Almotriptan, a New Anti-Migraine Agent: A Review

Jordi Gras, Jesús Llenas, Josep M. Jansat, José Jáuregui,
Xavier Cabarrocas, and José M. Palacios

Almirall Prodesfarma, Research Center, Barcelona, Spain

Key words: 5-HT_{1B/1D} receptors—Almotriptan—Migraine—Triptans.

ABSTRACT

Almotriptan is a new anti-migraine agent with nanomolar affinity for human 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors, weak affinity for 5-HT_{1A} and 5-HT₇ receptors and no significant affinity for more than 20 other pharmacological receptors. Almotriptan was effective in animal models predictive of anti-migraine activity in humans and had a good safety profile in animal studies. From the toxicological point of view, almotriptan has a profile similar to that of other marketed triptans. In animal studies, at levels substantially higher than required for therapeutic activity in humans, almotriptan was devoid of any oncogenic, genotoxic or teratogenic effects.

Almotriptan is well absorbed orally; its absolute bioavailability in humans is 70%. Its peak plasma levels are reached at 1 to 3 h after its administration; its elimination half-life is 3 to 4 h. Almotriptan is metabolized by monoamine oxidase-mediated oxidative deamination and cytochrome P450-mediated oxidation as the major metabolic route and by flavin monooxygenase as the minor route. No dose adjustment is required for gender or age, and only in the case of severe renal impairment the dose should not exceed 12.5 mg over a 24-h period. There was no significant interaction between a single dose of almotriptan and propranolol, fluoxetine or verapamil, at multiple doses.

The efficacy of almotriptan in the treatment of acute migraine was demonstrated in clinical trials on more than 3000 patients with migraine. At two h after oral administration of almotriptan, 12.5 mg, the percentages of patients showing pain relief and a pain-free score were 64 and 36%, respectively. The effects of almotriptan were significantly better than those of placebo. When almotriptan was administered in the early phase of migraine, the percentage of pain-free patients at 2 h rose to 84%. In a phase III, double-blind and placebo-controlled study, the incidence of adverse events with almotriptan was not statistically different from that of placebo. Based on the available data, it appears that almotriptan is the triptan of choice when good efficacy and high tolerability are desired.

Address correspondence and reprint requests to Dr. Jordi Gras, Pharmacological Development Department, Almirall Prodesfarma Research Center, Cardener 68-74, E-08024 Barcelona, Spain. Tel: +34 (93) 291-34-61; Fax: +34 (93) 291-34-45. E-mail: jgras@almirallprodesfarma.com

INTRODUCTION

Sumatriptan has been a breakthrough development in the treatment of acute migraine. It is more selective, efficacious and safer than its predecessors: ergotamine and dihydro-ergotamine (11). However, the oral bioavailability of sumatriptan is low; it has a high rate of headache recurrence and it is contraindicated in patients with coronary artery disease (41). It appeared, therefore, that there was still room for improvement in migraine therapy. Most migraine patients prefer oral formulation, making high oral bioavailability of paramount importance. Hence, second generation triptans have been developed with the aim of improving the treatment of migraine.

Triptans are 5-HT derivatives that have high selectivity and potent agonistic activity for 5-HT_{1B/1D}, 5-HT_{1F} and, to some extent, for 5-HT_{1A} receptors (44). Triptans have three main mechanisms of action in common: cranial vasoconstriction, peripheral trigeminal inhibition and the inhibition of transmission through second-order neurons of the trigeminocervical complex (18). It has not yet been clearly established which mechanism is the most relevant one. Some authors (13) maintain that only the compounds that induce carotid vasoconstriction, thus acting through a vascular mechanism, are effective in clinical practice. On the other hand, the compounds that inhibit the neurogenic plasma extravasation as their main mechanism of action (e.g., bosentan, a selective endothelin receptor antagonist and RPR100893, a tachykinin NK1 receptor antagonist) have been found clinically ineffective in the therapy of migraine. This observation reinforced the idea that drugs have to induce cranial vasoconstriction to be effective in migraine (30,43). In addition, recent studies have demonstrated that the vasoconstrictor effects of triptans are mediated through the 5-HT_{1B}-receptor subtype, and that the 5-HT_{1B} receptor protein is located only in vascular smooth muscle (31). Consequently, agonistic selectivity for 5-HT_{1B} receptor seems to be the principal target. The selective 5-HT_{1D} agonists have been shown to be clinically ineffective (20), whilst selective 5-HT_{1F} agonists have shown efficacy, but at doses that probably also affect cranial 5-HT_{1B} receptors (19).

The aim of this paper is to review animal and clinical studies with almotriptan, a new anti-migraine agent, member of the triptan family. In a recently published meta-analysis almotriptan compared favorably with other triptans because of its high tolerability and good efficacy (12).

CHEMISTRY

Almotriptan (Fig. 1) (3-[2-dimethylamino)ethyl]-5-(pyrrolidin-1-ylsulfonylmethyl)-1H-indole) is a tryptamine derivative with a pyrrolidinylsulfamoyl group attached at the 5 position of the indole nucleus through a methylene spacer. This pyrrolidinylsulfonamide substituent provides a molecule with physicochemical properties (for example $\log D = 0.35$), which could favor a good pharmacokinetic profile. Almotriptan was selected at the preclinical level as its properties were predictive of a better clinical profile than that of sumatriptan.

Fig. 1. Chemical structure of almotriptan.

