



Update on sumatriptan: new progress in migraine treatment

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The introduction of the 5-HT_{1B/1D} agonist sumatriptan in 1991 marked a significant advance in the management of migraine. Sumatriptan was the first migraine pharmacotherapy designed to selectively target the neurovascular origin of migraine pain. Sumatriptan was introduced in several formulations – injection, nasal spray, conventional tablet or suppository. The latest sumatriptan formulation, a fast-disintegrating/rapid-release oral tablet, has recently been introduced into clinical practice. Swallowed with liquid, this sumatriptan tablet was developed to disintegrate and disperse more efficiently in the gastrointestinal tract than the conventional tablet. This article reviews clinical data on the long-standing formulations, discusses recent findings on the new fast-disintegrating/rapid-release tablet, and considers the clinical applications of each of the sumatriptan formulations in the management of migraine.

Affecting an estimated one in ten individuals, migraine is a pervasive, often debilitating disease [1–3]. In general, the primary symptom of migraine is a moderate-to-severe, often unilateral headache, which may be accompanied by gastrointestinal disturbances such as nausea and vomiting, and neurologic symptoms such as sensitivity to light and sound. During a typical migraine attack, which can last from 4 h to 3 days, the patient experiences functional impairment that restricts or prevents normal activities. Often, patients are bedridden until symptoms subside.

The introduction of the 5-HT_{1B/1D} agonist sumatriptan in 1991 marked a significant advance in the management of migraine. Sumatriptan was the first migraine pharmacotherapy designed to target selectively the neurovascular origin of migraine pain [4], and is available in several formulations. The pharmacology, pharmacokinetics and clinical efficacy and safety of sumatriptan formulations that have been available for years (i.e., injection, conventional tablet, nasal spray and suppository) have been reviewed extensively elsewhere [4–11]. This review will examine clinical data on these long-standing formulations, discuss recent findings on a new fast-disintegrating/rapid-release oral form of sumatriptan, and consider the clinical applications of each of the sumatriptan formulations in the management of migraine.

Chemistry & pharmacology

Sumatriptan is the active ingredient in all sumatriptan formulations, the chemical name of which is 3-[2-(dimethylamino)ethyl]-N-methyl-

1H-indole-5-methanesulfonamide. The chemical structure is shown in Figure 1. Sumatriptan has an empirical formula of C₁₄H₂₁N₃O₂S, and a molecular weight of 295.4. A white to off-white powder, sumatriptan is soluble in water and saline.

Sumatriptan and similar compounds (triptans) have been hypothesized to relieve migraine headache and associated symptoms via three potential mechanisms of action [12]:

- Cranial vasoconstriction (mediated by activity at 5-HT_{1B} receptors)
- Peripheral neuronal inhibition (mediated by activity at 5-HT_{1D} receptors) to block the release of vasoactive peptides that cause neurogenic inflammation
- Inhibition of transmission through second-order neurons of the trigeminocervical complex (mediated by 5-HT_{1B} and _{1D} receptors)

Which mechanism or mechanisms are the most important is not yet known.

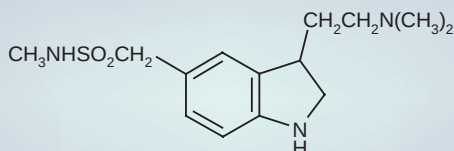
Sumatriptan in the context of other triptans

Sumatriptan, the first selective 5-HT_{1B/1D} agonist to be developed, is the most extensively studied medication in the history of migraine [13–17]. Sumatriptan facilitated the growing science of headache, stimulated an academic interest in headache across a variety of disciplines, and generated intense pharmaceutical research, which culminated in the development of a number of other triptans including almotriptan, eletriptan,

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Figure 1. Sumatriptan.



frovatriptan, naratriptan, rizatriptan and zolmitriptan [15–20]. All triptans are structural analogues of 5-HT and are chemically very similar. The triptans are available in oral formulations (including some as orally disintegrating wafers, a variation on the tablet), and zolmitriptan is also available as a nasal spray.

