Effective improvement of symptoms in patients with acute migraine by GR43175 administered in dispersible tablets

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GR43175, a selective 5-HT_1-like agonist, was administered as oral dispersible tablets in an open, uncontrolled dose-ranging study to assess its efficacy as an agent for acute migraine. Nine patients, all with well established attacks, were assessed for changes in severity of headache and associated symptoms over 2 h. Drug absorption was compared during and between attacks in five patients. Doses of 140 mg and 280 mg resulted in complete relief of all symptoms within 2 h. Treatment was well tolerated in all patients. □ *GR43175, dispersible tablets, acute migraine, absorption*

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In a series of dose-ranging studies with parenteral formulations GR43175 appeared effective in aborting well established, acute common or classical migraine attacks within 20–30 min. A single intravenous infusion of 2 mg over 10 min (1) or subcutaneous injection of 3 mg or 4 mg (2, 3) gave the most consistent results. Volunteer studies (4) with a dispersible tablet indicated that this may represent a suitable non-parenteral route of administration.

Subjects and methods

Previously identified patients aged between 18 and 60 years with a known history of common or classical migraine who were attending a pain clinic were eligible for the study. (Common migraine is defined as: recurrent, episodic severe headache, often unilateral and accompanied by anorexia, nausea and/or vomiting but without striking prodromes. Classical migraine is defined as: similar to the above but preceded by defined transient visual, and other sensory or motor prodromes.) Consenting patients were asked to attend at the time of their next migraine attack if symptoms were not improving.

Pregnant or breast-feeding women were excluded as were those patients with a history of ischaemic heart disease, chest pain, hypertension or serious systemic disease. To ensure that changes in migraine symptoms were not a result of previous medication, recent use of ergotamine (within 24 h) or simple analgesics such as aspirin (within 6 h) was prohibited.

All migraine symptoms were graded by the patient using simple rating scales for severity of headache (3 = severe, 2 = moderate, 1 = mild, 0 = none) the degree of functional disability (3 = requiring bedrest, 2 = working ability severely impaired, 1 = working ability slightly impaired, 0 = functioning normally), and presence or absence of associated symptoms (nausea, vomiting, photophobia). Serial pulse, blood pressure and ECG recordings were made with the patient supine. A small cannula was inserted in a dorsal forearm vein for withdrawal of blood.

The tablets (35 mg) were dispersed in 100 ml of tap water before administration. Doses of 70 mg, 140 mg and 280 mg were administered to separate patients.

Migraine symptoms were assessed at baseline, 1, 1.5 and 2 h. Patients not responding

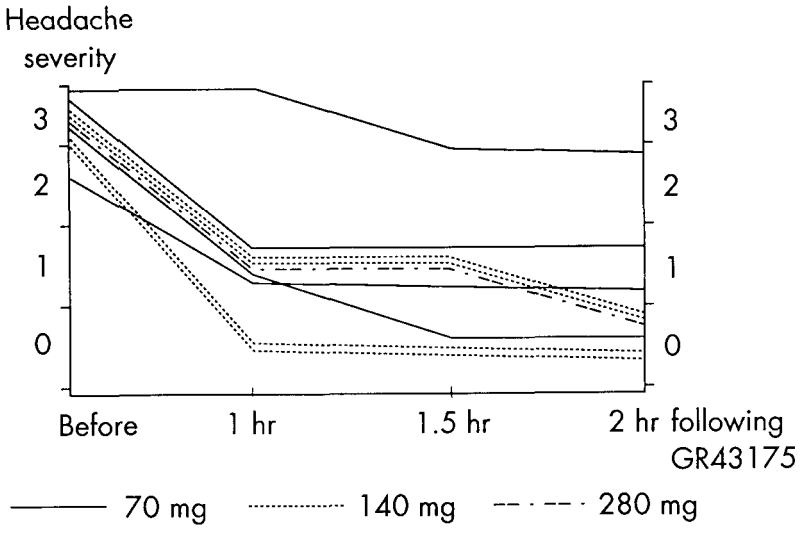

Fig. 1. Severity of headache following GR43175 administration. Each line represents one patient. Headache severity grade: 3 = severe; 2 = moderate; 1 = mild; 0 = none.

at 2 h were offered rescue medication without ergotamine. Blood pressure, pulse, ECG recordings and plasma samples (for drug assay) were taken at 1, 1.5, 2, 3 and 4 h after treatment. Blood samples were taken before and after treatment for routine haematological and biochemical analyses.

All patients were observed for a minimum of 4 h before they were allowed to leave the clinic. They were asked to report any untoward symptoms at any time during or following GR43175 administration.