PHARMACOLOGY

Binding Studies

The affinity of almotriptan was determined by using specific radioligand displacement assays for the different serotonin receptor subtypes. Almotriptan exhibited a high affinity for the cloned human 5-HT_{1B} and 5-HT_{1D} receptor subtypes ($IC_{50} = 12 \pm 7$ and 13 ± 1 nM, respectively) and a selectivity in excess of 60-fold for the closely related 5-HT_{1A} receptor. A significant affinity of almotriptan ($IC_{50} \approx 50$ nM) has been demonstrated for 5-HT_{1F} receptors, with lesser but significant affinity also for 5-HT₆ and 5-HT₇ receptors (1) (Table 1).

When tested against a panel of non-serotonergic receptors in radioligand binding assays, almotriptan, at a concentration of 100 μ M, showed less than 50% displacement of most receptors (Table 1).

Other *In Vitro* Studies

Almotriptan has also been characterized as an agonist at the 5-HT_{1B/1D} receptors in the model of the forskolin-stimulated cyclic AMP formation in HeLa cells transfected with human 5-HT_{1B} or 5-HT_{1D} receptors. Almotriptan exhibited the characteristics of a full agonist, showing very high affinity in the low nanomolar range ($EC_{50} = 1.6$ and 3.1 nM at the 5-HT_{1B} and 5-HT_{1D} receptors, respectively) (1).

Pharmacodynamic Properties

In vitro studies

Almotriptan produced potent concentration-dependent contractions of canine isolated saphenous veins ($EC_{50} = 394 \pm 40$ nM); it acted as a full agonist. As demonstrated by its sensitivity to inhibition by the selective antagonist GR127935 (1), this vasoconstrictor effect was due to an agonistic effect at 5-HT_{1B/1D} receptors. In pig and rabbit renal arteries and in rabbit mesenteric arteries, almotriptan was either ineffective or far less effective, suggesting vascular selectivity (1).

The contractile effects of almotriptan were also studied in isolated human vessels from the brain (meningeal, temporal, basilar, and internal carotid arteries), and in other relevant vascular beds, including coronary arteries. The effects of almotriptan and sumatriptan in a

TABLE 1. Binding affinities of almotriptan at various receptors

Receptors		Species	IC ₅₀ (nM)
Serotonergic	5-HT _{1B}	Human	12 ± 7
	5-HT _{1D}	Human	13 ± 1
	5-HT _{1A}	Rat	850 ± 70
	5-HT _{1F}	Human	50
	5-HT _{2A}	Human	25,000 ± 11,000
	5-HT _{2C}	Pig	≈100,000
	5-HT ₃	Mouse	>100,000
	5-HT ₄	Human	140,000 ± 110,000
	5-HT ₆	Rat	>1000
	5-HT ₇	Rat	>1000
Adrenergic	α ₁	Rat	80,000 ± 20,000
	α ₂	Rat	80,000 ± 6000
	β ₁	Rat	45,000
	β ₂	Rat	>100,000
Muscarinic	M ₁	Human	>10,000
	M ₂	Human	>10,000
	M ₃	Human	>10,000
Adenosine	A ₁	Rat	>100,000
	A ₂	Cow	>100,000
Dopamine	D ₁ and D ₂	Human	>100,000
Angiotensin	AT ₁	Rat	>100,000
	AT ₂	Cow	>100,000
Histamine	H ₁	Guinea pig	>10,000
	H ₂	Guinea pig	>100,000
Tachykinin	NK ₁ , NK ₂ , and NK ₃	Human	>100,000
Opiate	—	Rat	>10,000
Endothelin	ET _A and ET _B	Human	>100,000
CGRP	—	Rat	>100,000
ADO uptake	—	Guinea pig	>100,000
NE uptake	—	Rat	>100,000
5-HT uptake	—	Rat	>100,000

Modified from ref. 11 and data on file at Almirall Prodesfarma.

human perfused meningeal arteries preparation showed that almotriptan has a statistically significant, 7-fold greater potency and greater effectiveness in contracting this vessel, in comparison with sumatriptan (Fig. 2) (2). On human superficial temporal artery almotriptan had a vasoconstrictor effect, similar to that of sumatriptan (EC₅₀ = 0.7 and 0.4 μM, respectively). On human basilar artery, the vasoconstrictor potency of almotriptan was 9-fold lower than that of sumatriptan (EC₅₀ of 3.7 and 0.4 μM for almotriptan and sumatriptan, respectively). In comparison with sumatriptan, almotriptan showed no differences in the contractile effects on either internal carotid or ophthalmic arteries (2).

In human pulmonary arterial preparations, almotriptan produced smaller contractions than sumatriptan. Both almotriptan and sumatriptan contracted the pulmonary veins with similar potencies. In non-precontracted bronchial preparations, almotriptan and sumatriptan

Fig. 2. Cumulative concentration-response curves to almotriptan (■) and sumatriptan (▲) in human isolated meningeal arteries. Ordinate: percentage of the response elicited by a 0.1 μM of 5-HT. The values are means of 7 to 11 separate experiments, vertical bars represent S.E.M. Reproduced from ref. 2, with permission from Blackwell Publishing.

tan produced minor contractile responses that are unlikely to be relevant clinically and that were similar to those obtained with 5-HT. In human coronary arteries, almotriptan has a statistically significant ($p < 0.05$) lower spasmogenic capacity compared with sumatriptan (Fig. 3) (2).

In vivo animal studies

Given either intravenously (i.v.) or intraduodenally (i.d.) to anesthetized cats, almotriptan increased carotid vascular resistance with the same potency and efficacy as sumatriptan. At 9 $\mu\text{g}/\text{kg}$, i.v., it increased carotid vascular resistance by 100% (Fig. 4) (21). The effects seen with i.d. administration suggest effective enteric absorption. In beagle dogs, almotriptan, i.v., also increased carotid vascular resistance. Almotriptan appears to be more selective than sumatriptan for carotid versus femoral vascular beds (21). In the carotid vascular bed the contractile effects of either almotriptan or sumatriptan were almost completely reversed by methiothepin, consistent with its antagonism at the 5-HT₁ receptors (26).