For the triptans introduced after sumatriptan, attempts were made to improve upon the oral bioavailability and relatively short elimination half-life of sumatriptan. Eletriptan, naratriptan, rizatriptan and zolmitriptan are less susceptible to first-pass metabolic inactivation by monoamine oxidase (MAO)-A and are less hydrophilic than sumatriptan; characteristics that result in greater oral bioavailability (two- to fivefold more than the 14% reported for oral sumatriptan) [21]. Central penetration and increased receptor affinity and selectivity for the neuronal 5-HT_{1D} receptor also combine to allow for lower total oral dosing (i.e., unit doses of 40 mg or less, compared with 50- to 100-mg doses of sumatriptan). However, in clinical practice, all triptans in a given formulation appear to be very similar with respect to efficacy, tolerability and safety.

Triptan clinical profiles do differ as a function of the delivery system. The differences in clinical profiles arise because the delivery system (e.g., nasal spray or oral tablet) largely determines the pharmacokinetic profile of a triptan and, correspondingly, factors such as the speed at which drug reaches its site(s) of action. Available in up to five formulations depending on the country, sumatriptan is the most versatile of the triptans with respect to options for drug delivery.

Sumatriptan formulations

Sumatriptan was initially introduced in an injectable formulation, 6 mg, which was soon followed in many countries by the introduction of a conventional tablet form (available in 25-,

50- and 100-mg strengths, depending on the country) and a nasal spray form (available in 5-, 10-, and 20-mg strengths, depending on the country). In some countries, sumatriptan is also available in a suppository form. The latest sumatriptan formulation, a fast-disintegrating/rapid-release oral tablet, has recently been introduced into clinical practice [22,23].

The fast-disintegrating/rapid-release tablet was developed in response to the consistent findings that patients prefer tablet forms of migraine medication to others. However, maximizing the speed-of-onset of response is challenging with the preferred dosing form of an oral tablet. Speed of onset of pain-free efficacy depends, to a large extent, upon the speed of delivery of medication to its site(s) of action. Conventional oral tablets do not reach their site(s) of action as efficiently as nontablet forms, as they are less rapidly absorbed relative to parenteral forms, such as injection and nasal spray, which bypass the need for tablet disintegration and drug dispersion in the stomach. These considerations were taken into account when developing the sumatriptan fast-disintegrating/rapid-release tablet. Swallowed with liquid, these tablets disintegrate and disperse more efficiently in the gastrointestinal tract than conventional tablets.

Pharmacokinetics of sumatriptan

Long-standing sumatriptan forms

Each of the sumatriptan formulations have unique pharmacokinetic characteristics (Table 1)[4]. Of the long-standing sumatriptan formulations, the injection is most rapidly absorbed (time to maximum concentration [t_{max}]: 12 min), followed by the nasal spray (t_{max} 1–1.5 h) and the suppositories (t_{max} 1.5 h), followed by the conventional tablet (t_{max} 2 h).

Fast-disintegrating/rapid-release tablet

The fast-disintegrating/rapid-release form of sumatriptan differs from the conventional sumatriptan tablet in several pharmaceutical properties, all designed to improve tablet disintegration and/or dispersion in the stomach (Table 2)[22,23]. Reduced disintegration time and enhanced dispersion with the new formulation compared with the conventional tablet are realized in a reduction in the dissolution rate for sumatriptan [22]. In dissolution studies performed using US Pharmacopeia II apparatus in 0.01M HCl (aqueous) at 30 rpm, the dissolution rate with the fast-disintegrating/rapid-release form of sumatriptan was four-

to five-times faster than that of the conventional tablet [22].

Table 1. Pharmacokinetic characteristics of sumatriptan conventional tablets, nasal spray, injection and suppository [4].

