest dose, was not associated with effects on clinical laboratory tests or ECGs. Across the zolmitriptan clinical trial programme, reports of ECG changes following therapy have been rare, occurring with a frequency similar to that associated with placebo (Edmeads and Millson, 1997). Feelings of chest tightness or heaviness, which were reported with a low frequency in this study, are characteristic of this class of drugs (Simmons and Blakeborough, 1994; Visser *et al.*, 1996b; Mathew, 1997) and have not been associated with ischaemic ECG changes. Indeed no ischaemic changes have been attributed to date to zolmitriptan administration (Edmeads and Millson, 1997).

A dose relationship was evident for tolerability, with fewer adverse events being reported with 5 mg compared to the higher doses. This is consistent with the report by Rapoport *et al.*, (1997). Additional evidence for the favourable tolerability profile of the 5 mg dose was provided by a long-term study, in which only 25% of over 31 000 attacks treated with one or two 5 mg doses by 2058 patients were associated with one or more adverse events (Zagami, 1997).

The marginal efficacy gains seen above the 5 mg dose as shown by its position on the quadratic curve for 2-hour headache responses (see Fig. 2), in conjunction with the dose-response tolerability data in this study, suggested that the optimal therapeutic dose of zolmitriptan is below 5 mg. Data from subsequent studies have confirmed these findings; 2.5 mg zolmitriptan has been reported to have similar efficacy to a 5 mg dose (2-hour headache response). However, the frequency of adverse events with a 2.5 mg dose is reported to be

even lower than that with 5 mg and similar to that with a 1 mg dose (Rapoport *et al.*, 1997).

In conclusion, oral zolmitriptan doses across the range 5–20 mg were highly effective and well tolerated in the acute treatment of migraine. While the frequency of adverse events appears to be dose-related within this dose range, this is not the case for efficacy. Thus, a 5 mg dose demonstrated near maximal efficacy coupled with a particularly favourable tolerability profile. These findings led to studies using lower doses of zolmitriptan.

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