Mechanism of Action

In anesthetized cats almotriptan acted mainly on carotid arteriovenous anastomoses (21) and had a tendency to increase cerebral blood flow in absolute as well as relative terms. The effect of almotriptan was comparable to that of naratriptan, and more pronounced than that of sumatriptan. Almotriptan did not decrease the component of brain

Fig. 3. Cumulative concentration-response curves for the effects of almotriptan (■), sumatriptan (▲), and 5-HT (▼) in human isolated coronary arteries. Ordinate: percentage of the response elicited by 10 μ M of 5-HT. The values are means of 14 to 17 separate experiments, vertical bars represent S.E.M. Reproduced from ref. 2, with permission from Blackwell Publishing.

Fig. 4. Effects of intravenous almotriptan on carotid resistance, mean blood pressure, and heart rate in anesthetized cats ($n = 7$) at 15 min after administration of the drug. Baseline values (means $\pm$ S.E.M.) are: mean blood pressure = 115 ± 10 mm Hg, heart rate = 171 ± 11 beats/min, and carotid resistance = 2.94 ± 0.27 mm Hg/min/mL. There were no statistically significant changes in heart rate. Student's t -test was used for paired data with reference to baseline, * $P < 0.05$, ** $P < 0.01$. Reproduced from ref. 21, with permission from Elsevier Science.

blood flow supplied by the carotid artery (21). Furthermore, almotriptan inhibited meningeal extravasation produced by electrical stimulation of the trigeminal ganglion in anesthetized guinea pigs (21).

Safety and General Pharmacology

Cardiovascular safety

In Vitro. In isolated rabbit Purkinje fibers, almotriptan, 3 μM , did not modify the duration of the action potential; this finding suggested that the drug may be devoid of pro-arrhythmogenic effects (data on file at Almirall Prodesfarma). In addition, at 10 μM almotriptan had no effect on isolated guinea pig hearts (22). These concentrations of almotriptan were 20 and 50 times higher, respectively, than human plasma levels of almotriptan ($C_{\text{max}} = 150 \text{ nM}$), following oral administration of the therapeutic dose (12.5 mg) (3).

In vivo. As determined by telemetry, almotriptan, p.o., did not affect blood pressure or heart rate of normotensive Wistar rats (22). In open-chest anesthetized beagle dogs, almotriptan, at high doses, tended to increase total peripheral resistance to an extent similar to that described for sumatriptan (9), but far less than reported for ergotamine in cats and dogs (27,42). However, and in contrast to almotriptan, sumatriptan induced a cardiodepressant effect (mainly a fall in heart rate and dP/dt_{max}) (22). This bradycardic effect has been attributed to an effect on the central nervous system (4); it has also been observed in pigs (5).

In conscious beagle dogs, almotriptan, i.v., had no effect on the coronary blood flow, whereas sumatriptan tended to increase it. The effect of sumatriptan on coronary circulation may have been due to an increased heart rate, rather than to a direct vascular effect of the drug. The vasoconstrictor effects of sumatriptan on the coronary arteries of beagle dogs, clearly observed *in vitro* (33), require higher doses than those used in the present study. At doses up to 0.3 mg/kg i.v., neither almotriptan nor sumatriptan decreased coronary flow, or increased vascular resistance. Almotriptan produced no changes in the evaluated ECG intervals (22).

In conscious cynomolgus monkeys almotriptan, at 1 mg/kg, s.c., had no effect on cardiovascular parameters. Sumatriptan slightly increased blood pressure and heart rate. At 3 mg/kg, almotriptan and sumatriptan produced modest and transitory cardiovascular effects, but no morphological ECG alterations. The absence of any effects of sumatriptan, at doses up to 1 mg/kg, on either ECG or on main hemodynamic parameters in cynomolgus monkeys has previously been reported (25). In our experiment, however, at the subcutaneous dose of 3 mg/kg, sumatriptan produced slight but clear hemodynamic effects (22).

Intracoronary infusion of drugs to anesthetized beagle dogs has been proven to be a useful model for detection of ECG alterations, such as torsade de pointes (23). Administration of compounds directly into the heart via a coronary artery avoids possible first-pass metabolism, ensuring that higher levels of the parent compound are achieved in myocardial tissue. By intracoronary administration at 30 $\mu\text{g}/\text{min}$ for 1 h, neither almotriptan nor sumatriptan produced changes in the QTc interval (22).

Central Nervous System Safety

In the Irwin test no behavioral changes were observed in mice after almotriptan at doses up to 300 mg/kg p.o. (24). Almotriptan did not stimulate locomotor activity in mice (24), whereas anpirtoline, which has an affinity for 5-HT_{1B} and/or 5-HT_{1D} receptors, and has been shown to act on the central nervous system, increasing locomotor activity (8). Furthermore, almotriptan did not modify the increase in hexobarbital-induced sleep produced by diazepam (24), which is consistent with the previously demonstrated absence of sedative action (data on file, Almirall Prodesfarma), and did not interact with caffeine-induced increased spontaneous locomotor activity in mice (24). In guinea pigs, 5-HT_{1D} agonists cause hypothermia by acting on 5-HT_{1D} receptors that are present in guinea pig and human brains, as well as in brains of other species (45). As determined by telemetry in guinea pigs, 5-carboxamidotryptamine, a 5-HT_{1B/1D} agonist, at 0.3 mg/kg s.c., reduced body temperature by more than 2°C whilst almotriptan, at 10 mg/kg s.c., did not induce hypothermia (24); this finding further supports the assumption that almotriptan does not cross blood-brain barrier.