Parameters	Sumatriptan tablets 100 mg	Sumatriptan nasal spray 20 mg	Sumatriptan injection 6 mg	Sumatriptan suppository 25 mg
Maximum plasma concentration	51 ng/ml	16 ng/ml	71 ng/ml	27 ng/ml
Time to maximum plasma concentration	2 h	1 to 1.5 h	12 min*	1.5 h
Half-life	2.5 h	2 h	2 h	1.8 h

* After subcutaneous injection into the deltoid area of the arm.

Consistent with this pharmaceutic profile, the pharmacokinetic parameters measured 0 to 2 h after dosing suggest slightly faster absorption, on average, of the fast-disintegrating/rapid-release tablet compared with the conventional sumatriptan tablet [22]. In a randomized, open-label, four-way crossover study in 32 healthy volunteers, the t_{max} of the new sumatriptan formulation was estimated as 10 min earlier for the 50-mg dose and 15 min earlier for the 100-mg dose than for the corresponding doses of the conventional sumatriptan tablet [22]. Moreover, the area under the concentration–time curve through 30 min post dose was approximately 20% greater with the fast-disintegrating/rapid-release tablet. Although this pattern of results suggests that the rapid-release tablet is absorbed slightly more quickly than the conventional sumatriptan tablet, firm conclusions cannot be drawn, due to considerable intra- and interindividual variability in the pharmacokinetic data. Moreover, this study was undertaken in healthy volunteers rather than in patients during a migraine attack. The degree to which the pharmacokinetic data can be generalized from healthy volunteers to patients during a migraine is not established.

Pharmacokinetic differences between the two forms were not observed beyond 2 h post dose in this study. In fact, the fast-disintegrating/rapid-release formulation met predefined criteria for being bioequivalent with the conventional sumatriptan tablet. The bioequivalence of the two forms suggests that sumatriptan fast-disintegrating/rapid-release tablets can be dosed in the same way as conventional sumatriptan tablets in clinical practice [22].

Clinical efficacy of sumatriptan

Long-standing sumatriptan forms

Of the sumatriptan formulations, the injection, with a 10 min onset of headache relief versus placebo is the most rapidly effective [24,25]. A total of 2 h after dosing with the injection, approximately 80% of patients reported headache relief [4,24,25]. Across studies with sumatriptan injection, approximately 35% of patients reporting relief 2 h post dose experienced headache recurrence, or return of headache within 24 h of dosing [24,25]. Sumatriptan injection was similarly effective at alleviating nausea, photophobia and phonophobia, and at reducing clinical disability. Inpatient response consistency between attacks is high with sumatriptan injection – in a study in which patients treated up to three attacks with sumatriptan injection, headache relief 2 h post dose was reported by 73% of patients for all three attacks and 89% of patients for two out of three attacks [26].

Sumatriptan nasal spray has an onset of efficacy beginning as early as 15 min post dose, compared with placebo [8]. For sumatriptan nasal spray (20 mg), approximately 55 to 64% of patients across controlled studies reported headache relief 2 h post dose compared with 25 to 36% of placebo patients [8]. Headache recurrence was reported in 30 to 40% of patients treated with sumatriptan nasal spray. In a study in which patients used the same dose of sumatriptan nasal spray for up to three attacks, 67% of patients responded for two out of three attacks, and 35% of patients responded for all three attacks [8,27].

Sumatriptan conventional tablets are effective at alleviating headache beginning 30 min post dose, compared with placebo [28]. Approximately 65% of patients reported headache relief 2 h

after dosing [28–30]. The therapeutic gain (difference in response between active medication and placebo) with sumatriptan conventional tablets can be increased by treating migraine attacks early in their course when pain is mild, compared with delaying treatment until pain is moderate to severe [31,32]. Headache recurrence within 24 h of initial dosing was reported in

Table 2. Unique pharmaceuetic properties of the fast-disintegrating/rapid-release form of sumatriptan tablets [22,23].