Results

Nine patients (8F, 1M; mean age 42.3 years; range 29–60 years) all with common migraine were treated. Mean duration of their attacks before treatment was 6 h 23 min (range 55 min to 16 h 45 min). Before treatment eight (88%) patients had severe headache (grade 3) and seven (77%) were nauseated; no patients were vomiting. All either required bedrest or were unable to work normally.

Although the number of patients in the study was small there appeared to be a dose-related improvement in migraine symptoms. Doses of 140 mg or 280 mg gave complete headache relief (grade 0) within 2 h (Fig. 1)

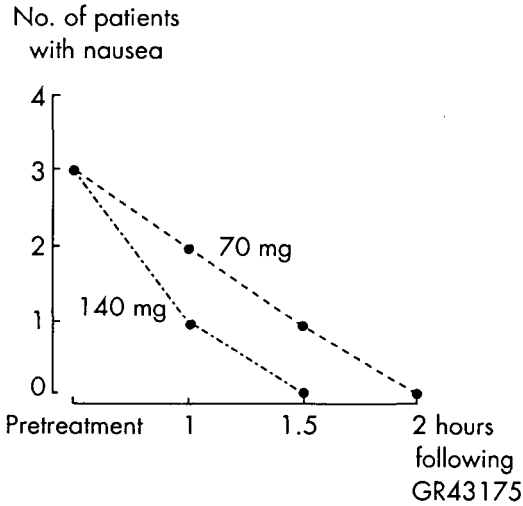

Fig. 2. Effects of GR43175 (oral) on nausea. (One additional patient treated with 280 mg GR43175 showed relief of nausea after 1 h.)

and associated symptoms (nausea, photophobia) had resolved by 1.5 h (Fig. 2). This was reflected by an overall improvement in clinical disability: in all cases patients felt able to function normally (grade 0) by 1.5 h (Table 1).

In comparison, only one of those patients receiving 70 mg had complete headache relief within 2 h. Of the remaining patients

Table 1. Effects of GR43175 on clinical disability.

Dose (mg)	Total no. of patients	Time (h)	Clinical disability			
			3	2	1	0
70	4	Before	1	3	0	0
		1	1	0	2	1
		1.5	0	1	2	1
		2	0	1	1	2
140	4	Before	2	2	0	0
		1	0	1	1	2
		1.5	0	0	1	3
		2	0	0	0	4
280	1	Before	0	1	0	0
		1	0	0	1	0
		1.5	0	0	0	1
		2	0	0	0	1

Clinical disability grading: 3 = requiring bedrest; 2 = working ability severely impaired; 1 = working ability impaired to some degree; 0 = able to work/function normally.

two reported a mild residual non-migraine headache and one a moderately severe migraine headache. Associated symptoms (nausea and photophobia) resolved completely within 2 h. This was reflected by a degree of improvement in overall clinical disability (Table 1). All doses of GR43175 were well tolerated and no adverse events were reported. There was no noticeable or consistent change in pulse rates, ECG recordings or laboratory parameters attributable to GR43175.

Drug plasma determinations showed that symptom relief was obtained within the range 18–60 ng GR43175/ml plasma. Mean peak plasma concentrations of 31, 68 and 136 ng/ml were obtained with doses of 70, 140 and 280 mg, respectively, suggesting that doubling the dose produces a corresponding doubling in the peak plasma concentration.

Discussion

Initial clinical experience with intravenous and subcutaneous GR43175 indicated that the drug may represent a fast, effective and well tolerated treatment for acute common and classical migraine. Whilst the subcutaneous formulation represents a convenient parenteral form for use by medical personnel, a non-parenteral formulation would be more convenient for patient self-administration.

An oral preparation in the form of a dispersible tablet was tested in healthy volunteers. Pharmacokinetic data indicated relatively rapid absorption, peak plasma concentrations being reached within 2 h. However, the degree of absorption of an oral formulation during a migraine attack, when nausea and vomiting often accompany the headache and gastric motility is known to be reduced, was uncertain.

This preliminary clinical study indicated good absorption of oral GR43175 in well established acute migraine attacks, despite the presence of nausea in most patients. Peak plasma concentrations similar to the proposed therapeutic range from intravenous dosing were obtained within 40–120 min.

Migraine headache and associated symptoms were rapidly resolved with the higher doses without affecting heart rate, blood pressure or ECG recording. No adverse effects were reported in this study.

The oral formulation seems to provide a suitable non-parenteral alternative. Further placebo-controlled studies, however, are required to confirm these early findings.

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