Finally, almotriptan slightly antagonized apomorphine-induced emesis in dogs (24).

Renal System Safety

In anesthetized beagle dogs, almotriptan, at 1 mg/kg i.v., produced a moderate increase in renal blood flow and a transient increase in diuresis and natriuresis. Both, glomerular filtration rate and filtration fraction remained unaffected (24). The renal effects of almotriptan are probably not relevant clinically, since these effects were of short duration and/or small magnitude. Furthermore, almotriptan had no effect on diuresis when administered orally to rats (24).

Respiratory System Safety

No symptoms of bronchospasm appeared in conscious guinea pigs following subcutaneous administration of almotriptan, at 10 mg/kg (24).

PHARMACOKINETIC AND METABOLISM PROPERTIES

ADME Studies

Unless otherwise indicated, the findings reported in this section are from data on file at Almirall Prodesfarma.

Single-dose pharmacokinetics of almotriptan, i.v., s.c., and p.o., has been well characterized in Sprague–Dawley rats, beagle dogs and cynomolgus monkeys (Table 2). When administered p.o. almotriptan was rapidly absorbed and eliminated from the body with a short half-life of about 1, 2.5, and 1.5 h in rats, dogs and monkeys, respectively. The absolute bioavailability was about 30% in rats, 80% in dogs, and 18% in monkeys.

The tissue distribution of a single dose of [¹⁴C]almotriptan was studied in Sprague–Dawley and Lister Hooded rats. In albino rats, at all time-points, the highest levels of radioactivity were found in the gastrointestinal tract, liver, kidney and urinary bladder. In

TABLE 2. Animal pharmacokinetics of almotriptan

Species	Route	Gender	Dose (mg/kg)	Mean values of parameters							Urinary elimination (% of the dose)
				$t_{\max}$ (h)	$C_{\max}$ ($\mu\text{g/mL}$)	AUC ($\mu\text{g} \cdot \text{h/mL}$)	$t_{1/2}$ (h)	V_z (L/kg)	Cl (L/h/kg)	F (%)	
Rats (Sprague–Dawley) ($n = 4$)	i.v.	males	10	0.1	3.43	1.69	0.8	6.4	5.9	–	15
		females	10	0.1	3.60	1.82	0.7	5.3	5.5	–	13
	s.c.	males	10	0.5	1.55	1.75	0.6	4.9	5.7	104	18
		females	10	0.5	1.58	1.99	0.8	5.5	5.0	109	18
	p.o.	males	10	0.25	0.57	0.62	2.0	–	–	37	7
		females	10	0.25	0.45	0.64	1.2	–	–	35	7
Dogs (Beagle) ($n = 4$)	i.v.	both	5	0.1	1.95	4.39	2.3	3.7	1.2	–	21
	s.c.	both	5	0.5	1.6	5.14	2.8	–	–	118	26
	p.o.	both	5	0.8	0.92	3.60	2.4	–	–	82	21
Monkeys (Cynomolgus) ($n = 2$)	i.v.	both	10	0.08	5.18	4.32	1.3	4.4	2.4	–	30
	p.o.	both	10	3.5	0.20	0.79	1.7	–	–	19	7

$C_{\max}$, maximal plasma concentration;

$t_{\max}$, time to maximal plasma concentration;

AUC, area under plasma concentration – time curve;

$t_{1/2}$, elimination half-life;

Cl, total body clearance from plasma;

V_z , volume of distribution during terminal phase;

F, bioavailability.

pigmented rats, the half-lives for melanin binding were calculated to be 22 days for almotriptan and 23 days for sumatriptan. Qualitative tissue distribution by autoradiography in albino rats confirmed very low levels of radioactivity in the central nervous system.

The transplacental distribution studies in pregnant rats indicated limited exposure of fetuses to almotriptan-related radioactivity. In addition, limited amounts of radiolabelled almotriptan were found in the milk of lactating rats.

Metabolism

The metabolism of almotriptan was studied in animals and humans. The major metabolic pathway was similar in all species studied. The main metabolite found in rats was the γ -aminobutyric acid derivative that showed an AUC approximately 5-fold higher than that of almotriptan. In dogs, two main metabolites were detected, viz. the same γ -aminobutyric acid derivative and the tertiary amine N-oxide derivative, the AUC ratio of these metabolites to almotriptan was estimated as 75 and 30%, respectively.

The profiles of almotriptan and its major metabolites were studied in urine, feces and plasma of humans treated with a single 25 mg dose of [14 C]almotriptan. Unchanged almotriptan, accounting for 35–45% of the administered dose, was excreted in urine during the first 24 h. The indole acetic acid derivative was the major urinary metabolite (17% of the dose), with the γ -aminobutyric acid, the N-demethylated, and the tertiary amine N-oxide derivatives detected as minor metabolites; they represented, 6, 3, and 1% of the administered dose, respectively. In feces, the major components: almotriptan and the indole acetic acid derivative, together accounted for 9% of the administered dose. Profiles of radioactivity in plasma indicated that unchanged almotriptan, the indole acetic acid and the γ -aminobutyric acid derivatives were the major components.