Property	Significance
Includes an effervescent agent	The effervescent agent reacts with stomach acid and/or the acidic properties of sumatriptan succinate to disperse medication actively. Differs from the conventional tablet, which does not contain this effervescent agent and, therefore, relies on less efficient passive dispersion of medication.
Contains an insoluble filler	The insoluble filler provides a surface against which the tablet can swell and break to enhance drug dispersion. The insoluble filler differs from the soluble filler in conventional tablets, which dissolves and causes the tablet to collapse as water is drawn into the tablet.
Contains higher levels of disintegrant and wicking agent than the conventional tablet	The wicking agent draws water and facilitates swelling of the disintegrant, which pushes against the insoluble filler in the fast-disintegrating/rapid-release form.

approximately 35% of patients in a study of sumatriptan tablets administered early during the course of an attack for mild pain. [32]. Inpatient consistency of response between attacks is high – in a three-attack study, 64% of patients reported headache relief 2 h post dose for two out of three attacks, and 32% reported headache relief for all three attacks [26].

Sumatriptan suppository is not widely available but is marketed in several countries, including Germany, Sweden, Switzerland and Greece. Similar to sumatriptan tablets, sumatriptan suppositories are effective compared with placebo, beginning 30 min post dose [33]. Across five placebo-controlled studies, the incidence of headache relief 2 h post dose ranged from 64 to 74% with the 25-mg dose and 43 to 69% with the 12.5-mg dose, compared with 21 to 48% with placebo [33].

Fast-disintegrating/rapid-release tablet

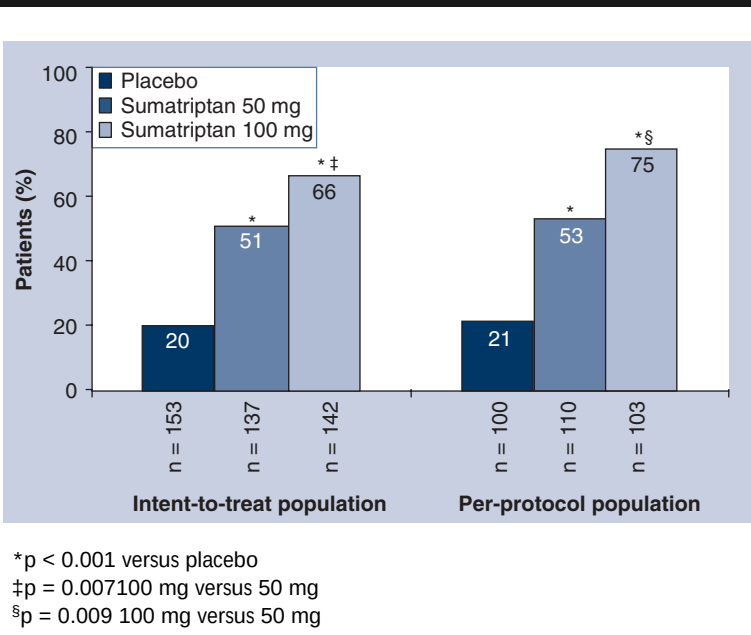
Clinical studies with the long-standing sumatriptan formulations typically included headache relief (i.e., reduction of moderate or severe predose pain to mild or no pain) as a primary end point. In contrast, recent studies with the fast-disintegrating/rapid-release tablet included the more stringent criterion of pain-free response (i.e., reduction of predose pain to no pain) as a primary end point in response to the growing evidence that pain-free response is a more meaningful criterion from the patient's perspective than headache relief. In a randomized, double-blind, parallel-group, placebo-controlled study of the fast-disintegrating/rapid-release form of sumatriptan (n = 137 for 50 mg;