Biotransformation studies have been conducted *in vitro* using microsomes and recombinant enzymes. The purpose of these studies was to establish what hepatic enzyme systems were involved in the metabolism of almotriptan. *In vivo* studies in Sprague–Dawley rats treated with almotriptan, at doses of up to 500 mg/kg p.o. for 2 weeks, showed that there were no hepatic changes normally associated with the induction of drug-metabolizing enzymes. Metabolism of [14 C]almotriptan was investigated during incubation with human liver microsomes. The data obtained in this *in vitro* study indicated that monoaminoxidase A (MAO-A), flavin monooxygenase (FMO), aldehyde dehydrogenase and two enzymes of the cytochrome P450 family, possibly CYP2D6 and CYP3A4, were involved in the metabolism of almotriptan (40). An *in vitro* study, intended to evaluate the ability of almotriptan to inhibit the major CYP enzymes in human liver microsomes, demonstrated that almotriptan was only a weak competitive inhibitor of CYP2D6. However, taking into account the reported plasma levels of almotriptan at clinically relevant doses, it appears very unlikely that almotriptan alters the metabolism of drugs that are substrates of the CYP2D6 enzyme. Another *in vitro* study also demonstrated that almotriptan had little or no capacity to reversibly inhibit MAO-A or MAO-B activities or to function as a metabolism-dependent irreversible inhibitor of these enzymes. Almotriptan would, therefore, not be expected to alter the metabolism of drugs that are metabolized by MAO-A or MAO-B enzymes. In summary, almotriptan clearance in humans relies on renal function and MAO-A and CYP 3A4 metabolism (Fig. 5). Additionally, all metabolites found in human plasma were also detected in animals.

Clinical Pharmacokinetics

After oral administration, the absorption of almotriptan was reasonably fast with at least 75% of $C_{\max}$ achieved in less than 1 h, while $t_{\max}$ values ranged from about 1.5 to about 2.5 h. In healthy volunteers after a single oral dose of 12.5 mg $C_{\max}$ values reached about 45 ng/mL and AUC values 250–300 ng/(mL · h), with the elimination half-life of ~3.5 h. In a bioavailability study involving p.o., i.v., and s.c. administration of almotriptan (10), the absolute oral bioavailability of almotriptan was 70%, one of the highest among triptans (44).

In healthy volunteers the pharmacokinetics of almotriptan, at doses ranging from 1 to 200 mg p.o., was linear with respect to the dose. Following oral administration of almotriptan at least 75% of the dose was absorbed. After i.v. administration the volume of distribution was 195 L, suggesting an extensive distribution in the body. The protein binding of almotriptan is somewhat less than 40%; it is, therefore, unlikely that protein binding could substantially affect human pharmacokinetics of almotriptan.

In patients suffering from severe renal impairment, $C_{\max}$ of almotriptan can be increased two-fold and AUC three-fold. In this population the dose of almotriptan should not exceed 12.5 mg over a 24-h period. On the other hand, there is no food interaction with almotriptan. Minor variations in the pharmacokinetics of almotriptan have been observed in the elderly population and with respect to gender. They do not warrant dose adjustment.

Drug interaction studies have been carried out with almotriptan and either fluoxetine (a potent inhibitor of the isozyme of cytochrome P-450, CYP2D6), moclobemide (a reversible MAO-A inhibitor), propranolol (a compound eliminated by the CYP2D6 pathway) or verapamil (a compound metabolized by the CYP3A4 pathway and also an inhibitor of this enzyme). These studies have demonstrated that:

a) When fluoxetine and almotriptan are administered concomitantly there is a modest increase in the $C_{\max}$ of almotriptan, without any significant change in the AUC. No adjustment in the dose of almotriptan is, therefore, warranted (14).

b) The coadministration of moclobemide and almotriptan leads to an increase in plasma concentration and lengthening of the half-life of the latter. However, the combined administration of these two compounds was well tolerated. The interaction between moclobemide and sumatriptan, or zolmitriptan, is more substantial (15),

c) Propranolol had no effect on the pharmacokinetics of almotriptan. The concomitant administration of both compounds has been well tolerated (17), and

d) The concomitant administration of verapamil and almotriptan leads to an increase in the AUC and a decrease in the volume of distribution of almotriptan. Nevertheless, this effect is modest, so that a reduction in the dose of almotriptan is not required (16).

TOXICOLOGY

Acute Toxicity

The toxicity of almotriptan in either mice or rats is low when administered by p.o., i.v. or s.c. routes.

The maximal non-lethal doses of the drug were 1000 mg/kg p.o. and 50 mg/kg i.v. in either of the two species. By s.c. route the maximal non-lethal dose of almotriptan was

Fig. 5. Major metabolic pathways of almotriptan in humans.

300 mg/kg in mice and 600 mg/kg in rats. The maximal non-lethal i.v. doses of sumatriptan were 20 mg/kg in rats and 15 mg/kg in mice (32).

Chronic Toxicity

When almotriptan was administered chronically to rats and dogs, the most outstanding effects were observed in the central nervous and cardiovascular systems. Central nervous system effects were observed in rats at doses equal to or greater than 100 mg/kg/day, but were seen in dogs at 5 mg/kg/day. This discrepancy is probably due to the high oral bioavailability of almotriptan in dogs (82% as compared to 37% for rats). The oral bioavailability of sumatriptan was 58% and 37% for dogs and rats, respectively (6). In addition, dogs are more sensitive to the central effects of triptans than rats (25). The most relevant symptoms in dogs were spreading and stiffness of hind legs, abnormal gait, dilated pupils, increased heart rate, tremors, and vocalization. These symptoms are common to triptans.

The exposures elicited by the doses of almotriptan that caused no observable adverse effect (NOAEL) in pivotal chronic toxicity studies were between 6 and 9 times higher than the exposure to the maximal recommended daily dose of almotriptan for humans (25 mg) (Table 3).

Oncogenicity

Almotriptan did not increase the incidence of tumors in mice or rats when administered at doses producing exposures that were 40 and 78 times higher than the human exposure at the dose of 25 mg.