n = 142 for 100 mg; n = 153 for placebo) given during the mild-pain phase of a migraine episode, both sumatriptan doses were significantly more effective than placebo for the primary end point of pain-free response 2 h post dose (Figure 2)[23]. In the intent-to-treat population, 66% of patients treated with sumatriptan 100 mg and 51% of patients treated with 50 mg were pain free 2 h post dose compared with 20% of placebo-treated patients [23]. In the per-protocol population (i.e., the subset of patients who completed the study, complied with the treatment regimen and the study protocol, and practiced early intervention by using randomized medication within 1 h after the onset of migraine pain to treat mild pain: n = 103 for sumatriptan 100 mg; n = 110 for sumatriptan 50 mg and n = 100 for placebo), 75% of patients treated with sumatriptan 100 mg and 53% of patients treated with 50 mg were pain free 2 h post dose, compared with 21% of placebo-treated patients. Sumatriptan fast-disintegrating/rapid-release tablets were also significantly more effective than placebo for secondary efficacy end points including incidences of relief of nausea, sensitivity to light, and sensitivity to sound 2 h post dose, freedom from migraine (i.e., no pain and no symptoms of nausea, vomiting, or light or sound sensitivity) 2 h post dose, and sustained freedom from pain from 2 through 24 h post dose [23].

Whether or not the fast-disintegrating/rapid-release tablets confer more rapid relief of pain than the conventional tablets has not been studied. That the therapeutic gain with the fast-

disintegrating/rapid-release tablet exceeds that with the conventional tablet is consistent with the possibility that the new form confers more rapid relief, but no conclusions can be drawn in the absence of research directly comparing the two forms. The therapeutic gains for the new formulation are 46% for 100 mg and 31% for 50 mg, compared with respective ranges of 24 to 37% and 19 to 30% for the conventional tablet [32,34,35].

Figure 2. Percentage of patients pain free 2 h after treating a migraine episode with the fast-disintegrating/rapid-release formulation of sumatriptan tablets, 50 mg and 100 mg or placebo [23].



Safety & tolerability of sumatriptan Long-standing sumatriptan formulations

The most common adverse event with sumatriptan injection is burning or stinging at the injection site, which was reported in approximately 60% of patients in clinical trials [4]. Patients may also experience a warm/hot sensation, tightness, tingling, flushing and feelings of heaviness or pressure in areas such as the face, limbs and chest. These events have been designated triptan sensations because they appear to occur with all sumatriptan-like compounds developed to date. The fact that these symptoms sometimes occur in the chest has prompted concern among some prescribers regarding the cardiovascular safety of triptans. Having undertaken a comprehensive review of the pharmacological and clinical data on the cardiovascular

effects of triptans, a panel of experts convened in 2002 by the American Headache Society concluded that [36]:

- Chest symptoms occurring during the use of triptans are generally nonserious and are not explained by ischemia
- Incidence of serious cardiovascular events with triptans appears to be low
- The cardiovascular risk–benefit profile of triptans favors their use in the absence of contraindications

This assumption is strongly supported by the results of two recently published retrospective studies [37,38]. In one of these studies, 13,664 out of 63,575 (21.5%) migraine patients were using a triptan. In the second, 50,383 out of 130,411 (38.6%) were using a triptan. The use of triptans was not associated with increased risk of any ischemic events, including myocardial infarction and stroke or mortality.

The most common adverse event in clinical trials of sumatriptan nasal spray was a disturbance of taste, usually described as bad, bitter, unpleasant or unusual, and reported in approximately a quarter of patients receiving sumatriptan nasal spray 20 mg [4,8]. Other than disturbance of taste, adverse events with sumatriptan nasal spray were reported at frequencies similar to those of placebo.

The most common adverse event in clinical studies of sumatriptan conventional tablets was nausea, which is possibly attributed to the migraine rather than to the sumatriptan [4]. In several clinical studies, the adverse-event profile of sumatriptan tablets did not differ from that of placebo [29,30]. Triptan sensations occur less frequently with sumatriptan tablets than with injection.

The tolerability profile of the suppository was similar to that of placebo in controlled clinical trials [33]. Anorectal adverse events such as burning, itching, or irritation were reported in less than 1% of patients.