Genotoxicity

Almotriptan was studied *in vitro* in Ames, thymidine locus mouse lymphoma, and cytogenic assay in human lymphocytes, as well as *in vivo* in mouse micronucleus test. It was non-mutagenic in all assays, with or without metabolic activation.

TABLE 3. Summary of pivotal toxicity studies and comparisons of exposure to the maximum recommended daily dose of 25 mg for humans

Study (doses in mg/kg/day)	NOAEL		Ratio Animal/human AUC
	mg/kg/day	AUC ($\mu\text{g} \cdot \text{h/mL}$)	
26-Week oral rat (20, 100, or 500)	20	2.8	6
52-Week oral dog (2, 5, or 12.5)	5	3.8	9
Teratology rat (125, 250, 500, or 1000)	1000*	479	1081
Teratology rabbit (5, 20, or 60)	60*	14	32
Oncogenicity rat (10, 27, 75)	75	35	78
Oncogenicity mouse (40, 100, or 250)	250	18	40

Abbreviations: *Non-teratogenic dose; NOAEL non-observed-adverse-effect level; AUC, area under the curve of plasmatic levels. Human AUC at 25 mg is 0.443 $\mu\text{g} \cdot \text{h/mL}$ (10).

Teratology

Almotriptan, administered to rats by gavage at 1000 mg/kg and to pregnant rabbits at doses up to 60 mg/kg/day p.o. during organogenesis, was not teratogenic. The maternal exposure obtained at these doses were 1081 times (rats) and 32 times (rabbits) the human exposure at the dose of 25 mg/day.

CLINICAL PROFILE

Efficacy

The efficacy studies with almotriptan were carried out on patients diagnosed with acute migraine with or without aura. The patients met the International Headache Society (IHS) guidelines and were otherwise healthy. Various multi-center, randomized, double-blind, placebo-controlled trials encompassing more than 3000 migraine patients demonstrated the efficacy of almotriptan. Recent publications reviewed the clinical trials with almotriptan (7,35). For this reason, only the main clinical trials will be summarized here.

The choice of 12.5 mg as the optimal dose of almotriptan was based on the results of oral dose-finding, phase II clinical trials and consideration of the incidence of adverse effects as well as the efficacy parameters (34). A meta-analysis of the efficacy of almotriptan considered 4 double-blind, randomized, placebo-controlled trials, involving a total of 2294 patients. The analysis demonstrated that at 2 h after oral administration of almotriptan, 12.5 mg, 64% of patients experienced pain relief and 36% had a pain-free score. The differences from placebo were highly significant statistically ($p < 0.001$) (38).

A recurrence was defined as any moderate or severe headache that occurred within 24 h of initial treatment in a patient who achieved a response at 2 h. The global recurrence of 12.5 mg almotriptan across the three double-blind studies was 26% (29). At 12.5 mg almotriptan was consistently effective “across and within” patients; the percentage of pain relief at 2 h in at least two out of three attacks was 75% (37).

A recent publication has studied the “within-patient” early vs delayed treatment of migraine with almotriptan. The efficacy and tolerability parameters were compared in IHS-diagnosed migraine patients who had treated at least 3 mild attacks and at least 3 moderate-severe attacks with almotriptan 12.5 mg. The results were derived from 118 migraine patients suffering 708 attacks; 354 treated when the pain was mild and 354 when the pain was moderate to severe. The results showed that at 1 h. after administration of almotriptan 47% of mild attacks were free of pain in comparison with 14% of patients with moderate to severe attacks ($p < 0.001$), and that at 2 h the values were 84% and 53% ($p < 0.001$), respectively. Other parameters evaluated, such as the need for rescue medication or recurrence, also showed statistically significant improvements in favor of the early treatment (36).

Safety and Tolerability

In a phase III, double-blind, placebo-controlled study, almotriptan, 12.5 mg, was administered as a single dose to treat each of three migraine attacks. The treatment-emergent adverse effects were not statistically significantly different from those caused by placebo (Fig. 6). Adverse effects were defined in this study as events that first occurred or, if

Fig. 6. Most frequent drug-related adverse events reported over three migraine attacks in a randomized, double-blind, placebo-controlled clinical trial of oral almotriptan.

Fig. 7. Most frequent drug-related adverse events reported over a 1-year open-label clinical trial of 12.5 mg oral almotriptan.

present at drug intake, worsened after intake of almotriptan or placebo. The most frequent adverse events, that occurred in more than 2% of the patients, were dizziness and paresthesia. Only the incidence of paresthesia was higher with almotriptan than with placebo (Fig. 6) (7).

In a long-term, open-label trial in which 66% of patients were treated for more than 6 months (10,305 migraine attacks treated over one year), the safety profile of 12.5 mg almotriptan was similar to that seen in controlled clinical trials (Fig. 7) (7).

In a phase III clinical trial of oral almotriptan, chest symptoms occurred in only 0.2% of patients (7), while in pre-marketing clinical trials of sumatriptan the incidence of chest symptoms ranged from 3 to 5% (28).

The cardiovascular safety of almotriptan at single oral doses of 12.5, 25, and 50 mg was evaluated in a double-blind, placebo-controlled, crossover trial. A small, statistically significant, but clinically unimportant rise in systolic and diastolic blood pressures was observed after almotriptan at 25 or 50 mg. Prolongation of QTc interval beyond the normal range was not observed in any of the subjects studied (39).

A double-blind, randomized, parallel-group clinical trial analyzed treatment satisfaction, functional status, and the health-related quality of life in 1173 patients taking either almotriptan, 12.5 mg, or sumatriptan, 50 mg. The patients in the almotriptan group were significantly better satisfied with the treatment (lack of side effects) than those receiving sumatriptan (28).