Fast-disintegrating/rapid-release tablet

The fast-disintegrating/rapid-release form of sumatriptan tablets is well tolerated, as demonstrated by the adverse-event data from the parallel-group, placebo-controlled study described above [23]. Adverse events that the investigator considered to be at least possibly caused by study medication and that were reported in at least 3% of patients in a treatment group were nausea or vomiting, chest symptoms, and malaise or fatigue. Both nausea or vomiting,

and malaise or fatigue, can be symptoms of migraine. No adverse events that were new and unusual based on previous experience with conventional tablets were reported. No serious adverse events were reported and no patient taking study medication prematurely withdrew from the study.

Summary

Among the insights gained through the research conducted over the past 10 years, one of the most important is an understanding of specific attributes that patients require from migraine therapy. Rapid freedom from pain and an ability to return rapidly to normal daily activities are of paramount importance to patients.

Sumatriptan was the first migraine pharmacotherapy designed to selectively target the neurovascular origin of migraine pain and to confer significant improvements over nonselective medicines in both efficacy and side-effect profiles. Sumatriptan was introduced in several formulations (injection, conventional oral tablet, nasal spray and suppository). The availability of several sumatriptan formulations provides an opportunity to tailor therapy to individual patients' needs. For patients who desire particularly rapid relief that cannot be provided by a tablet form, sumatriptan injection with a 10-min onset of action or sumatriptan nasal spray with a 15-min onset of action may be appropriate choices. Patients with very severe attacks and those with vomiting may also benefit from the injection. For patients with nausea who do not wish to take tablets or who fear injections, the suppository or nasal spray are appropriate options.

The latest sumatriptan formulation, a fast-disintegrating/rapid-release oral-tablet form, has recently been introduced into clinical practice. This form was introduced to help meet the need for an oral tablet formulation that confers faster systemic drug delivery than currently available oral forms. Swallowed with liquid, sumatriptan fast-disintegrating/rapid-release tablets were formulated to disintegrate and disperse efficiently in the gastrointestinal tract. The pharmaceutical properties, pharmacokinetics and clinical data on the new form are consistent in suggesting that it may constitute an advance, in that it can confer rapid freedom from pain in an oral tablet, which is patients' preferred dosing form. However, whether the new fast-disintegrating/rapid-release tablet confers clinically relevant advantages over the conventional tablet will be deter-

mined during the course of additional study and use in clinical practice.

Expert opinion

Migraine attributes such as severity of headache and presence of associated symptoms vary from one patient to another, as well from one episode to another within an individual patient. The variable presentation of migraine can complicate therapeutic management – treatment strategies suitable for some patients or migraine episodes are not necessarily optimum for others. Guidelines for the management of migraine accordingly recommend that treatment approaches be tailored to patients' individual needs [39]. The first triptan to be introduced, sumatriptan, continues to evolve through the development of new formulations that allow therapy to be better customized to the needs and goals of the individual patient. The flexible array of sumatriptan dosing forms is a culmination both of an increased understanding of what the patient wants in migraine therapy and an increased scientific and technological ability to deliver what the patient desires.

Although oral formulations are most popular among patients, they are not the most appropriate route of administration for drug delivery during a migraine attack. Owing to gastrointestinal dysmotility, the intestinal absorption of any triptan given orally may be impaired and treatment effects become inconsistent. Therefore, more consideration should be given to prescribing triptans in a nonoral formulation (i.e., injection, nasal spray or suppository). Parenteral administration of a triptan is more likely to provide relief of symptoms, even when it is used later in the course of the migraine attack.

Outlook

It is expected that 5 years from now, the increasingly flexible array of sumatriptan delivery options will be complemented by increased use of sumatriptan and other triptans as components of combination regimens or as combination products including nontriptan medications with different mechanisms of action. The combined use of medications, such as triptans and nonsteroidal anti-inflammatory drugs, with different pain-relieving mechanisms of action may prove to offer clinically meaningful advances in efficacy and reducing the likelihood for headache recurrence. Additionally, combination therapy may offer clinically meaningful advances in

tolerability by permitting the use of lower doses of each component drug than are used when the components are employed as monotherapy. Use of nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors in combination with triptans should be studied and undertaken cautiously in the context of the possibility of cardiovascular sequelae with long-term use of these agents.

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