CONCLUSION

The studies reviewed in this manuscript characterize almotriptan as a potent and selective 5-HT_{1B/1D} agonist in binding studies, and as an efficacious drug in pharmacological animal models predictive of anti-migraine activity in humans. In comparison to other available triptans the human pharmacokinetic profile of almotriptan showed some improvement in oral bioavailability and metabolic aspects (44). In clinical trials, almotriptan was as effective in the treatment of acute migraine attacks as the most active triptans. The improved safety indicates an advantage over other triptans. The outstanding safety profile of almotriptan and its effectiveness in mild migraine attacks suggested its use early, at the onset of a migraine attack.

It is reasonable to assume that a direct comparison of all triptans will never be undertaken. The meta-analysis published recently by Ferrari et al (12), is, therefore, extremely useful. It compared the results of 53 clinical trials with seven triptans (sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan and frovatriptan). In this analysis almotriptan, 12.5 mg, appears to be as effective as sumatriptan in terms of headache response, but superior to sumatriptan when the pain-free rate at 2 h is assessed. "Sustained pain-free" were the patients who were pain free at two hours, had no recurrence of moderate or severe headache and did not use any rescue medication at 2 to 24 h after treatment. In accordance with this definition, more patients treated with almotriptan 12.5 mg, rizatriptan 10 mg or eletriptan 80 mg were "sustained pain-free" than those treated with sumatriptan. When the parameter studied was the inpatient consistency of efficacy over three attacks, the highest consistency rates were for sumatriptan 100 mg and almotriptan 12.5 mg. Finally, when assessing adverse events, almotriptan 12.5 mg showed fewer central nervous system, chest and global adverse events than sumatriptan. These results led Ferrari et al to conclude that almotriptan 12.5 mg is the triptan of choice when high tolerability and good efficacy are required (12). It appears that almotriptan has a highly competitive pharmacological profile that will allow it to occupy an outstanding place in the treatment of migraine.

REFERENCES

1. Bou J, Domènech T, Puig J, et al. Pharmacological characterization of almotriptan: An indolic 5-HT receptor agonist for the treatment of migraine. *Eur J Pharmacol* 2000;410:33–41.
2. Bou J, Gras J, Cortijo J, Morcillo E, Llenas J, Palacios J. Vascular effects of the new anti-migraine agent almotriptan on human cranial and peripheral arteries. *Cephalalgia* 2001;21:804–812.
3. Cabarrocas X, Salvà M. Pharmacokinetic and metabolic data on almotriptan, a new antimigraine drug. 8th Congress of the International Headache Society, Amsterdam, 10–14 June 1997.
4. Coote JH, Dalton DW, Feniuk W, Humphrey PPA. The central site of the sympatho-inhibitory action of 5-hydroxytryptamine in the cat. *Neuropharmacology* 1987;26:147–154.
5. Den Boer MO, Villalón CM, Heiligers JPC, Humphrey PPA, Saxena PR. Role of 5-HT₁-like receptors in the reduction of porcine cranial arteriovenous anastomotic shunting by sumatriptan. *Br J Pharmacol* 1991;102:323–330.
6. Dixon CM, Saynor DA, Andrew PD, Oxford J, Bradbury A, Tarbit MH. Disposition of sumatriptan in laboratory animals and humans. *Drug Metab Dispos* 1993;21:761–769.
7. Dodick DW. Oral almotriptan in the treatment of migraine: safety and tolerability. *Headache* 2001;41:449–455.
8. Engel J, Scheffler G, Nickel B, et al. Anpirtoline Hydrochloride. *Drugs Future* 1989;14:614.
9. Feniuk W, Humphrey PPA, Perren MJ. The selective carotid arterial vasoconstrictor action of GR 43175 in anaesthetized dogs. *Br J Pharmacol* 1989;96:83–90.
10. Fernandez FJ, Jansat JM, Cabarrocas X, Costa J, Salva P. Absolute bioavailability of oral and subcutaneous almotriptan. *Cephalalgia* 1999;19:363 (Abstr.).
11. Ferrari MD. Migraine. *Lancet* 1998;351:1043–1051.
12. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT_{1B/1D} agonists) in acute migraine treatment: A meta-analysis of 53 trials. *Lancet* 2001;358:1668–1675.
13. Ferrari MD, Saxena PR. 5-HT₁ receptors in migraine pathophysiology and treatment. *Eur J Neurol* 1995;2:5–21.
14. Fleishaker JC, Ryan KK, Carel BJ, Azie NE. Evaluation of the potential pharmacokinetic interaction between almotriptan and fluoxetine in healthy volunteers. *J Clin Pharmacol* 2001;41:217–223.
15. Fleishaker JC, Ryan KK, Jansat JM, et al. Effect of MAO-A inhibition on the pharmacokinetics of almotriptan, an antimigraine agent in humans. *Br J Clin Pharmacol* 2001;51:437–441.
16. Fleishaker JC, Sisson TA, Carel BJ, Azie NE. Pharmacokinetic interaction between verapamil and almotriptan in healthy volunteers. *Clin Pharmacol Ther* 2000;67:498–503.
17. Fleishaker JC, Sisson TA, Carel BJ, Azie NE. Lack of pharmacokinetic interaction between the antimigraine compound, almotriptan, and propranolol in healthy volunteers. *Cephalalgia* 2001;21:61–65.
18. Goadsby PJ. The pharmacology of headache. *Prog Neurobiol* 2000;62:509–525.
19. Goldstein DJ, Roon KI, Offen WW, et al. Selective serotonin 1F (5-HT_{1F}) receptor agonist LY334370 for acute migraine: A randomised controlled trial. *Lancet* 2001;358:1230–1234.
20. Gomez-Mancilla B, Cutler NR, Leibowitz MT, et al. Safety and efficacy of PNU-142633, a selective 5-HT_{1D} agonist, in patients with acute migraine. *Cephalalgia* 2001;21:727–732.
21. Gras J, Bou J, Llenas J, Fernandez AG, Palacios JM. Functional profile of almotriptan in animal models predictive of antimigraine activity. *Eur J Pharmacol* 2000;410:43–51.
22. Gras J, Cardelus I, Llenas J, Palacios JM. Cardiovascular safety profile of almotriptan, a new indolic derivative for the treatment of migraine. *Eur J Pharmacol* 2000;410:53–59.
23. Gras J, Llenas J, Palacios JM. Ebastine is without effect in a sensitive experimental model for detecting prolongation of the QTc interval. *Allergy* 1996;31:188 (Abstr.).
24. Gras J, Lluçà J, Llenas J, Palacios JM. Safety profile of almotriptan, a new antimigraine agent. Effects on central nervous system, renal function and respiratory dynamics. *Arzneimittelforschung* 2001;51:726–732.
25. Humphrey PPA, Feniuk W, Marriott AS, Tanner RJN, Jackson MR, Tucker ML. Preclinical studies on the anti migraine drug, sumatriptan. *Eur Neurol* 1991;31:282–290.
26. Humphrey PPA, Feniuk W, Perren MJ, Connor HE, Oxford AW. The pharmacology of the novel 5-HT₁-like receptor agonist, GR43175. *Cephalalgia* 1989;9(Suppl 9):23–33.
27. Johnston BM, Saxena PR. The effect of ergotamine on tissue blood flow and the arteriovenous shunting of radioactive microspheres in the head. *Br J Pharmacol* 1978;63:541–549.
28. Lloyd K. The clinical profile of sumatriptan: safety and tolerability. *Eur J Neurol* 1994;34(Suppl 2):40–43.
29. Martínez E, Cabarrocas X, Peris F, Ferrer P, Luria X. Meta-analysis of the efficacy and safety of almotriptan in the treatment of migraine. *Cephalalgia* 1999;19:362 (Abstr.).
30. May A, Gijsman HJ, Wallnofer A, Jones R, Diener HC, Ferrari MD. Endothelin antagonist bosentan blocks neurogenic inflammation, but is not effective in aborting migraine attacks. *Pain* 1996;67:375–378.

31. Nilsson T, Longmore J, Shaw D, Olesen IJ, Edvinsson L. Contractile 5-HT_{1B} receptors in human cerebral arteries: Pharmacological characterization and localization with immunochemistry. *Br J Pharmacol* 1999; 128:1133–1140.
32. Owen K, Hartley K, Tucker ML, Parkinson MM, Tweats DJ, Jackson MR. The preclinical toxicological evaluation of sumatriptan. *Hum Exp Toxicol* 1995;14:959–973.
33. Parsons AA, Stutchbury C, Raval P, Kaumann AJ. Sumatriptan contracts large coronary arteries of beagle dogs through 5-HT₁-like receptors. *Naunyn-Schmiedeberg's Arch Pharmacol* 1992;346:592.
34. Pascual J. Therapy with other triptans: Almotriptan. In: Diener HC, ed. *Monographs in Clinical Neurosciences. Volume 17. Drug treatment of migraine and other frequent headaches*. Basel: Karger, 2000; 197–205.
35. Pascual J. Almotriptan: A novel 5-HT_{1B/D} agonist for the symptomatic treatment of migraine. *Exp Rev Neurother* 2001;1:20–27.
36. Pascual J, Cabarrocas X. Within-patient early vs delayed treatment of migraine attacks with almotriptan: The sooner the better. *Headache* 2002; 42:28–31.
37. Pascual J, Falk RM, Piessens F, et al. Consistent efficacy and tolerability of almotriptan in the acute treatment of multiple migraine attacks: Results of a large, randomized, double-blind, placebo-controlled study. *Cephalalgia* 2000;20:588–596.
38. Pascual J, Peris F, Cabarrocas X, Luria X. Meta-analysis of the efficacy of almotriptan in the treatment of acute migraine attacks. *Cephalalgia* 2001;21:427 (Abstr.).
39. Robert M, Warrington S, Zayas JM, Cabarrocas X, Ferrer P. Cardiovascular safety of almotriptan in healthy volunteers. 41st Meeting of the Association for the Study of Headache, Boston, 11–13 June, 1999.
40. Salvà M, Palacios JM, Martinez-Tobed A. Metabolism of the novel anti-migraine compound almotriptan (LAS 31416) in humans. 6th ISSX meeting, 30 June to 3 July, 1997:174 (Abstr).
41. Saxena PR, Ferrari MD. Pharmacology of antimigraine 5-HT_{1D} receptor agonists. *Exp Opin Invest Drugs* 1996;5:581–593.
42. Saxena PR, Vlaam-Schluter GM. Role of some biogenic substances in migraine and relevant mechanism in antimigraine action of ergotamine-studies in an experimental model for migraine. *Headache* 1974;13:44–54.
43. Schoenen J. Acute migraine therapy: The newer drugs. *Curr Opin Neurol* 1997;10:237–243
44. Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine. A comparative review of pharmacology, pharmacokinetics and efficacy. *Drugs* 2000;60:1259–1287.
45. Waeber C, Dietl MM, Hoyer D, Palacios JM. 5-HT₁ receptors in the vertebrate brain: regional distribution examined by autoradiography. *Naunyn-Schmiedeberg's Arch Pharmacol* 1989;34:486.